Characterization of the Clinical Features of Patients with Asthma and Nasal Polyposis

Mary Grace Baker, MD[1]; Geoffrey L Chupp, MD[2]

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Rationale: The patient population with asthma and nasal polyposis remains poorly characterized in current literature. This study was undertaken with the goal of describing clinical features of patients with asthma and nasal polyposis compared to patients with asthma alone.

Methods: The Yale Center for Asthma and Airway Diseases (YCAAD) maintains a robust database of demographic, clinical, and laboratory data for patients with asthma and sinus disease. Enrolled patients complete a phenotyping visit that includes a detailed asthma, sinus disease, and allergy history, lung function testing, and sputum inflammatory cell analysis. We conducted a case-control study of patients selected from this database with asthma and nasal polyposis compared to patients with asthma but no nasal polyposis that were matched by sex. For all patients, demographic, clinical, laboratory, and pulmonary function data were extracted. Statistical analysis of the difference between groups was performed using the Fisher's exact test and student t-test.

Results: Review of the YCAAD database revealed 53 patients with asthma and nasal polyposis, including 25 men and 28 women. Seventy-four sex-matched subjects with asthma but no nasal polyposis were identified. There was no difference observed in age of symptom onset, age at diagnosis, smoking history, secondhand smoke exposure, healthcare utilization, steroid use, incidence of allergic rhinitis, or asthma control measured by ACT score. However, patients with asthma and nasal polyposis were noted to have a higher fraction of exhaled nitric oxide (FeNO) (p=0.03) and slightly lower FEV1/FVC ratio (p=0.03) compared to patients with asthma alone.

Discussion: In this study, subjects with asthma and nasal polyposis demonstrated few differences in clinical characteristics compared to sex-matched subjects with asthma alone. The slightly higher FeNO and lower FEV1/FVC ratios in patients with nasal polyposis suggest that these individuals may have more active airway inflammation than their asthmatic counterparts and may represent a unique endotype of disease.

Mary Grace Baker
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Research Summary Abstract

Title: Evaluation of induction regimens in MDS and AML after hypomethylating agent failure

Brian Ball, M.D., Thomas, Prebet, M.D. Ph.D.

Background: Hypomethylating agents (HMA) failure in patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) inevitably occurs either by a lack of response to treatment (primary failure) or progression of disease after an initial response (secondary failure). In both AML and MDS, HMA failure carries a poor prognosis with median overall survival of 4-6 months and has few treatment options, being limited to investigational agents in clinical trials or allogeneic stem cell transplantation (allo-SCT). Allo-SCT, while potentially curative, is limited by age, availability of donors, and disease control, with a majority of patients requiring cytoreductive treatments prior to transplantation. While intensive, remission induction chemotherapy is often used subsequently, in particular to bridge to allo-SCT, it is not clear whether an advantage exists for any particular regimen.
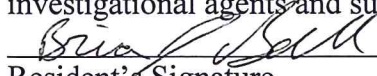
Specific Aim: To compare outcomes for intensive chemotherapy regimens in AML and MDS patients experiencing HMA failure.
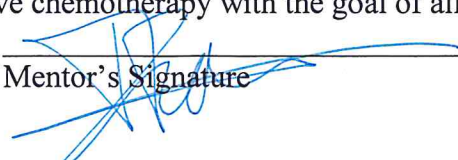
Hypothesis: There will be no difference in outcomes between induction chemotherapy regimens in AML and MDS patients experiencing HMA failure.

Methods: We retrospectively analyzed data from 11 registries from January 2005 to September 2015. Inclusion criteria were diagnosis of MDS and AML as defined by the WHO, treatment with AML-type chemotherapy, age>18 years, and primary or secondary HMA failure until progression or at least 4 cycles of HMA. Patients who discontinued HMA for intolerance or who were allotransplanted while responding to HMA were excluded from the analyses. We classified the regimens into 3 groups, defined by the first cycle of induction therapy: 7+3 for combinations of cytarabine and anthracycline, IDAC for intermediate and high dose cytarabine regimens (more than 1000mg/m2/d for at least 3 days), and PNA for purine nucleoside analog based inductions (i.e. Fludarabine, cladribine, clofarabine). Response to HMA was evaluated by 2006 MDS International Working Group response criteria (IWG) and response to induction therapy by 2008 WHO criteria. Outcomes evaluated included overall response rate (ORR), overall survival (OS), cumulative incidence of relapse (CIR), 8-week mortality and the incidence of allo-SCT. Baseline characteristics were evaluated by Chi-square analysis and t-tests. Kaplan-Meier estimates were used to summarize OS and CIR. A logistic regression model was used for response evaluation and a cox regression model for survival. All variables with an impact on response or survival in univariate analyses (p<0.15) were included in the MVA.

Results: A total of 366 patients met criteria to be included in the study. For the whole cohort, the ORR was 39.6%, 8-week mortality was 7.9%, median OS was 10 months and CIR was 71% at 2 years. 35% of responding patients bridged to allo-transplantation. In multivariate analyses, adverse cytogenetics negatively impacted chance of response (HR: 0.71, p=0.008) while use of IDAC improved response (HR: 2.42, p=0.007). Shorter survival was associated with diagnosis of AML (HR: 1.47, p=0.046), adverse cytogenetics (HR: 1.29, p=0,002), history of intensive chemotherapy given prior to HMA (HR: 1.93, p=0.012), and progression of disease at the time of HMA failure (HR 1.93, p<0.001). Choice of induction regimen did not impact overall survival. For IDAC and PNA patients, addition of anthracyclines improved response and survival with borderline statistical significance.

Conclusions: The choice of induction regimen seems to have a limited impact on outcomes. Although the IDAC group had a superior response rate this did not significantly alter survival or risk of relapse. Among patients treated with IDAC and PNA, the addition of anthracycline led to a superior response rate and a trend towards a longer survival. Our results suggest that IDAC or at least an anthracycline containing regimen may be the best platform for induction. Additionally, our results were in general more favorable than what has been observed with investigational agents and support the use of intensive chemotherapy with the goal of allo-sct.

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Research Summary Abstract

<u>Title</u>: Serum and urine albumin: Influence on loop diuretic responsiveness in heart failure?
Antonios Charokopos MD MS, Jeffrey Moore Testani MD MTR

Background: Resistance to loop diuretics can limit successful decongestion and maintenance of euvolemia in heart failure (HF). Loop diuretics are highly bound to albumin in both the serum and the urine. Thus, low serum albumin and high urine albumin can theoretically limit diuretic delivery to their tubular site of action. It is unknown if this physiology is relevant to contemporary heart failure patients and if it affects diuretic response in a clinically meaningful way.

Specific Aim and Hypothesis: To examine whether hypoalbuminemia and albuminuria are significant drivers of reduced diuretic efficiency (DE) and/or loop diuretic delivery in real world HF patients. We hypothesized that they are likely not, and that any significant association between albumin and DE will likely primarily reflect confounding.

Methods: 190 HF outpatients in the Yale Transition Care center, who were administered oral torsemide or intravenous bumetanide, were prospectively studied. Blood and urine chemistries were collected at baseline and at 1.5 hours post diuretic administration. Albuminuria was quantified by the microalbumin-to-creatinine-ratio (MACR). Diuretic efficiency (DE) was defined as total sodium excreted per doubling of the diuretic dose. Excreted Loop Diuretic was calculated via urine torsemide and bumetanide concentrations, which were quantitated via mass spectrometry, normalized to urine creatinine, and converted to furosemide equivalents.

Results: The median dose of administered diuretic was 160mg (IQR 40-270mg) of furosemide equivalents. Mean serum albumin was 3.7 and 29.7% of patients had albumin less than or equal to 3.5 g/dl. Higher serum albumin levels were weakly correlated with better DE ($r = 0.17$, $p = 0.02$), even following adjustment for variables such as eGFR, sodium, interleukin-6, and B type natriuretic peptide BNP ($p = 0.03$). Interestingly, this effect did not appear to be mediated by reduced drug delivery in hypoalbuminemic patients since the Excreted Loop Diuretic was actually higher in hypoalbuminemic patients ($r=-0.22$, $p<0.01$). Median MACR was 35 mg/g and microalbuminuria (30-300 mg/gCr) was present in 39.0% and macroalbuminuria ($\geq$ 300 mg/gCr) in 17.6% of the cohort. Higher levels of urine albumin demonstrated a weak trend toward a correlation with lower DE ($r = -0.15$, $p = 0.08$). However, this trend was eliminated following adjustment for eGFR ($p = 0.78$).

Conclusions: Lower serum albumin and increased urinary albumin, at levels observed in unselected HF patients, do not have a clinically meaningful association with loop diuretic response. Notably, a weak, independent relationship between lower serum albumin and poor diuretic response was observed, but this was unrelated to the presumed mechanism of reduced diuretic delivery to the tubular site of action.

Antonios Charokopos

Dr. Jeffrey Testani

Impact of Transcatheter Aortic Valve Replacement in Patients with Symptomatic Severe Aortic Stenosis and Depressed Left Ventricular Function

Mohsin Chowdhury, MD; Lissa Sugeng, MD, MPH

Background:

Aortic Valve Stenosis (AS) is the most common valvular heart disease in western countries. Transcatheter Aortic Valve Replacement (TAVR) has been shown to improve mortality, reduces hospitalizations, and improve NYHA class in patients with severe aortic stenosis who are intermediate to high risk surgical candidate. Left ventricular (LV) recovery after TAVR is not well studied. The aim of this study is to assess long-term recovery of LV function after TAVR in patients with decreased LV function.
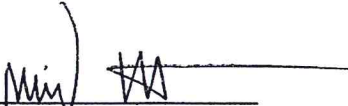
Methods:

Retrospective study of 254 TAVR patients between July 13, 2011- August 10, 2015 was performed. Patient demographics, co-morbidities and echocardiographic findings pre- and post-TAVR were reviewed. Patient who had baseline echocardiograms done at an outside facility or had a follow up period of less than 30 days were excluded.
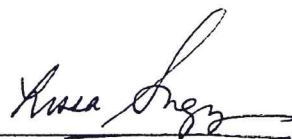
Results:

We analyzed data from 195 patients, 132 (67.7%) received CoreValve prosthesis and 63 (32.3%) received Sapien valves. At median follow-up of 386 days, all valves were well positioned and none had severe regurgitation. Only 7 (3.6%) had moderate regurgitation with no difference between those who received Sapien versus CoreValve. Patients (55/195, 28.2%) who had depressed (<50%) left ventricular ejection fraction (LVEF) at baseline had a mean LVEF of 37.5 ± 8.2% which improved to 46.2 ± 14.2 at the end of follow-up period. In this group, 38 (69%) had ischemic cardiomyopathy (ICM) and 17 (31%) had non-ischemic cardiomyopathy (NICM). NICM patient's LVEF improved significantly compared to ICM patients (94.1% vs 71.1%, p=0.05). The magnitude of improvement of the NICM group was also larger compared to the ICM group, though not significant (14.5 ± 8.7 % vs 12.4 ± 7.8%, p = 0.21). In this depressed LVEF group, 40% (22/55) had low-flow/low-gradient aortic stenosis of which 11 had dobutamine stress testing, 10 had good contractile reserve and 7 had corresponding improvement in LVEF with a mean improvement of 11.9 ± 5.2%.

Conclusions:

Prosthetic valves continued to function well and were without significant intra or paravalvular regurgitation at a median follow-up greater than one year. TAVR patients with baseline depressed LV systolic function demonstrates LV recovery, particularly patients with NICM. There is underutilization of dobutamine stress testing in low-flow/low-gradient aortic stenosis patients, of which the majority had contractile reserve and corresponding improvement in LVEF post-TAVR.

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Combination Immunotherapy with PD-1/PD-L1 Checkpoint Inhibition and MEK Inhibitor Chemotherapy in *Kras*-drive Lung Cancer

Jong Woo Lee, Yu Zhang, Miguel Sanmamed, **Justin Choi**, Lieping Chen, Roy S. Herbst, and J. Peter Koo

Background: In recent years, the emergence of immune checkpoint inhibitors such as anti-PD-1/PD-L1 for the treatment of advanced non-small cell lung cancer (NSCLC), among other solid tumors including advanced melanoma, renal cell carcinoma, and bladder cancer, has demonstrated improved survival compared to standard chemotherapy. However the response rate in NSCLC is still estimated to be just 20%. Furthermore, the *Kras* mutant accounts for the largest mutation-driven subgroup of NSCLC for which there has not yet been any targeted therapy approved for clinical use. This has prompted investigation into downstream targets in the *Kras* signaling pathway, including MEK inhibition. MEK inhibition monotherapy has not yet proven to be efficacious in *Kras*-mutant NSCLC.

Specific Aim: To determine the anti-tumor efficacy and characterize the immunomodulation of the tumor microenvironment in combination therapy with the MEK inhibitor trametinib and PD-1/PD-L1 checkpoint immune inhibition in a *Kras* transgenic lung cancer mouse model.

Hypothesis: Combination therapy trametinib and anti-PD-1/PD-L1 will augment tumor response and survival in a *Kras*-mutant NSCLC mouse model by suppressing myeloid-derived suppressor cells (MDSCs) and promoting infiltration of cytotoxic T lymphocytes (CTLs) in the tumor microenvironment.

Methods: Lung tumors were harvested from $Kras^{G12D/+};Trp53^{floxflox};Rosa26^{LSL\text{-}Luciferase/LSL\text{-}Luciferase}$ transgenic mouse model (PKL) as well as normal lung tissues under treatment with single-agent trametinib or anti-PD-1/PD-L1 compared with combination trametinib and anti-PD-1 or anti-PD-L1 treatment groups. CyTOF2 analysis and flow cytometry of lung tumor cells as well immunofluorescent and immunohistochemical staining of tissue sections were performed to characterize changes in the immune cell population across the different treatment groups, as well as responses in tumor growth and mouse survival.

Results: In untreated PKL tumors we found increased granulocytic MDSCs as well as increased PD-L1 expression within the tumor microenvironment compared to non-tumor bearing mice. Treatment with anti-PD-1 or anti-PD-L1 was ineffective in suppressing tumor growth. Single-agent trametinib and in combination with either anti-PD-1 or anti-PD-L1 of PKL tumor-bearing mice demonstrated decreased tumor growth compared to control vehicle-treated group. However, only combination treatment groups with trametinib and either anti-PD-1 or anti-PD-L1 demonstrated improved survival in PKL tumor-bearing mice, where as no survival benefit was shown with single-agent therapy. The combination treatment groups showed increased percentage of CTLs and decreased percentage of granulocytic MDSCs in the tumor microenvironment when compared to the single-agent treatment groups.

Conclusion: By targeting both the KRAS signaling pathway and checkpoint immune inhibition, combination therapy with MEK inhibition and anti-PD-1 or anti-PD-L1 in the *Kras*-mutant NSCLC mouse model demonstrated a synergistic response in tumor growth and improved survival and may be promising as a future treatment modality for advanced NSCLC.

J Peter Koo

Justin Choi

Comparison of Outcomes for Diabetic Patients in an Interprofessional Primary Care Team Based Academic Patient Centered Medical Home Compared to a Traditional Academic Patient Centered Medical Home within a Large Academic Integrated Healthcare System

Jessica Deslauriers, M.D., Rebecca Brienza, M.D., MPH

Background: Chronic diseases, such as diabetes, are becoming increasingly more prevalent. Although innovative healthcare models, such as the interprofessional medical home are being piloted, it is unclear if they improve the quality of chronic disease care. The Veterans Health Administration (VHA) is currently implementing both the traditional and interprofessional medical home model in select primary care settings. The Centers of Excellence in Primary Care Education (COEPCE) is the interprofessional medical home model at the VHA that incorporates collaborative primary care training and provision of clinical care among nurse practitioners, physicians, pharmacists, health psychologists and physical therapists. Most primary care settings within the VHA, such as Firm B, utilize the traditional medical home model.

Specific Aim: This study will attempt to determine if the interprofessional academic medical home model (COEPCE) improves management of poorly-controlled diabetes more than the traditional medical home model (Firm B).

Hypothesis: COEPCE will have better outcomes for managing diabetes as compared to Firm B because patients are likely to have improved access to multidisciplinary team care with members who have different areas of expertise and scope of practice that contribute to disease outcomes.

Methods: This retrospective cohort study evaluated West Haven Veterans Affairs administrative EHR data over a 2 year period (09/2013 – 09/2015). All patients with a diagnosis of type 2 diabetes from Firm B and COEPCE who did not meet study exclusion criteria (age > 80, a diagnosis of metastatic cancer or other terminal illness) were evaluated. A1c values for patients with uncontrolled diabetes (as indicated by elevated A1c values ≥8.0% during the first 18 months of the study) were followed for six months after the initial 18 month data collection period. The proportion of COEPCE patients who were previously poorly controlled who subsequently demonstrated control (as defined by one or more A1C value <8.0%) was compared to Firm B.

Results: Over the 24 month study period, there were 534 patients (118 in COEPCE and 416 in Firm B) who met the study criteria. COEPCE and Firm B demographics were similar for age, percent service connected, gender, marital status and period of service (theater). The proportion of patients who had all A1c value less than 8.0% during the 6 month evaluation period was 41.5% for COEPCE and 36.1% for Firm B patients (p = 0.28). The proportion of poorly controlled diabetics who attained an A1c value less than 8.0% during the 6 month evaluation period was 49.5% for COEPCE and 45.4% for Firm B patients (p = 0.47). Analysis is ongoing with respect to the following outcomes: faculty vs resident care, A1c control and referral patterns to other professions in COEPCE vs Firm B.

Conclusions: Hemoglobin A1c among diabetic patients in an interprofessional medical home model did not differ significantly when compared to the traditional medical home model. Although not statistically significant, COEPCE had a lower proportion of poorly controlled diabetics. If the 6 month study window was extended, the difference between A1c among COEPCE and Firm B might be statistically significant.

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Outcomes in Tunneled Pleural Catheter placement for Non-Malignant Pleural Effusion
Jacqueline Hirsh, MD; Margaret Pisani, MD

Background: The tunneled pleural catheter (TPC) was approved by the FDA in 1997 and has since been used as a tool for recurrent pleural effusion. Countless studies demonstrate significant improvement in quality of life and dyspnea in recipients of TPCs. There exist studies looking at efficacy of TPC placement with regard to pleurodesis rates in patients with malignant pleural effusion (MPE), however, there is a paucity of data on this outcome in those who receive a TPC for non-MPE.

Specific Aim: To evaluate the rate of pleurodesis in patients with non-malignant indication for TPC placement.

Hypothesis: There will be a lower rate of pleurodesis in TPC recipients with non-malignant effusion versus a MPE.

Methods: A retrospective chart review was undertaken looking at 103 patients in whom a TPC was placed between 1/2013 and 11/2015 at YNHH by the interventional pulmonary service. Of the 103 charts reviewed, 17 were excluded because of attempts at pleurodesis concurrent with or subsequent to TPC placement. Of the 86 patients remaining, TPC indication was recorded for 85, and 18 had a TPC placed for recurrent non-MPE. All 86 patients had laterality recorded, and 20 had bilateral TPCs placed. Number of prior thoracenteses, pleurodesis rate, mortality, and rate of complications, including infection, pneumothorax, and non-functioning catheter were recorded. Time to and indication for removal of TPC were assessed. We recorded indications for TPC placement based on standard criteria in the literature. In patients with MPE, additional variables captured included type of cancer, chemotherapy and/or radiation to thoracic region within one month of TPC placement, and pleural cytology results.

Results: Of the 86 TPC recipients, mean age was 65 years, 50% were male, and 82% identified as Caucasian. 79% had a TPC placed for MPE and 77% had unilateral TPC placement. Indications for placement of a TPC for non-MPE included congestive heart failure (CHF), cirrhosis, and chronic kidney disease (CKD). The TPC was removed in 34/81 (42%) of patients and reason for removal was recorded in 28/34 (82%). In those patients with reason recorded, 16/28 (57%) of TPCs were removed due to documented pleurodesis.* In the MPE cohort, the most common cancers were lung (23/67) and breast (10/67).** With regard to mortality, 76/86 had died by the time of chart review: 64/67 with MPE and 12/20 with non-MPE.***

Conclusions: <u>Pending further data analysis.</u> Pleurodesis rates in TPC placement for MPE versus non-MPE— **data pending**. One notable fact is that the MPE population had a high mortality rate (though this will have to be confirmed with time-to-death analysis). Many of the patients (number tbd) went straight to hospice or died in the hospital, so their pleurodesis potential was never able to be evaluated (i.e. mortality is a potential confounder of pleurodesis in a sick, inpatient population). This, in the end, may skew the pleurodesis rate in favor of non-MPE when it stands to reason that there should in fact be a lower rate of pleurodesis in this cohort due to the transudative nature of their effusions. Of note, one variable not studied, which should be evaluated in subsequent review is inpatient versus outpatient placement of TPC as a surrogate for how sick the patient population is.

Jacqueline Hirsh _____

Margaret Pisani _Margaret Pisani_____

INCREASED MORTALITY WITH EARLY AND LATE STAGE LUNG CANCER AMONG HIV-INFECTED PATIENTS

Resident: Kristen Hysell, PGY-3
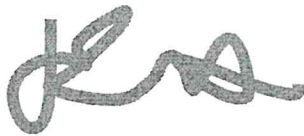Mentors: Brinda Emu, Lydia Barakat

Abstract

Introduction: Lung cancer is the most common non-AIDS related malignancy among HIV-infected patients. This study details the characteristics of HIV-infected lung cancer patients at an urban institution in the recent antiretroviral era.

Methods: Medical records of all patients with HIV diagnosed with lung cancer between 2000-2015 at Yale New Haven Hospital (New Haven, CT) as identified by ICD9 and ICD10 coding were reviewed. Controls included (1) the entire YNHH HIV-infected patient population as well as (2) all patients treated for lung cancer at YNHH during the same time period (data from Yale tumor registry).

Results: A total of 32 patients with lung cancer and HIV were identified. 17 patients were Black (53%), 12 were Caucasian (38%). 72% were male. At time of cancer diagnosis, median age was 53 (range 40-65), median CD4 count was 478 cells/uL (range 26-1240), 84% of patients were on anti-retrovirals, and 59% had an undetectable viral load. 97% were past or former smokers with a median 32 pack-year history. 75% had a history of illicit drug use. 63% were co-infected with hepatitis C, as compared with a 30% co-infection rate among the general HIV-infected population. 67% of all patients had stage III or IV lung cancer at diagnosis. In patients with Stage I or II, 90% patients had surgery, 40% had radiation, and 30% had chemotherapy. In contrast, of the patients with stage III or IV, only 4.5% had surgery, 45% had chemotherapy, and 44% had radiation. The one-year mortality for the cohort was 59% (versus 47.8% for the general population) and was associated with male gender, advanced stage of cancer, and the presence of AIDS at the time of cancer diagnosis. Of note, among HIV-infected patients with Stage I/II cancer, one-year mortality was 25% compared with 6.7% in the general population.

Conclusion: This study provides detailed characterization of patients with HIV infection and lung cancer from an urban institution. At the time of cancer diagnosis, the majority of patients were on anti-retroviral therapy and virally suppressed with a relatively high CD4 count. Presentation occurred at a young age with high rates of smoking and illicit drug use. Strikingly, mortality among individuals with early stage lung cancer was significantly worse than in the general population, despite aggressive cancer therapy. The rate of co-infection with hepatitis C among patients with HIV and NSCLC is higher than the general clinic population, warranting further study about the impact of co-infections on NSCLC incidence.

Kristen Hysell

Lydia Barakat

Title: A Survey Assessment of Clinical Practice Patterns, Knowledge, and Utility of Procalcitonin Levels in Antibiotic Decision in the Management of Septic Critically Ill Patients
Rebecca A Israel, M.D., Margaret Pisani, M.D., M.P.H.

Background: Procalcitonin (PCT) has been established as a sensitivity and specific biomarker in the treatment of sepsis associated with bacterial infection. There is a growing body of evidence suggesting that PCT levels can safely be used to guide antibiotic duration in critically ill patients without an increase in mortality or relapse of infection. Despite this, PCT appears to be underutilized and appropriate implementation remains poorly understood.
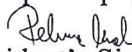
Specific Aim: Assess knowledge and patterns of practice of critical care physicians in a tertiary academic setting regarding the utility of PCT in antibiotic decision making in septic patients.
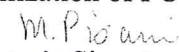
Hypothesis: Experience treating critically ill patients with sepsis and knowledge of the data supporting a PCT based algorithm correlates with use of PCT levels in clinical practice.

Methods: An anonymous electronic survey was distributed to critical care physicians at Yale-New Haven Hospital (YNHH) using Qualtrix software. Potential participants were identified based on their affiliation with YNHH via departmental websites, internal email lists, and staffing schedules. Participants were sent an email with explanation of the study and a link to the survey. The survey included questions about demographics, patterns of practice in the treatment of sepsis and use of PCT levels, and self-reported knowledge of the utility of PCT in the critical care setting. Results were compared between specialties, years of experience treating sepsis, and self-reported knowledge of the data regarding PCT levels and antibiotic decision making in sepsis.

Results: The survey was distributed to 150 potential participants—48 fellows and 102 faculty. Fifty-three responses (35%) were collected— 62% of respondents identified as faculty. Approximately half (53%) of respondents were trained in Pulmonary-Critical Care Medicine (PCCM) and 66% reported treating more than 10 cases of sepsis annually. There was consensus (>80%) among PCCM trained physicians to measure baseline and serial PCT levels in septic patients. Although 50% of these respondents replied that they would never change management based on a low (<0.5ng/mL) initial PCT level, there was consensus (88%) among PCCM physicians to consider antibiotic de-escalation based on PCT-guided algorithm. There was no consensus among non-PCCM trained physicians regarding measurement of PCT levels or interpretation of the results. Among respondents with experience treating >10 cases of sepsis per year and those with a "good" or "fair" self-reported knowledge of the literature, there was consensus (83% and 84%) to measure baseline PCT levels. Respondents who do not routinely measure PCT levels cited weak evidence (36%) followed by lack of generalizability (24%), lack of knowledge (20%), and personal experience (16%) as the main reasons to refrain. Twenty percent (30%) of non-PCCM trained physicians also reported a lack of knowledge compared to 0% of PCCM physicians.

Conclusions: The results from this small sample suggest that there are knowledge gaps regarding the evidence for the use of PCT in sepsis. Definitive conclusions from this survey are limited based on small sample size and single center. Within these constraints, marked variability in the perception and use of PCT in antibiotic decision making was noted across specialties. This seems to reflect confusion about appropriate implementation and interpretation of PCT levels and concerns about generalizability of current data. The results of this data can be implemented to improve physician awareness and appropriate utilization of PCT.

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Predictors of Right Ventricular Pacing in ICD Recipients Without Baseline Pacing Needs

Shadi Kalantarian, MD, MPH, Joseph G Akar, MD, PhD

Background: Identifying ICD recipients who will develop a need for right ventricular pacing (RVP) would inform appropriate device selection in order to reduce future ICD upgrades and for consideration of subcutaneous ICD.

Specific Aim: To determine predictors of RVP in patients who did not have a pacing indication at the time of initial ICD implant.

Hypothesis: We hypothesized that certain patient or device factors (e.g. age, arrhythmias, conduction system abnormalities, length of AV delay, etc) at the time of implant can predict need for RVP in the future.

Methods: A limited dataset of patients undergoing first-time single (n=1635) or dual chamber (n=283) ICDs (programmed VVI or VDI mode at 40 bpm) implanted from 2006 to 2010 was derived from Boston Scientific's ALTITUDE database and linked to the NCDR® ICD Registry. RVP burden was calculated from remote monitor transmissions. The outcome was defined as development of >5% RVP averaged over any continuous 90-day period between 6 and 24 months after ICD implant. The study population was randomly divided into training and validation cohorts (70/30) and characteristics associated with RVP were identified using logistic regression.

Results: Of 1918 patients, 155 (8.1%) developed >5% RVP. Exploring other RVP cutoffs, 116 (6.1%) developed >10% and 87 (4.5%) developed >20% RVP. Patients who developed >5% RV pacing were significantly more likely to have received the ICD for secondary prevention (32% vs. 20%), to be older (66±15 vs. 58±15 yrs), white (90% vs. 75%), have a history of atrial fibrillation (AF) (15% vs. 7.5%), on ongoing AF at implant (40% vs. 7%), ventricular tachycardia (46% vs. 31%), CHF hospitalization (19% vs. 11%), QRS duration>120 ms (27% vs. 16%) and sinus node dysfunction (30 vs. 7.6%). In multivariate analysis, prolonged PR interval, history of AF and ongoing AF at implant were associated with >5% RVP (table 1). The model performed well in the derivation and validation samples (both C statistics >0.7).

Conclusion: Prolonged PR interval, AF history and ongoing AF at ICD implant are predictors of RVP in patients without baseline pacing indications, and should be considerations in selecting single chamber or subcutaneous ICD.

Table 1. Characteristics that were significantly associated with >5% right ventricular pacing in the multivariate analysis in the full cohort.

Effect	Odds Ratio (95% CI)	P value	Overall P value
PR interval & AF			
No AF/ PR interval <230 ms	Reference		
No AF/ PR interval≥230 ms	3.10 (1.35 - 7.08)	0.0075	<0.0001
Historical AF	3.98 (2.39 - 6.62)	<0.0001	
Ongoing AF at implant	10.96 (7.39 - 16.25)	<0.0001	

Shadi Kalantarian, MD, MPH

Joseph Akar, MD, PHD

Question answered: Germinal center T follicular helper cells produce cytokines *in vitro*

Elena Kopeikin, MD   Joseph Craft, MD

Background: Germinal center (GC) Tfh cells secrete IL-21, IL-4, and CXCL13 to help B cells. However, *in vitro*, GC Tfh cells have not demonstrated robust cytokine production. Some studies showed very little IL-21, IL-4, and IFN-γ production by GC Tfh cells after stimulation. The purpose of this experiment was to evaluate whether GC Tfh cells are truly pauci-immune cytokine producers.

Methods: We compared GC Tfh cells from human tonsil and circulating Tfh-like (cTfh) cells in PBMCs of healthy controls by comparing activation and upregulation of Tfh markers as well as Tfh activation markers in response to anti-CD3/CD28, as a T cell activator. Using flow cytometry, healthy control PBMCs and tonsillar cells were analyzed for PD-1 and ICOS (Tfh markers) expression as well as OX40 and CD25 (activated Tfh markers) expression at steady state and following stimulation with anti-CD3/CD28 for 20 hours. They were then sorted into CXCR5+ and CXCR5- populations (to differentiate between Tfh-like and non-Tfh-like populations), and further sorted into OX40+ and OX40- populations (to differentiate between activated and not activated T cell populations). Sorted cells were stimulated with PMA and ionomycin for 4 hours, then underwent intracellular cytokine staining, and analyzed using FACS for IFN−γ, IL-21, and IL4 production.

Results: Upon stimulation, we saw enrichment of CXCR5+PD1+ICOS+ (GC Tfh cells) populations among the tonsillar cells, but not PBMCs. We saw enrichment of activated (OX40+CD25+) populations both in PBMCs and tonsillar cells upon stimulation. Within both CXCR5+ (Tfh) populations and CXCR5- (non-Tfh) populations in PBMCs that were OX40+, we observed increase in IL-21 production (particularly pronounced within CXCR5+ cells). We also found increase in IL-4 production, which was more pronounced in the non-Tfh cell population, which suggested Th2 cell enrichment. We also saw an increase in double producers -- IL-21/IFN-γ and IL-21/IL-4 (but not IL-4/IFN-γ), especially within CXCR5+ cells within PBMCs. Activated tonsillar cells did not demonstrate presence of populations of cytokine double-producers, but we did see increase in IL-21 production.

Conclusions: Activated Tfh cells (OX40+CD25+) increased in the tonsillar and PBMCs upon stimulation as expected. In contrast to previous opinions that tonsillar GC Tfh cells are pauci-immune cytokine producers, we saw increase of IL-21 production within the activated GC Tfh cell population, suggesting the capability of providing B cell help for antibody production in infectious and autoimmune diseases.

Elena Kopeikin

Joseph Craft

Title: Comparison of Upper and Lower Gastrointestinal Bleeding Risk Assessment Tools in Consecutive Patients with Hematochezia: The Glasgow-Blatchford Score Provides the Best Risk Stratification.

Rebecca Kosowicz, M.D., Loren Laine, M.D.

Background: Risk stratification of patients with gastrointestinal bleeding (GIB) is recommended by guidelines. Risk assessment tools for upper GIB (UGIB) are well studied. However, studies evaluating such tools for lower GIB (LGIB) are far more limited with numerous shortcomings. Also, risk assessment tools developed for LGIB have only poor to fair performance with areas under the receiver operating characteristic curve (AUROCs) of 0.60-0.77. We believe evaluation of risk assessment tools should simulate their use in clinical practice: e.g., evaluated in all patients presenting with hematochezia whether or not admitted rather than restricted to patients diagnosed with a LGIB source after work-up. Furthermore, use of the same risk assessment tool for all patients with GIB (UGIB and LGIB) would be helpful in practice.
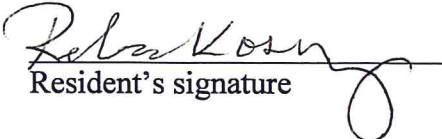
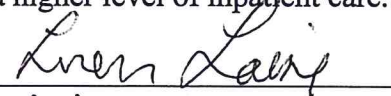**Specific Aim:** To assess the predictive ability of six risk assessment tools for patients with hematochezia.

Hypothesis: Lower GIB tools will be most accurate to predict outcomes in this study population.

Methods: Consecutive patients presenting to the emergency department with hematochezia were included. Scores for UGIB tools (Glasgow-Blatchford Score (GBS), pre-endoscopic Rockall score, AIMS65) and LGIB tools (Strate, BLEED, Noblads) were calculated. Primary outcome was a composite of red cell transfusion, hemostatic intervention (endoscopic, radiographic, or surgical), and death; secondary outcomes were the individual components of the composite. AUROCs were determined with the predefined threshold requirement of good-excellent performance (AUROC ≥ 0.80).

Results: To date, 206 patients have been included in this ongoing study. Only the GBS achieved good-excellent performance and GBS was superior to all other tools for the primary outcome (p<0.0001). Among 63 patients with GBS=0-1, only 1 (1.6%) had the composite outcome and 0 required hemostatic intervention or died. Among 56 patients with GBS >6, 39 (70%) had the composite endpoint (16 (29%) required intervention or died), and among 20 patients with GBS >10, 19 (95%) had the composite endpoint (7 (35%) required intervention or died).

Conclusion: GBS provided the best performance in patients with hematochezia among the tools studied. GBS also is reported to have good-excellent performance for UGIB: e.g., a similar study from our center of 799 consecutive patients with hematemesis or melena found AUROC=0.89 for the composite outcome (BMJ, in press). The results of the current study, coupled with prior studies in UGIB, suggest GBS provides good-excellent risk stratification for all patients presenting with GIB and is superior to other commonly studied tools. GBS scores of 0-1 indicate low-risk patients who might be considered for outpatient management, while GBS scores >6 suggest higher-risk patients who may benefit from admission to a higher level of inpatient care.

Resident's signature

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Rates of Right-Sided Polyp Detection Pre- and Post- Implementation of High Resolution Colonoscopy at the West Haven VA

Suzannah Luft, MD, Avlin Imaeda, MD

Background: While mortality from left sided colon cancer has significantly decreased since the advent of screening colonoscopy, the mortality associated with right-sided colon cancers has not. One hypothesis for this difference is that sessile serrated adenomas/polyps (SSA/Ps) are more likely to be located in the proximal colon and are associated with a high malignant potential. SSA/Ps are characterized flat with indistinct margins and coloration similar to surrounding colonic mucosa, and thus they are more frequently missed during standard colonoscopy than other types of polyps. Thus as high resolution colonoscopes are becoming more widely used, it is useful to characterize the impact of this intervention on the rates of right-sided polyp detection.

Specific Aim: To determine if high resolution colonoscopy improves the rates of right-sided polyp detection in the West Haven VA population.

Hypothesis: Higher resolution colonoscopes will lead to better detection of right-sided colon lesions that would likely have been missed with use of non-high resolution colonoscopes.

Methods: This study was done via chart review using CPRS. High resolution colonoscopy was implemented at the West Haven VA in 2010. Several hundred colonoscopies done before and after this time were reviewed, and data including the location, number and histology of polyps was abstracted into a database. Patient demographic information was also abstracted, including patient age, race, gender and conflict, as well as the reason for the colonoscopy. Patients with a history of colorectal cancer or resection of colon or rectum were excluded, as well as incomplete exams or exam with poor prep and exams completed by an endoscopist whose exam documentation was different than the other endoscopists at the West Haven VA. The data was then analyzed for the overall rate of exams with right-sided polyp (located in the cecum, ascending colon and hepatic flexure) detection between the pre- and post- high resolution colonoscopy groups, as well as the histologic subtypes of right sided polyps identified.

Results: A total of 518 colonoscopies in the pre- and 484 colonoscopies in the post- high resolution group met inclusion criteria. Percentages of colonoscopies with polyps identified were 58.3% and 62.8% (p=0.155) in the pre- and post- high resolution groups respectively using a Fisher's Exact 2-sided test. The percentage of exams with right-sided polyps identified were 29.0% and 33.5% (p=0.07) in pre- and post- high resolution groups respectively using a Fisher's Exact 1-sided test. Right-sided polyps were then separated by histology into adenoma, hyperplastic and SSAP. The differences in based on histology between the two groups were not significant (p=0.151 using Person Chi-Squared test); however, number of SSAPs detected compared to all other histologic subtypes trended towards significance (0.4% in the pre- group vs 2.6% in the post- group, p=0.052) using Fisher's Exact 1-sided test. Of relevance, the absolute numbers of polyps in this category was very small (1 in the pre- group vs 7 in the post- group).

Conclusions: The implementation of higher resolution colonoscopes at the West Haven VA did not lead to higher rates of overall numbers of exams with polyps detected. The rates of right-sided and SSAP detection trended towards increase in the post-high resolution group, although they did not reach statistical significance. Given the relatively small sample size in the study, the plan is to enlarge the database, especially given the relative rarity of SSAP lesions.

Suzannah Luft
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Suzannah Luft, MD

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Avlin Imaeda, MD

Early TIPS in Esophageal Variceal Bleeding

Resident: Thomas McCarty   Mentor: Loren Laine

Background: Early transjugular intrahepatic portosystemic shunt (TIPS) used as preventive therapy prior to recurrent bleeding has been recommended in patients presenting with acute esophageal variceal bleeding (EVB) who are at high risk of further bleeding and death. Small, randomized trials of early TIPS report benefit in patients at high risk for further bleeding and death, such as those with a hepatic venous pressure gradient (HVPG) greater than 20 mmHg or with Child-Pugh class C cirrhosis (Child-Pugh score 10-13) or Child-Pugh class B cirrhosis with active bleeding.[5,6] However, population-based studies of the impact and timing of TIPS on outcomes of patients with EVB are not available.

Specific Aim: To investigate the impact of early TIPS on outcomes of United States (U.S.) patients with Baveno V class cirrhosis hospitalized with EVB. The primary measured outcome measured was in-patient hospital death. Secondary outcomes included rebleeding, hepatic encephalopathy, sepsis, length of hospital stay, and hospitalization cost.

Hypothesis: Early TIPS will result in a decreased rebleeding rate and improved mortality in patients with decompensated cirrhosis and esophageal variceal bleeding.
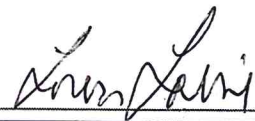
Methods: The Nationwide Inpatient Sample database was queried to identify patients with EVB and decompensated cirrhosis from 2000 to 2010. ICD-9 codes and Baveno classification were used to identify a subgroup of decompensated patients who had a Child-Pugh score <14 (for which early TIPS is recommended). Only patients with decompensated liver disease as defined by Baveno V classification (Stages 3 and 5) were included. Early preventive TIPS was defined by placement within 3 days of hospitalization for acute EVB after one session of endoscopic therapy. Rescue TIPS was defined as TIPS after two interventions for EVB.

Results: This study included 142,539 patients with early TIPS performed in 0.5% (n=713). Mean hospital stay was 5.5 days with a mean hospitalization cost accrued for one visit of $35,453 – largest proportion of patients covered by Medicare (n=60,722 or 42.6%). From 2000 to 2010, the age-adjusted in-hospital mortality rate decreased 37.2% from 656 per 100,000 to 412 per 100,000 (p <0.01), while early and rescue TIPS increased (0.22% to 0.70%; p<0.01 and 1.1% to 6.1%; p<0.01), respectively. Early TIPS demonstrated a lower rate of rebleeding when compared to no TIPS and rescue TIPS (0.5% versus 15.4%; p <0.01 and 0.5% versus 2.2%; p <0.01, respectively). On multivariate analysis, as compared to no TIPS, early TIPS was associated with decreased inpatient mortality (RR=0.87; 95% CI, 0.84-0.90) and rebleeding (RR=0.56; 95% CI, 0.45-0.71) without an increase in hepatic encephalopathy (RR=1.01; 95% CI, 0.93-1.11).

Conclusions: Early preventive TIPS in patients with EVB and decompensated cirrhosis was associated with significant in-hospital reductions in rebleeding and mortality without a significant increase in encephalopathy. The small percentage of eligible cases receiving early TIPS suggests that there is room for further improvement in the treatment of patients with decompensated cirrhosis and EVB.

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Medicaid Reimbursement for Oral Direct Antiviral Agents for the Treatment of Chronic Hepatitis C

Kohtaro Ooka, M.D., James J. Connolley, M.D., Joseph K. Lim, M.D.

Background: All-oral direct-acting antiviral (DAA) regimens are an excellent modality to treat chronic hepatitis C virus (HCV) infection. Federal Medicaid law requires states to cover all drugs from manufacturers with rebate agreements with the Department of Health and Human Services within their FDA label. However, because of their high cost, many state Medicaid agencies do not cover DAAs for those who have mild liver disease or who abuse substances. These restrictions persist despite many analyses that confirm that DAA regimens are cost-effective and result in savings in healthcare spending.

Specific Aim: To assess whether and how these restrictions have changed since oral DAAs first came on the market.

Hypothesis: On the basis of our experience and anecdotal evidence, we expected that despite loosening of restrictions, the majority of states have restrictions in excess of those recommended by professional societies.

Methods: We searched publicly available state fee-for-service (FFS) Medicaid websites from 20 August 2016 to 10 September 2016 to obtain reimbursement criteria for DAAs. We reviewed reimbursement criteria across several domains, including: liver fibrosis, decompensated cirrhosis, biopsy requirement, prescriber specialty, HIV status, renal function, and substance abuse. We documented which DAAs were covered, and in cases in which criteria differed between agents, the most liberal or inclusive criteria were used. Inconsistencies and gaps were resolved by direct phone calls to state Medicaid agencies. We included policy criteria that were in effect or stated on state Medicaid documents to take effect on a future date; future policies reported by media sources without state confirmation were not included. Coverage requirements for DAA regimens were compared with reimbursement criteria for sofosbuvir in 2014 as summarized by Barua et al.

Results: We found Medicaid reimbursement criteria for all but Hawaii. Many states have loosened restrictions since 2014. Fifteen states loosened restrictions based on fibrosis; none tightened restrictions. Five states explicitly exclude patients with decompensated cirrhosis and twenty-two states restrict coverage to patients with a METAVIR score of F3–4. South Dakota requires biopsy. Thirty-four states require a specialist or consultation with a specialist, although some states allow certain other practitioners with special training to also prescribe DAAs. Nineteen states require patients to pass a drug screen prior to treatment. Five states require abstinence from alcohol and drugs in patients with a history of abuse, while 20 require abstinence in all patients. Nine require periodic drug testing. Seven cover patients co-infected with HCV and HIV regardless of fibrosis score. Six states require such patients to have HIV under control. Six states do not reimburse DAAs for patients with creatinine clearance of <30 ml/min or with end-stage renal disease (ESRD). The majority of states cover one or more newer combination regimens other than sofosbuvir-ledipasvir (Harvoni).

Conclusions: Clinical criteria for the reimbursement of DAAs by state Medicaid agencies suggest a loosening of restrictions between 2014 and 2016. Yet significant barriers to hepatitis C drug access remain, largely based on factors such as stage of liver fibrosis, substance abuse, and medical comorbidities. These restrictions appear to be in conflict with federal Medicaid law and national practice guidelines. Coordination of state Medicaid plans to establish evidence-based, transparent, and cost-effective policies are needed to promote a more rational and patient-centered approach to coverage of DAAs for the treatment of HCV.

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Association of FDAAA with Trial Registration, Publication, and Outcome Reporting: A Cross-Sectional Analysis

Adam T. Phillips, MD, Joseph S. Ross, MD

Background: Selective clinical trial publication and outcome reporting has the potential to bias the medical literature. The 2007 Food and Drug Administration (FDA) Amendment Act (FDAAA) mandated clinical trial registration and outcome reporting on ClinicalTrials.gov, a publicly-accessible trial registry.

Specific Aim: To determine whether FDAAA was associated with improvements in trial registration, publication, and accurate outcome reporting for trials supporting FDA approval of new drugs for cardiovascular disease and diabetes.

Hypothesis: FDAAA was associated with improvements in trial registration, publication, and accurate outcome reporting for trials supporting FDA approval of new drugs in cardiovascular disease and diabetes.

Methods: We performed a cross-sectional analysis using publicly available data from ClinicalTrials.gov, FDA documents, and PubMed, determining registration, publication, and reporting of findings for all efficacy trials supporting FDA approval of new drugs for cardiovascular disease and diabetes between 2005 and 2014, before and after FDAAA. For published trials, we compared the published interpretation of the findings (positive, equivocal, or negative) with the FDA reviewer's interpretation. We used Chi-Square and Fischer Exact tests as appropriate to compare rates of registration, publication, and outcome reporting among groups. For each categorization, we stratified trials as pre- or post-FDAAA.

Results: Between 2005 and 2014, the FDA approved 30 drugs for 32 indications for cardiovascular disease (n=17) and diabetes (n=15) on the basis of 183 trials (median per indication 5.7 [IQR, 3-8]). Compared with pre-FDAAA, post-FDAAA studies were more likely to be registered (78 of 78 [100%] vs. 73 of 105 [70%]; p<0.001), published (76 of 78 [97%] vs. 93 of 105 [89%]; p=0.03), and present findings concordant with the FDA reviewer's interpretation (74 of 76 [97%] vs 78 of 93 [84%]; p=0.004). Pre-FDAAA, the FDA reviewer interpreted 80 (76%) trials as positive and 91 (98%) were published as positive. Post-FDAAA, the FDA reviewer interpreted 71 (91%) trials as positive and 71 (93%) were published as positive.

Conclusions: Registration, publication, and FDA-concordant outcome reporting significantly increased after FDAAA for trials supporting FDA approval of new drugs for cardiovascular disease and diabetes.

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Variation in the Use of Direct Oral Anticoagulants and Associated Cost Implications – Findings from the Medical Expenditure Panel Survey 2010 to 2013
Benjamin Rodwin, MD. Research Mentor: Nihar Desai, MD

Background: Atrial fibrillation is the most common cardiac arrhythmia in the United States and affects up to one in four adults over age 40. Despite its prevalence, little is known about national patterns of anticoagulant use among patients with atrial fibrillation after the availability of direct oral anticoagulants (DOACs) in 2010 and the associated implications for health care spending across the United State. We sought to examine contemporary patters of anticoagulant use in atrial fibrillation among a nationally representative cohort and to determine the implications of contemporary patterns of care on costs for patients and the health care system as a whole.

Methods: The Medical Expenditure Panel Survey (MEPS), an annual nationally representative survey of individuals as well as their medical providers and employers across the United States, collects detailed information about prescription drug use, cost, and medical diagnoses. Adults with atrial fibrillation between 2010 and 2013 were identified in the MEPS using validated ICD-9 codes. We examined the proportion of patients receiving warfarin and DOACs (dabigatran and rivaroxaban) overall and across key sociodemographic and clinical groups. Total drug costs and out of pocket spending were calculated across these groups.

Results: Over 5.3 million adults with atrial fibrillation were evaluated. Between 2010 and 2013, approximately one in three patients with atrial fibrillation were prescribed any anticoagulant. The use of DOACs increased from 0.6% to 11.8% while warfarin use declined from 32.8% to 22.2% (p<0.001). Adults who were male, non-Hispanic Whites, had higher income, and those with the lowest CHA_2DS_2-VASc scores (0 or 1) were significantly more likely to receive DOACs than warfarin (p<0.001 for all). No clinical or sociodemographic subgroup had greater than 50% use of any anticoagulant. Prescription drug spending on DOACs increased from $92 million in 2010 to $1.29 billion in 2013 while spending on warfarin declined from $219 million to $128 million over this time period. Out of pocket costs for DOACs increased from $10 million to $174 million while decreasing for warfarin from $102 million to $62 million.

Conclusions: In a large, nationwide cohort of adults with atrial fibrillation, we observed a significant increase in the use of DOACs, accompanied by a decline in warfarin use between 2010 and 2013. Despite the increase in DOAC use, there remains substantial underuse of anticoagulation overall in patients with atrial fibrillation. There are marked disparities in the use of DOACs and overall anticoagulation based on sex, race, income and risk of stroke. Understanding the patterns and costs of anticoagulation in atrial fibrillation remains an important priority with implications for quality of care as well as health care spending.

Benjamin Rodwin
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Effect of Portal Pressure Changes on Cirrhosis Decompensation

Jordan Sack MD, Guadalupe Garcia-Tsao MD
Research in Residency Abstract

April 2017

Background:

Cirrhosis has two prognostic stages, compensated cirrhosis (median survival >12 years) and decompensated cirrhosis (median survival 2 years). Decompensation is defined by the development of clinically overt complications: ascites, variceal hemorrhage, and encephalopathy. Data from a multicenter randomized control trial of timolol versus placebo in patients with compensated cirrhosis with portal hypertension (hepatic venous pressure gradient or HVPG ≥ 6mmHg) and without varices demonstrated that the strongest predictor of varices and clinical decompensation was an HVPG ≥ 10 mmHg (clinically significant portal hypertension or CSPH). However, the effect of changes in HVPG in the development of decompensation has not been analyzed in the setting of this study. With the advent of anti-fibrotic and anti-portal hypertensive therapies aimed at preventing decompensation, it is important to determine if a specific reduction in HVPG is associated with a lower decompensation rate.

Specific Aim:

Our aim is to identify whether changes in HVPG can delay the development of the first episode of decompensation in patients with compensated cirrhosis, portal hypertension and no varices.

Hypothesis:

We hypothesized that reduction in HVPG at 1-year would be associated with a reduced incidence of cirrhosis decompensation.
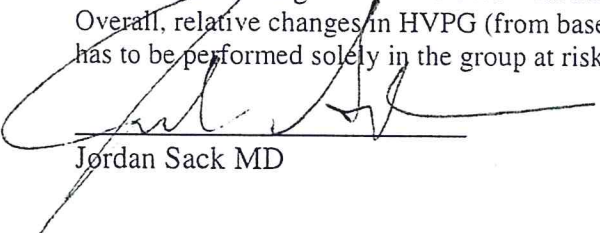
Methods:

Retrospective analysis of data from timolol study prospectively collected between August 1993 to March 1999. HVPG was measured at baseline and annually until the development of a decompensation or end of study (September 2002). Changes in HVPG at 1 year were analyzed (separately for patients with mild and CSPH and for patients on timolol vs. placebo) and correlated to the primary outcome (decompensation) in a mean follow-up period of 108 months.

Results:

213 patients were enrolled in the original timolol study of which 154 had one-year HVPG measurements and constitute the basis of the present study. Of these, 62 (40%) had mild PH (30 on timolol) and 92 (60%) had CSPH (42 on timolol). In patients with mild PH there were no significant changes in HVPG, while in those with CSPH, HVPG decreased significantly in both the timolol and placebo groups (with a tendency for a greater decrease in the timolol group, p=0.08). In the overall group, reduction in HVPG ≥10% had a tendency to be associated with decreased decompensation (10 vs. 24 events, p=0.13). In patients with CSPH, a reduction in HVPG to levels below 10 or below 12 mmHg at one-year were significantly associated with a reduced incidence in decompensation (p=0.0002 and p=0.02, respectively).

Conclusion:

Changes in HVPG (either spontaneous or through pharmacological therapy) vary in patients with CSPH vs. mild PH. Changes in HVPG below certain threshold levels are protective of decompensation. Overall, relative changes in HVPG (from baseline) seem to be protective of decompensation but analysis has to be performed solely in the group at risk, that is, that of patients with CSPH.

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Jordan Sack MD

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Approaches to Predicting Outcomes in Patients with Acute Kidney Injury
Danielle Saly, M.D., F. Perry Wilson, M.D.

Background: Despite recognition that Acute Kidney Injury (AKI) leads to substantial increases in morbidity, mortality, and length of stay, accurate prognostication of these clinical events remains difficult. It remains unclear which approaches to variable selection and model building are most robust. Due to the vast amounts of clinical data generated in the process of patient care, made easily accessible by the electronic health record (EHR), there has been increased interest in applying novel strategies to medical prognostic modeling. Several advanced modeling techniques used in the clinical setting to predict disease have shown enhanced accuracy for diagnosis when compared with regression methods. Whether more advanced modeling approaches are superior to conventional approaches of model building in predicting outcomes of AKI remains unclear.

Specific Aim: We used data from a randomized trial of AKI alerting to develop time-updated prognostic models using stepwise regression compared to more advanced variable selection techniques. We sought to compare regression-based models to more advanced models to predict progression of AKI to RRT, death, or LOS in a time-updated manner.

Hypothesis: We hypothesized that the more advanced models would better prognosticate outcomes of AKI when compared to the conventional models in a validation cohort.

Methods: Individuals in this study were enrolled in a randomized trial of an AKI alert system conducted at U.Penn. All patients had AKI as defined by the KDIGO creatinine criteria. Data extracted electronically from the EHR included all laboratory, medication, and procedural information as well as demographics and hospital discharge disposition. For the conventional model we used backwards stepwise time-varying logistic regression (p-threshold 0.05) to model the outcomes of both dialysis within seven days and death within seven days. We used backwards stepwise linear regression (p-threshold 0.05) to model LOS using a variable selection approach identical to that described above. For the alternative model predicting dialysis, we used random forests to select independent covariates, which were ranked by their importance vectors. To predict death and LOS, we used logistic regression on features extracted from principal components analysis of the lab values, and another set of principal components derived from medications data, the latter after being transformed with an exponential kernel to simulate the physical action of the drug.
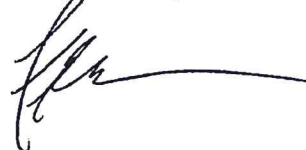
Results: We assessed model discrimination using the area under the receiver operator characteristic curve and r-squared values. 2241 individuals were available for analysis. Both modeling techniques created viable models with very good discrimination ability, with AUCs exceeding 0.85 for dialysis and 0.8 for death prediction. Model performance was similar across model building strategies, though the strategy employing more advanced variable selection was more parsimonious.

Conclusions: Very good to excellent prediction of outcome events is feasible in patients with AKI. More advanced techniques may lead to more parsimonious models, which may facilitate adoption in other settings.

Danielle Saly, M.D.

F.Perry Wilson, M.D

Comparing patient satisfaction and clinical outcomes for HIV-infected patients followed by resident trainees or HIV providers in an academic-based clinic.

Jacqueline Sherbuk, MD
Lydia Aoun-Barakat, MD

Background: Patient satisfaction has become a key measurement in the delivery of patient-centered care nationwide. In patients with human immunodeficiency virus (HIV), patient satisfaction with their primary care provider (PCP) is associated with higher rates of adherence to antiretroviral therapy. Resident trainees are heavily involved in the care of those with HIV at large academic centers, yet studies evaluating the impact of provider's level of training on patient satisfaction are limited.
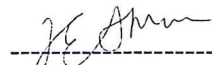
Specific Aim: The primary aim is to compare patient satisfaction based on the level of training of the PCP, either a resident in training or an attending trained in HIV care. A secondary aim is to compare outcomes of HIV management and compliance with Infectious Disease Society of America (IDSA) guidelines for routine health maintenance based on providers' level of training.

Hypothesis: Patient satisfaction will be higher in patients with an attending physician as their PCP than those with a trainee. Outcomes and compliance with guidelines will be similar among the two groups given that trainees are supervised by an attending.

Methods: A cross-sectional study was performed at an academic hospital based HIV clinic between May and October 2016. All patients presenting to clinic on dates of study recruitment were invited to participate. Inclusion criteria included age 18 years or older and 2 prior visits with the same provider. Exclusion criteria included primary language other than English, active mental illness, and assignment to a mid-level PCP. Patients who agreed to participate signed a informed consent form. Participants completed a survey including demographic information and a modified Consumer Assessment of Healthcare Providers and Survey adult clinic. A chart review was performed to evaluate HIV-specific health outcomes and compliance with guidelines. Categorical variables were compared using Chi-square test or Fischer's exact based on number of data points. Continuous variables were compared using student's T-test.

Results: Eighty-four participants were recruited, including 51 with attending physician as PCP and 33 with a trainee as PCP, including 24 assigned to a resident and 9 to a fellow. Those with fellows as PCPs were excluded given the small numbers. The attending group was older (54 yrs vs 45 yrs, p=0.01) and less likely to identify as white (29% vs 54%, p=0.04). The attending group showed a trend towards being better able to identify their PCP by name (82% vs 63%, p=0.06). A minority of patients in both groups were able to identify their PCP's level of training (45% in attending group vs 35% in resident group). Overall, patient satisfaction was similar for attendings and trainees (9.6 out of 10 and 9.7, respectively). Those in the trainee group were significantly more likely to answer that their PCP "always" spends enough time with them. (97% vs 81%, p=0.04). On comparison of adherence to IDSA guidelines, the resident group had lower rates of CD4 measurements meeting guidelines (94% vs 71%, p=0.01). Rates of vaccination were similar except for the resident group having higher rates of pneumococcal vaccination (73% vs 88%, p=0.03). Trainees had higher rates of counseling on both risk reduction and treatment adherence (47% vs 83%, p=0.005 and 66% vs 100%, p=0.001, respectively).

Conclusions: Patients at this single center academic-based HIV clinic showed high rates of satisfaction with their PCP and satisfaction did not differ based on provider's level of training. This center is unique in having a resident program focused on training HIV providers. Our study suggests that residents in a well-designed training program can provide high quality HIV-specific care at a level that meets patient satisfaction of those who are fully trained in HIV-care.

Resident's Signature

Lydia Barakat

Mentor's Signature

Digitally signed by Lydia Barakat
DN: cn=Lydia Barakat, o=Yale University, ou,
email=lydia.barakat@yale.edu, c=US
Date: 2017.04.25 19:57:42 -05'00'

Correlation of High Resolution Anorectal Manometry with MR Defecography in Fecal Incontinence Compared to Constipation
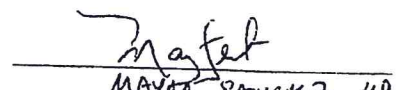
Dennis Shung, M.D., Mayra Sanchez, M.D.

Background & Aims: MR defecography (MR-D) is an expensive modality that provides structural and functional information about global pelvic floor anatomy. In the era of value-based healthcare, characterization of patient subgroups most likely to benefit from MR-D is essential to limit costs and optimize quality. This study aims to correlate physiologic parameters from high resolution anorectal manometry with degree of abnormal pelvic floor relaxation or posterior prolapse in patients with fecal incontinence (FI) and compare them to patients with constipation (C).

Methods: The study is a retrospective, single-center study of 17 patients with FI and HD-ARM and MR-D in the outpatient specialty clinic of an academic tertiary care center from January 2013 through December 2015. The MR-D readings were independently performed using a structured approach by two radiologists. 17 age and sex-matched patients with C who underwent both HD-ARM and MR-D were used to compare manometric characteristics of the two populations. Pearson's correlation coefficient, multiple linear regression, ANOVA, and Student's t test were utilized and performed using R software 3.3.2 using the Survival, HMisc and MatchIt packages.

Results: Change in H line was significantly correlated with maximum resting sphincter pressure ($r = 0.68$, $p < 0.01$), residual anal pressure ($r = 0.59$, $p = 0.05$), and balloon volume at urge ($r = 0.59$, $p = 0.01$). A weighted multiple linear regression model using maximal squeeze sphincter pressure and change from resting pressure predicted change in H-line (R squared 0.63, $p < 0.01$). Intrarectal pressure at rest was significantly correlated with change in M line ($r = 0.52$, $p = 0.03$) and balloon volume at urge ($r = 0.50$, $p = 0.04$). Gel evacuation (%) was significantly correlated with mean rectal compliance ($r = 0.49$, $p = 0.03$) and balloon volume sensation at urge ($r = 0.52$, $p = 0.05$). A nonweighted multiple linear regression model using mean rectal compliance and balloon volume at urge sensation predicted gel evacuation (R squared $= 0.46$, $p < 0.05$). No correlation was found between internal and external sphincter thicknesses with any of the manometric parameters. Matched patients with C showed no significant differences in MR-D measures compared to patients with FI, but significantly increased resting sphincter pressure (96.3 vs 65.8 in FI, $p < 0.01$), squeeze sphincter pressure (216.4 vs. 119.8 in FI, $p < 0.01$), residual anal pressure (72.0 vs 47.9 in FI, $p < 0.01$), and intrarectal pressure (68.4 vs 38.8 in FI, $p < 0.01$).

Conclusions: In patients with FI, change in H line on D-MR can be predicted by change from resting pressure and maximal squeeze sphincter pressure on HD-ARM. Gel evacuation on D-MR can also be predicted by mean rectal compliance and balloon volume at urge sensation. Matched patients with C have similar D-MR findings to patients with FI but significantly decreased sphincter pressures on HR-ARM.

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Resident's Signature

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Mentor's Signature   MAYRA SANCHEZ, MD.

Synergism between Diabetes and HIV in increasing risk for tuberculosis

Pranay Sinha, MD and Sheela V. Shenoi, MD

Background: Human immunodeficiency virus (HIV) infection and diabetes mellitus (DM) are both independently associated with increased risk of tuberculosis (TB). Globally, an estimated 30% of TB cases are attributable to these two conditions collectively. Rates of DM are increasing in high TB burden countries like China, India, Indonesia, Brazil, and South Africa. HIV continues to be highly prevalent in countries like Russia and South Africa with high TB burdens. HIV disease itself can contribute to development of DM, as can treatment with nucleoside reverse transcriptase inhibitors and protease inhibitors. Interaction between DM and HIV in increasing the risk of TB has not been evaluated hitherto.

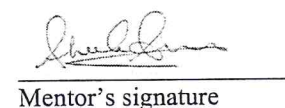**Specific aim:** To assess synergism between DM and HIV infection in increasing risk of TB.

Hypothesis: Patients with both HIV and DM will have an increased risk of TB when compared to patients with just one of these conditions.

Methods: This is a cross-sectional study of two datasets (n=7403) comprised of community-based screenings in a rural resource-limited region of KwaZulu-Natal province, South Africa (2010-2015) where integrated communicable and non-communicable (NCD) disease screening was offered to community members. Demographic factors, socioeconomic factors, DM status, and HIV positivity were analyzed. Individuals with a history of diabetes or a random blood glucose of of >11mmol/L were designated to have diabetes mellitus type 2. Individuals with a reported history of HIV or a positive screening result were designated to have HIV. Multivariate analysis was performed and interaction between HIV and DM was tested. The primary outcome was the presence of at least one of the four effective TB screening symptoms endorsed by WHO (cough of any duration, fevers of any duration, weight loss, and night sweats). The impact of having sequentially increasing number of TB symptoms was also evaluated.

Results: In the multivariate model, the use of pit or flush toilet (OR: 0.52; 95% CI: 0.27-0.98; p=0.01) was associated with decreased risk of TB symptoms. Age over 65 years (OR: 1.64; 95% CI: 1.39-1.94; p<0.001), HIV (OR: 1.64; 95% CI: 1.35-1.98; p<0.001), and DM (OR: 1.44; 95% CI: 1.15-1.80; p=0.001) were independently associated with the increased risk of having at least one TB symptom. The odds ratios for HIV and DM corresponding to TB symptoms rose when analysis was restricted to patients with increasing numbers of TB symptoms. The OR for patients with DM having at least two symptoms was 1.59 (95% CI: 1.15-2.21; p=0.006) and the OR for at least three symptoms was 2.08 (95% CI: 1.21-3.57; p=0.008). The OR for patients with HIV having at least two symptoms was 1.98 (95% CI: 0.83-4.71; p<0.001), and the OR for at least three symptoms was 2.71 (95% CI: 1.73-4.26; p<0.001). The interaction between HIV and DM was not significant, but trended toward synergy. The OR for patients with both HIV and DM having at least one symptom was 1.15 (95% CI: 0.56-2.34; p=0.36), the OR for at least two symptoms was 1.98 (95% CI: 0.83-4.71; p=0.12), and the OR for at least three symptoms was 3.11 (95% CI: 0.99-9.78; p=0.05).

Conclusion: To our knowledge, this is the first study evaluating interactions between HIV and DM for increasing risk for TB. DM and HIV are independently associated with the increased risk of TB symptoms, but there was no significant interaction in this cross-sectional analysis The findings are limited by lack of results from clinical evaluation. Presumably, patients with more TB symptoms had a higher risk of having TB disease than individuals with just one symptom. Future studies should evaluate for synergism prospectively among high risk groups.

Resident's signature

Mentor's signature

The Use of Hypomethylating Agents (HMAs) in Patients with Relapsed and Refractory Acute Myeloid Leukemia (RR-AML): Clinical Outcomes and Their Predictors in a Large International Patient Cohort

Maximilian Stahl and Nikolai Podoltsev

1. Restatement of specific aim and hypothesis: The purpose of this retrospective chart review was to examine the effect of hypomethylating agents (HMA) on overall response rate (ORR) and overall survival (OS) in patients treated for relapsed or primary treatment refractory AML at the Yale Cancer Center from 2006 (the year decitabine was approved) to 2016. My research hypothesis was that the effect of hypomethylating on response and OS is favorable compared to other treatment modalities in this very difficult to treat patient population.

2. Brief review of methods actually used in the project: I collected data, spanning a period from 2006 to 2016, from 7 centers in the United States and 4 centers in Europe regarding patients treated with HMAs for RR-AML. Responses were defined by International Working Group criteria. Kaplan-Meier methods estimated overall survival (OS) from initiation of HMAs to death or end of follow-up. Multivariable logistic regression models estimated odds for response, and multivariable Cox Proportional Hazard (CPH) models estimated hazards ratios (HR) for OS.

3. Description of Results: Of 514 patients, 217 patients (42.2%) had refractory and 297 (58%) had relapsed AML. By end of study, 415 patients (88.5%) had died. Median follow-up for living patients was 11.6 months. Median age at diagnosis was 64 years (range [R], 16-92). AML-MRC was diagnosed in 29.0% while 8.2% had t-AML. Median number of prior therapies was 2 (R, 1-7), with 48.3% receiving 1 prior line, 30.2% receiving 2 prior lines, and 21.5% receiving >=3 prior lines. Prior alloSCT was performed in 21.2%. Only 1.9% had good risk (core binding factor) karyotype, while 56.2% had intermediate risk karyotype, and 41.9% had poor risk karyotype. Azacitidine was used in 45.8% and decitabine in 54.2%; median number of azacitidine cycles was 4 (Interquartile range [IQR], 2-6) compared to 2 for decitabine (IQR, 1-4, p <0.001). Best response to HMAs was CR in 11.7% (95%CI, 9%-14%), CRi in 6.4% (95%CI, 4.3%-8.8%), hematologic improvement (HI) in 8% (95%CI, 5.7%-10.5%), stable disease (SD) in 9.8% (95%CI, 7.2%-12.5%), while 64.1% (95%CI, 57.7%-66.2%) had progressive disease (PD). Median OS from HMA initiation for all patients was 6.9 months (IQR, 3.0-13.3). Following HMA therapy, the median number of subsequent therapies was 0 (R, 0-6), and only 12.8% underwent alloSCT. In a multivariate logistic regression model, only more lines of pretreatment predicted worse response to HMA (2 vs. 1 prior lines of therapy OR 0.47, p = 0.02) In the multivariate CPH model, the HMA used was not significantly associated with OS (HR=0.80, 95%CI, 0.42-1.51, p=0.49), while the presence of PB in the blood (PB >5% vs. ≤ 5% HR 1.3, p = 0.01) was a predictor of worse OS. The addition of gemtuzumab ozogamicine did not improve survival or response rates.

4. Conclusion: In this largest reported cohort of patients with RR-AML treated with HMAs, we found that HMAs are often used as a last line of therapy, with a minority of patients receiving subsequent treatment. Nonetheless, the minority of patients who achieve CR (11.7%) with HMA therapy had a median OS of 25.6 months. Therefore, use of HMAs for management of RR-AML is a reasonable intervention in the absence of clinical trial options.

Resident: Maximilian Stahl *(signature)* 04/03/2017

Faculty mentor: Nikolai Podoltsev *(signature)* 4/4/2017

Title: PrEP implementation in an urban HIV clinic: Real world observations

Authors: Perry Tiberio (RESIDENT), Onyema Ogbuagu (MENTOR)

Additional Authors: Kelly Williams, June Holmes, E. Jennifer Edelman, Lydia Barakat, Ritche Hao, Michael Virata

Background: Multiple clinical trials have demonstrated the efficacy of pre-exposure prophylaxis (PrEP) for HIV prevention. However, the slow adoption of PrEP has resulted in low numbers of eligible individuals in the US utilizing this prevention tool. Its implementation has been hindered by lack of knowledge about or unwillingness of providers to offer the service, in part related to their concerns about cost/affordability, adherence and sexual risk compensation among PrEP users.

Specific Aims: 1) Provide an evidence-based clinical service consistent with and adapted from CDC guidelines in a residency training program; 2) To understand the demographic and characteristics of individuals presenting to the PrEP program; and 3) To develop the capacity to support adherence and HIV risk reduction services.

Methods: We reviewed the medical records of all clients attending two PrEP clinics within the Yale-New Haven Hospital system, Connecticut, USA. Data was collected on demographics, referral sources, indications for PrEP, self-reported adherence, HIV test results, sexually transmitted infections (STIs), hepatitis B (HBV) immunity and anal or cervical pap smear results.
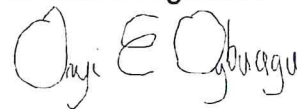
Results: Eighty clients have been enrolled, median age - 34 years, 77 (96%) are males. Majority of clients are MSM (76.2%), 7% self-identified as bisexual and 11% are heterosexual individuals in serodiscordant relationships. No clients tested positive for HIV at screening, 51% were non-immune to HBV. All but 4 clients were able to initiate PrEP with barriers being low creatinine clearance (1), lack of insurance (1), cost (1) and 1 individual was determined to be low risk for HIV. Twenty-nine percent of all clients had sexually transmitted Infections (STIs) at screening or subsequent follow up visits including pharyngeal (8.3%), rectal (2.4%) and urethral (2.4%) gonorrhea; rectal (4.8%) and urethral (3.6%) chlamydia; and syphilis (4.8%). Of 33 pap smear results, 10 (30%) were abnormal. No HIV seroconversions have occurred. The majority of clients were not previously engaged in primary care.

Conclusions: PrEP implementation is feasible with high uptake, adherence and effectiveness. In addition to HIV prevention, PrEP clinics have to be prepared to offer vaccinations, medication adherence counseling, manage STIs and refer individuals with abnormal pap smears for appropriate care.

Resident's Signature

Mentor's Signature

Rising Lysosomal Gene Expression During Sepsis is Associated with Worse Patient Outcomes

Background: Sepsis remains an incompletely understood clinical syndrome associated with high mortality and a significant burden on the healthcare system. Patient outcomes are difficult to predict with routine laboratory data. Biomarkers have emerged as potentially helpful measurements in the diagnosis, management, and prognosis of sepsis. The lysosomal pathway offers many potential biomarkers given a significant role in cell signaling, immune response, and cell turnover. We aimed to study whether lysosomal genes could predict patient outcomes.

Methods: We recruited patients admitted to the medical intensive care unit (MICU) who met criteria for sepsis by the presence of the systemic inflammatory response syndrome (SIRS) and the suspected presence of an infection. Over sequential days during each patient's MICU course, peripheral blood samples were drawn and analyzed for expression levels of 15 lysosomal genes, measured by RNA transcript levels with the fluorescence-barcoded hybridization-based nanoString nCounter. At least two peripheral blood samples from separate days over the course of illness were analyzed for each patient in order to track changes in transcript counts over time. Changes in gene expression levels were expressed as log2 fold changes from admission values, allowing trending of gene expression levels over the course of illness. We compared changes in gene expression levels between survivors and non-survivors at 60 days using Welch's t-testing, with a p-value of less than 0.05 considered significant.

Results: A total of 22 patients were included in the final analysis, 6 of whom died within 60 days. Initial systolic blood pressure was lower in non-survivors (92 ± 11.9 mmHg) than in survivors (122 ± 6.9 mmHg), a difference that approached but did not achieve statistical significance ($p = 0.056$). However, average blood pressure values were significantly lower in non-survivors (102 ± 3.8 mmHg) than in survivors (119 ± 4.2 mmHg) ($p = 0.008$). Initial and average lactate values were lower in non-survivors than in survivors, but these differences were not statistically significant. Five of the 15 studied genes had significantly higher log2 fold changes in transcript levels in non-survivors than in survivors ($p < 0.05$). These were ATP6AP1 ($p = 0.036$), CD63 ($p = 0.004$), LAMP1 ($p = 0.02$), LAMP2 ($p = 0.023$), and SLC11A1 ($p = 0.008$). For each of these 5 genes, log2 fold changes were on average negative in surviving patients and positive in non-surviving patients. That is, expression levels of these genes fell over the course of sepsis in survivors but rose over the course of sepsis in non-survivors.

Conclusion: Trending lysosomal gene expression on separate days over the course of sepsis may offer valuable information on underlying disease severity and prognosis. Rising transcript counts measured from peripheral blood over sequential days may portend a poorer outcome. Greater lysosomal activity may play a role in the pathophysiology of worsening sepsis. LAMP1, LAMP2 and CD63 have all been previously identified to be present in the granules of cytotoxic T cells and NK cells. SLC11A1 plays a role in cytotoxic T cell and NK cell activity. Greater activity of cytotoxic T cells and NK cells has been associated with a predisposition to septic shock, consistent with lower blood pressure values and higher lactate levels observed in non-survivors in this study. Further studies specifically assessing cytotoxic T cell and NK cell activity in relation to expression of these genes in patients with sepsis are warranted.

Thomas Tolbert, MD, Resident _____ Date 4/10/17

Charles Dela Cruz, MD, PhD, Mentor _____ Date __April 10, 2017_

Research Summary Abstract

Survival after Curative Treatment for Hepatocellular Carcinoma among Patients with versus without Nonalcoholic Fatty Liver Disease

Carrie Wong, M.D., Joseph Lim, M.D.

Background: Hepatocellular carcinoma (HCC) has the highest rate of cancer-related mortality in the United States. While the increasing rate of HCC incidence and mortality in the United States is largely from chronic hepatitis C (HCV) infection, nonalcoholic fatty liver disease (NAFLD) is expected to become a leading cause of HCC incidence and mortality in the United States. Curative treatments for HCC, including orthotopic liver transplantation (OLT), resection, and radiofrequency ablation (RFA), can improve survival in appropriate candidates. Large studies to compare overall survival after receipt of curative treatment for HCC among patients with NAFLD and non-NAFLD etiologies have yet to be performed.

Specific Aim: Our primary aim was to identify and compare survival differences after receipt of curative treatment (OLT vs. resection vs. RFA) by NAFLD and non-NAFLD etiologies of HCC including chronic hepatitis B (HBV), HCV, and alcoholic liver disease (ALD).

Hypothesis: Survival after any curative treatment had no difference between the NAFLD and non-NAFLD HCC groups.

Methods: A retrospective cohort study was assembled using linked Surveillance, Epidemiology, and End Results and Medicare data from 1991 to 2011 with confirmed diagnosis of HCC by International Classification of Disease for Oncology, Third Edition topography and morphology codes. HCC diagnosis, comorbidities, and treatments were identified using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Exclusion of patients with other liver diseases and primary malignancies was performed. To ensure a consistent cancer staging classification, the SEER historic stages were used. Survival was calculated from the date of the curative treatment to death or censor date (January 31, 2014).

Results: The total cohort was mostly male, aged 70 (21-106) years, without cardiovascular disease, and had liver cirrhosis without decompensation, metastatic HCC, or large tumor size (>5cm). The NAFLD-HCC group was mostly female and older with more cardiovascular disease, metastatic HCC, and large tumor size and less cirrhosis and decompensated liver disease than the non-NAFLD-HCC groups. NAFLD-HCC had worse survival after OLT: median survival for HBV (4.4, 0-11.2 years), HCV (3.5, 0-13.3 years), ALD (3.3, 0-10.0 years), and NAFLD (3.2, 0-12.9 years), $p<0.001$. Median survival after resection for NAFLD-HCC was more favorable as survival rates after resection by etiology were as follows: HBV (2.7, 0-12.7 years), NAFLD (2.4, 0-12.0 years), HCV (2.0, 0-11.8 years), and ALD (1.6, 0-12.6 years), $p<0.001$. Survival after RFA by HCC etiology was not statistically significant.

Conclusions: While NAFLD had the worse median survival after OLT, the group had better median survival after resection as compared with other HCC etiologies, which is likely related to lower rates of cirrhosis among patients with NAFLD-related HCC. Our study provides new evidence that hepatic resection is a viable treatment option for HCC among patients with non-cirrhotic NAFLD. In summary, survival differences between NAFLD and non-NAFLD HCC existed after OLT or resection and not with RFA.

Resident's signature	_Mentor's signature_

Research Summary Abstract

Title: Genetic characteristics of non-small cell lung adenocarcinoma with distant metastases

Hao Xie, MD, PhD, Sarah Goldberg, MD, MPH

Background: The metastatic pattern of non-small cell lung cancer (NSCLC) can vary widely between patients, and though it is recognized that the presence of activating driver mutations may impact prognosis and treatment response, it is unknown if the molecular profile of the tumor impacts pattern of spread. KRAS is the most commonly mutated gene in advanced NSCLC, present in approximately 25% of patients. While previous studies have suggested that KRAS mutations and co-mutations (specifically TP53 and STK11) may be important predictors of clinical outcomes, their influence on pattern of spread is unknown.

Specific Aim: To characterize the genetic profile of NSCLC tumor samples and evaluate the pattern of metastatic spread in patients with KRAS mutations and co-mutations.

Hypothesis: Advanced NSCLC with metastases at different locations may have distinctive genetic mutation profiles.

Methods: In this retrospective study, we identified patients previously treated for stage IIIB/IV NSCLC at Yale-New Haven hospital and collected clinical data regarding sites of metastatic disease, treatment history and survival history. We chose to focus on patients with brain, soft tissue, and lung only metastases because these represent unique metastatic patterns of disease. We then obtained archived formalin-fixed paraffin-embedded tissue blocks from these patients and extracted 3 mm-diameter tissue cores and utilized AmpliSeq™ Targeted Resequencing platform for next-generation DNA sequencing to evaluate a 50-gene panel. Statistical analysis for this study was descriptive in nature. Categorical variables were summarized as frequency counts and percentages.

Results: A total of 157 NSCLC patients with adenocarcinoma were included in the study, but only 127 patients had successful DNA sequencing. We identified 11 patients (7%) who had metastases only within the lungs, with 9 who had successful DNA sequencing. We identified 14 patients (9%) who had soft tissue (cutaneous or muscular) metastases, with 13 who had successful DNA sequencing, and 63 patients (40%) who had brain metastases with 49 who had successful DNA sequencing. There were 54 patients (43%) with a KRAS mutation regardless of co-mutations, 13 (10%) with both KRAS and TP53 mutations and 9 (7%) with both KRAS and STK11 mutations. A high percentage of patients with lung only metastases (7/9 or 78%) had a KRAS mutation. One (11%) of them had both KRAS and TP53 mutations, and one (11%) of them had both KRAS and STK11 mutations. Five of the 13 (38%) patients with soft tissue metastasis had KRAS mutation and a high percentage of them (3/13 or 23%) had both KRAS and TP53 mutations.

	Entire cohort (n=127)	Lung Only (n=9)	Soft tissue (n=13)	Brain (n=49)
KRAS	54 (43%)	7 (78%)	5 (38%)	22 (45%)
KRAS + TP53	13 (10%)	1 (11%)	3 (23%)	6 (12%)
KRAS + STK11	9 (7%)	1 (11%)	0 (0%)	5 (10%)

Conclusion: The molecular profile of a tumor may impact pattern of metastases, with KRAS mutations and KRAS/TP53 co-mutations being found in a greater than expected percentage of patients with lung-only metastases and soft-tissue metastases, respectively. No correlation was noted between KRAS mutations and brain metastases.

Resident's signature: *Haolen*

Mentor's signature: *[signature]*

Title: Multi-site qualitative study on the characteristics of effective chief resident-led morning reports in internal medicine residency programs
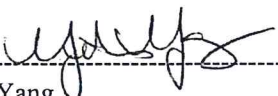
Resident: Yihan Yang, MD   **Mentor:** Stephen Holt, MD, MS

Background: Morning report (MR) is a fundamental component of internal medicine residency training, rated by residents as their most valuable educational activity, and, at many institutions, represents the most substantial portion of the teaching responsibilities of Chief Residents (CR). No prior studies have characterized the specific chief resident behaviors essential to a successful MR. We sought to conduct semi-structured interviews of residents, CRs, and faculty regarding the characteristics of effective CR-led morning reports.
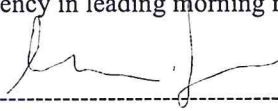
Methods: We conducted a multi-site qualitative study in 2016 using in-depth key informant interviews of morning report stakeholders. The authors developed a 9-item semi-structured interview guide that was utilized at all study sites. A total of 32 residents, 7 chief residents, and 10 faculty members from four academic Internal Medicine training programs in the New England region were interviewed. In-person interviews with chief residents and faculty were conducted on an individual basis; interviews with residents were conducted as focus groups. Transcripts of all interviews were analyzed and themes coded line-by-line by the authors independently using inductive reasoning and a grounded-theory approach. Regular working sessions were held between the authors to reach unanimous consensus on transcript codes. A preliminary coding structure was developed using a constant comparative method of analysis. We compared coded texts in an iterative process to identify novel themes and expand existing themes until a final coding structure that captured all codes was reached. The final code structure was used to recode all transcripts.

Results: From our interviews, we identified three major domains of CR behaviors that lead to a successful MR. First, a successful MR requires preparation on the part of the CR. Specifically, participants felt that the CR should be deliberate regarding the selection of cases, development of targeted learning objectives, inclusion of a suitable amount of content, as well as organization of the report itself. The second domain pertains to delivery of the report. Participants described basic presentation skills, learner facilitation techniques, and innovative teaching strategies that tend to be more effective and engaging. Specific examples of basic presentation skills leading to a good morning report include effective verbal and non-verbal communication, utilization of the physical space, and incorporation of multiple media that enhances organization of learning points. Within the facilitation skills sub-domain, morning reports where chief residents foster safe learning environments, promote clinical reasoning, demonstrate learner-centered interactions, and consolidate learning points were described by participants to be more successful. CR behaviors identified that contribute to a safe learning climate include using learner names, inviting divergent opinions, demonstrating humility regarding his/her own knowledge gaps, and providing tactful, non-intimidating feedback. CR facilitation skills that promote clinical reasoning include using effective question types; acknowledging, embracing and potentially resolving areas of uncertainty; and role modeling steps in decision-making. Learner-centeredness was defined by participants as a CR's ability to engage all learners, "diagnose" learners, be flexible with addressing learner's objectives, and encourage peer teaching. The third and final domain emerging from the interviews pertained to a CR's ability to titrate the involvement of faculty and specialists in morning report, ensuring that faculty contributed meaningfully to the report without either dominating the discussion or negatively impacting learner climate. Slight variations between training programs and participant types were noted during our analysis and will be presented.

Conclusion: We identified three primary domains of CR behavior that residents, chief residents, and faculty recognize as essential to a successful MR. These include preparation, delivery, and faculty titration. In order to deliver a successful MR, a CR must adequately prepare for the report; utilize effective basic presentation skills; facilitate discussion that is learner-centered and emphasizes clinical reasoning while nurturing a safe learning environment; utilize innovative teaching strategies; and titrate the level of faculty involvement when appropriate. Future research should incorporate the domains and subdomains described above in the creation of a validated instrument to both train and evaluate chief resident competency in leading morning reports.

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Yihan Yang   Stephen Holt

Characterization of right-sided colon cancer in African Americans versus Whites

Elinor Zhou, MD, Rosa Xicola, PhD, Xavier Llor, MD, PhD (Section of Digestive Diseases)

Background: Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer, with over 1.4 million new cases and 600,000 deaths estimated per year worldwide. The United States has one of the highest incidence rates of CRC in the world. In the United States, CRC is the second leading cause of cancer death, comprising about 9% of all cancers. African Americans (AA) have a 30% higher rate of death from colorectal cancer compared with Whites, and this health disparity is not well understood. Xicola et al. (2014) found that a higher number of AAs are diagnosed with CRC before age 50 compared to Whites, and that their tumors are usually more advanced at diagnosis. In addition, they found that in AAs, there is a significant excess of proximal colorectal cancers.

Specific Aim: To identify clinical characteristics of AA vs. Whites with colon cancer, particularly right-sided colon cancer.

Hypothesis: We hypothesize that AAs with right-sided colon cancer have higher rates of co-morbidities, including hypertension and diabetes, and that this may have a correlation with right-sided colon cancer.

Methods: Retrospective analysis using data compiled by the Yale Cancer Center Registry. The registry contains demographic, diagnostic, staging, treatment and follow-up information. We created summary tables of the data to compare frequencies of variables, and performed association statistical tests (chi square).

Results: In this series, we had data on 1,702 patients, which included 194 AAs (44.8% men) and 1,379 Whites (49.4% men). The mean age of diagnosis of colon cancer was 66 years (64 for AAs, 67 for Whites), with mean age of diagnosis of right-sided colon cancer being 69 years (66 for AAs, 70 for Whites) and left-sided being 63 years (62 for AAs, 64 for Whites). In AAs, 31.6% of right-sided colon cancers are diagnosed younger than 60, compared to 44.9% of left-sided colon cancers (p=0.06). In Whites, these percentages were 22.7% and 35.7% respectively (p=0.00). In AAs, 40.6% of right-sided colon cancers were diagnosed in-situ or stage I, compared to 32.6% of left-sided colon cancers (p=0.25). In Whites, 30.7% of right-sided colon cancers are in-situ or stage I, compared to 35.4% of left-sided colon cancers (p=0.07). Overall, AAs had a higher prevalence of hypertension than Whites (55.7% vs. 32.6%, p=0.000), as well as more diabetes (43.3% vs. 29.6%, p=0.0001). However, there was no significant correlation between hypertension (53.4% vs. 57.3% p=0.59) or diabetes (43.6% vs. 42.7%, p=0.91) with right-sided colon cancer compared to left-sided colon cancer in AA.

Conclusions: This series suggested a trend towards a higher prevalence of right-sided colon cancers in AAs compared to Whites, as well as a younger mean age of diagnosis. There was no significant correlation between colon cancer site and stage at diagnosis in this series. Hypertension and diabetes did not have a correlation with right-sided colon cancer in AAs. Further studies need to be done to identify existence of other factors that may associate with right-sided colon cancer.