Mortality, Re-Hospitalization, and Anginal Symptoms in Patients with Subjective Anxiety and Depression Undergoing Non-Emergent Percutaneous Coronary Intervention

**Resident:** Aaron Soufer MD  **Mentor:** Jeptha Curtis MD

**Background:** Coronary artery disease (CAD) patients with co-morbid depression and anxiety experience worse outcomes when compared to patients without these psychiatric co-morbidities\(^i\) \(^ii\). Major depression identified at the time of coronary angiography was associated with higher rates of percutaneous revascularization over 5 years\(^iii\), and higher rates of re-hospitalization and mortality at 6 months\(^iv\). Patients with co-morbid depression and CAD experience higher rates of angina\(^v\) and poorer quality of life\(^vi\) \(^vii\). These relationships have been shown to be independent of whether or not depression is new, transient or persistent over time\(^viii\). It is important to further characterize depression and anxiety in CAD patients prior to PCI, as these psychiatric comorbidities have been identified as risk factors for adverse outcomes after coronary intervention. Although PHQ questionnaires are traditionally used to identify these patients\(^ix\), some data suggest that perceived stress by patients at the time of acute myocardial infarction is associated with inferior outcomes\(^x\). Therefore, we will explore whether or not subjective reports of depression and anxiety at the time of non-emergent PCI are associated with adverse outcomes and recurrent chest pain within one year, and will determine if these subjective reports of mood fluctuate after initial coronary intervention. The results of this study will be used to further our understanding of the trajectory of these symptoms among patients undergoing PCI, and may identify a subset of patients who may benefit from closer monitoring.

**Aims:** To determine the frequency and trajectories of patient reported symptoms of depression and anxiety at baseline, 6 months and 12 months after non-emergent PCI. We will also determine if baseline reports of depression and anxiety are associated with anginal symptoms, mortality, and all cause re-admission at 6 months and 12 months.

**Hypothesis:** Higher levels of anxiety and depression at baseline in patients undergoing non-emergent PCI will correlate with increased rates of anginal symptoms, all cause re-admission, and mortality at 6 and 12 months.

**Methods:** We will study survey data of patients in the PRISM cohort undergoing non-emergent PCI. We will exclude participants with STEMI, PCI complicated by cardiogenic shock, hemorrhagic complications due to vascular access, or any other major procedural complications. Each subject will be scored at baseline as having no, moderate, or severe depression or anxiety based on the EQ-5D scale. Changes in severity of each subject’s depression or anxiety will be established from baseline to 6 and 12 months using EQ-5D data, and we will use latent class analysis to identify underlying patterns of symptoms. We will also divide subjects into groups of no, moderate, or severe depression or anxiety based upon their baseline responses to the EQ-5D. Comparison will be made between these groups based on hospital re-admission rate, mortality, and Seattle Angina Questionnaire scores. We will determine if any relationships between these variables are attenuated by use of SSRIs or SNRIs at discharge from index hospitalization, low reported medication compliance at baseline, and comorbid conditions including renal disease, diabetes, CHF with EF<40%, and tobacco use. Subgroup analysis stratified by presentation (ACS versus non-ACS) will be conducted if sufficient numbers of patients are available.

**Results:** Pending

**Conclusion:** Pending
i Watkins, Lana; Koch Gary; Sherwood, Andrew; Blumenthal James; Davidson, Jonathan R.T; O’Connor, Christopher; Sketch, Michael H. Association of Anxiety and Depression With All-Cause Mortality in Individuals With Coronary Heart Disease. *Journal of the American Heart Association* 2013;2:e000068 doi: 10.1161/JAHA.112.000068


Research-in-Residency Research Summary

Title: The effect of a daily inpatient checklist on resident attitudes

Authors: Albert Do MD MPH, Naseema Merchant MD, John Moriarty MD

Background: Workflow represents a target to improve medical care quality. Interventions designed to expedite care and reduce medical errors have been reported in the literature. In recent years, task-oriented checklists have been reported for use in medical care as a tool to reduce errors and retain a volume of information fast approaching the limits of human memory. However, to date there have been no assessments of daily workflow checklists on patient or provider-centered outcomes or attitudes.

Specific Aims: To determine baseline attitudes and impact of a resident-produced daily rounds check list on internal medicine residents during an inpatient rotation.

Hypothesis: Use of a daily checklist is feasible, and results in an improved opinion of the checklist and of resident performance in health care provision.

Results: 47 residents participated in this study, comprising 36.2% Post-Graduate Year-1 (PGY-1), 36.2% PGY-2, and 27.7% PGY-3 residents. Most residents reported antecedent usage of a formal checklist or a checklist method (17.5% and 69.6%, respectively). Study participants generally believed checklists result in better quality and reduce avoidance of care delays while not imposing a significant workload burden. They also believed that when using a checklist, they were more efficiency, timely, organized, and able to think about daily care requirements. Participants also believed using a checklist improved efficiency, timeliness, organization and ability to think about daily care requirements. Despite no significant differences in attitudes were noted after checklist use, 46% of participants reported being likely to use this specific checklist in the future. In addition, 75% and 93% of participants reported they would be likely to use a formal checklist or a checklist method in the future, respectively.

Conclusions: Internal medicine residents generally feel that use of a checklist results in improved quality of patient care, and though no differences were seen in attitudes after two weeks of use, many participants report plan to use the developed checklist or another formal checklist in the future. Further studies are required to assess patient-centered outcomes associated with checklist use, and to determine the optimal format for its incorporation into physician daily workflow.

<table>
<thead>
<tr>
<th>Attitude</th>
<th>Agree or strongly agree, %</th>
<th>Attitude</th>
<th>Agree or strongly agree, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td></td>
</tr>
<tr>
<td>I believe that a checklist…</td>
<td></td>
<td></td>
<td>When using a checklist, I…</td>
</tr>
<tr>
<td>Potential to avoid care delays</td>
<td>48.9</td>
<td>45.5</td>
<td>Am more efficient</td>
</tr>
<tr>
<td>Should be incorporated into EHR</td>
<td>17.8</td>
<td>23.4</td>
<td>Am more timely in my tasks</td>
</tr>
<tr>
<td>Increases patient care quality</td>
<td>86.9</td>
<td>88.6</td>
<td>Make more medical errors</td>
</tr>
<tr>
<td>Imposes unreasonable workload</td>
<td>8.7</td>
<td>2.3</td>
<td>Am more organized</td>
</tr>
<tr>
<td>Necessary for quality care</td>
<td>86.9</td>
<td>88.6</td>
<td>Am better able to think about daily care requirements</td>
</tr>
<tr>
<td>Allows more free time</td>
<td>28.3</td>
<td>38.7</td>
<td>Improve my ability to organize required tasks</td>
</tr>
</tbody>
</table>

EHR: electronic health record; Attitudes assessment on 5-point Likert scale
Title: Population well-being and life expectancy

Resident, Mentors: Anita Arora MD, Erica Spatz MD, MHS, Harlan M. Krumholz MD, SM

Background: Increasing interest in population health has focused attention on community health. Interventions that promote community health may seek to promote quality and quantity of life, but little is known about how the quality of life within a community, as measured by well-being, is associated with the quantity of life in that community, as measured by life expectancy.

Specific Aim and Hypothesis: We aimed to determine the relationship between well-being and life expectancy at the community-level. Our hypothesis is that communities that achieve higher levels of well being also have longer life expectancy – and that the association will be strong.

Methods: We used the 2010 Gallup-Healthways Well-Being Index, a national survey of community-residing individuals ≥ 18 years (N=3,132). The survey evaluates 6 constructs of well-being (emotional health; life evaluation; basic access; physical health; healthy behaviors; and work environment). The primary independent variables were: emotional health - a composite of 9 daily experiences and emotions plus diagnosed depression; and, life evaluation – a ranking of life situation now and 5 years from now. Both constructs were measured on a scale of 0 to 100. The Well-Being Index was only available at the congressional district (CD) level and we mapped CDs to counties to match life expectancy estimates. We used 2009 county-level life expectancy estimates for men and women, which were based on pooled mortality data from the years 2005-2009. We first stratified counties into quartiles based on life expectancy, examining county-level emotional health and life evaluation across quartiles, along with county-level estimates of race (Census data), income (SAIPE) and education (American Community Survey) and three additional well-being domains included in the survey: basic access, physical health and healthy behaviors. We performed unadjusted and adjusted linear regressions of emotional health and life evaluation with life expectancy, adjusting for characteristics previously described.

Results: County emotional health index scores ranged from 70 to 85 while life evaluation index scores ranged from 35 to 64. For both men and women, the mean emotional health score among counties in the lowest quartile of life expectancy was 77 compared to 80 in the highest quartile, while the mean life evaluation score in all four quartiles only ranged between 47.5 and 48.5. Counties in the lowest quartiles of female and male life expectancy were primarily located in the South, had a higher percentage of Blacks, and lower education and income compared with counties in the highest quartile of life expectancy, the majority of which were located in the Midwest. Emotional health and life evaluation were both significantly associated with female and male life expectancy at the county level. For every 1 point higher emotional health index, female life expectancy was 0.40 years higher and male life expectancy was 0.56 years higher (p<0.001 for both). Similarly, a 1 point higher life evaluation index was associated with a 0.04 year higher female life expectancy and a 0.05 year higher male life expectancy (p<0.001). When socio-demographic covariates (race, income, education and basic access) were introduced, emotional health and life evaluation became negatively associated with female life expectancy (p<0.005) while the relationships became insignificant for males. Similarly, when adjusted for physical health and healthy behaviors, emotional health and life evaluation became negatively associated with life expectancy (p<0.001 for males and females).

Conclusions: In this national study, emotional health and life evaluation were positively associated with county-level life expectancy. Yet socio-demographic and physical health covariates nullified or reversed the relationship, perhaps because emotional well-being interacts with or mediates the effects of other covariates known to influence life expectancy. Although this analysis suggests that well-being may serve as a target for interventions aimed at increasing life expectancy, more research is needed to explore this complex relationship.

Anita S. Arora
Title: Lifetime and recent incarceration and risk of uncontrolled blood pressure control in a multi-site cohort


Background: Incarceration is associated with increased risk of hypertension and cardiovascular disease mortality. Our objective is to measure the independent impact of a history of incarceration on control of hypertension and receipt of antihypertensive medications.

Methods: The Veterans Aging Cohort Study (VACS) is a longitudinal, prospective, multi-site observational study of HIV-infected and matched uninfected patients seen in the Veterans Health Administration (VHA). VACS contains survey data linked to the electronic medical record. Among participants who completed study follow-up between October 1, 2009 and September 30, 2010, we examined the role of self-reported incarceration history on control of blood pressure in the subsequent 12 months. We restricted our sample to those participants who responded to questions on incarceration history, had at least one blood pressure measurement in the 12-24 months before and in the 12 months after the survey, and who met criteria for having hypertension prior to the survey. Participant’s self-reported incarceration history was defined as a recent history of incarceration (within the last 12 months), a past history of incarceration (during lifetime but not during the prior 12 months), or no history of incarceration. We considered participants to meet criteria for hypertension if at any point during the 12-24 month period prior to the survey they had a systolic blood pressure ≥140, a diastolic blood pressure ≥90, or were treated with an antihypertensive drug. Hypertension treatment was measured using the VHA pharmacy records.

We measured the effect of both recent incarceration and past history of incarceration on hypertension control in the subsequent 12 months following the survey. Uncontrolled hypertension was defined as having a systolic blood pressure ≥140 or a diastolic blood pressure ≥90 in the 12 months following the study survey. To analyze the independent effect of incarceration on hypertension control and receipt of antihypertensive medications, we used logistic regression to control for age, race/ethnicity, gender, educational attainment, income, illicit drug use, unhealthy alcohol use, HIV status, and history of smoking.

Results: Among the 3515 VACS participants who completed study follow-up between October 1, 2009 and September 30, 2010, 2580 participants met our inclusion criteria. Of this group, 180 (7%) reported recent incarceration, and 1031 (40%) reported a past history of incarceration. Participants with recent incarceration were significantly more likely to be younger and male, to have low income, to not have completed high school, and to report illicit drug and unhealthy alcohol use compared with those never incarcerated. In an unadjusted model, recent incarceration (OR=2.06 95% CI: 1.37-3.11) and past history of incarceration (OR=1.32 95% CI: 1.10-1.59) were associated with uncontrolled hypertension in the year after the survey when compared with those who were never incarcerated. The association between recent incarceration and uncontrolled hypertension persisted in the adjusted model (AOR=1.69 95% CI: 1.11-2.58) when compared with those who were never incarcerated. However, the association between past history of incarceration and uncontrolled hypertension did not persist in the adjusted model (AOR=1.17 95% CI: 0.96-1.42). Recent history of incarceration was not associated with decreased receipt of antihypertensive medications while past history of incarceration was, though this result similarly did not persist after adjustment.

Conclusions: Among patients with a history of hypertension, recent incarceration is independently associated with having uncontrolled hypertension in spite of receiving treatment for hypertension.
Quantitative Measurement of BIM Protein in Lung Cancer
B. S. Henick1, E. Zarrella1, M. Altan1, J. McLaughlin1, K. Schalper1, V. Velcheti2, D. L. Rimm1, 1Yale School of Medicine, New Haven, CT, 2Cleveland Clinic, Cleveland, OH

Purpose/Objectives: A proportion of EGFR-mutant and ALK-rearranged lung cancers do not respond to tyrosine kinase inhibition for as-yet unknown reasons. The BH3-only Bcl-2 family member BIM has been implicated as a potential biomarker of clinical benefit from kinase inhibitors. Quantifying BIM expression in tumor samples of patients with lung cancer may help to predict outcome, and potentially to guide therapy.

Materials/Methods: An index tissue microarray (TMA282) was constructed using cancer cell lines with various BIM levels and human FFPE tumors, and was used for antibody validation and optimal titration. We then measured the levels of BIM in 309 lung carcinomas represented in one TMA (YTMA250) using the rabbit monoclonal clone C34C5 (Cell signaling technology) and quantitative immunofluorescence (QIF).

Results: Preliminary data showed that levels of BIM determined by QIF were comparable to those obtained by western blot in the same samples. Lung cancer samples showed a wide range of BIM levels, and were directly related to histological tumor differentiation grade (P<0.05). No significant differences in BIM levels were observed according to age, gender, major histology variants, tumor size, and stage. Preliminary survival analysis using the median score as cutpoint demonstrated no association between BIM levels and recurrence-free or overall survival (log-rank P>0.05).

Conclusions: We have validated an immunofluorescence assay for quantitative BIM measurements in FFPE samples. Our preliminary results indicate that BIM is significantly associated with histological grade, but not with other clinical or pathological variables. Preliminary survival analysis suggests that BIM is not prognostic in lung cancer. Validation of these results is ongoing. Future studies will be required to determine the value of BIM measurements to predict response to TKIs in EGFR-mutant lung adenocarcinomas.
Inhibition of Antigen Specific T cells by Nanoparticle-mediated Targeting of BDCA2 receptor on Plasmacytoid Dendritic Cells

Catherine Adams, MD, PhD, Madhav Dhodapkar, MD

**Background:** Dendritic cells (DCs) are potent antigen-presenting cells capable of both enhancing and suppressing immunity. The DC system consists of several subsets with distinct functions. The development of polymer based lipid nanoparticles has allowed a more physiological approach involving the in vivo delivery of antigen directly to DCs. Moreover, utilizing avidin coated nanoparticles and biotin labeled antibodies, antigens can be targeted to a particular subset of DCs.

**Specific Aim:** To test the *in vitro* delivery of antigen via nanoparticles to plasmacytoid dendritic cells (pDCs)

**Hypothesis:** Using influenza as a model antigen, our initial hypothesis was that delivery of flu antigen to pDCs will result in a more robust T cell activation.

**Methods:** Human dendritic cells and T cells were isolated via Miltenyi Biotec purification columns from peripheral blood mononuclear cells of healthy volunteers. Dr. Tarek Fahmy generated nanoparticles containing influenza antigen and coated with avidin for biotin antibody mediated targeting to the desired dendritic cells population. Human pDCs were loaded with nanoparticles containing flu matrix peptide (FMP) or empty controls +/- conjugation with anti-BDCA2. Costimulation was provided in either nanoparticle-bound or soluble form with the TLR9 agonist, CPG, and after 10-14 days, the cells were analyzed for expansion of flu tetramer positive CD8 cells.

**Results:** First, we demonstrated that BDCA2 antibodies conjugate to nanoparticles using an anti-mouse IgG antibody to detect the presence of anti-BDCA2 antibody on the surface of the nanoparticles. Next, we confirmed pDC activation in response to antigen delivered by nanoparticles when human pDCs were loaded with nanoparticles coated with CPG and containing flu matrix peptide (FMP) or empty nanoparticles as controls. The presence of flu antigen in the nanoparticles increased T cell activation from 0.06% to 27%. When we used this system to target nanoparticles to BDCA2 on pDC, however, we found that BDCA2 targeting, contrary to our hypothesis, inhibited T cell activation, decreasing it from 27% to 4%. To assess whether the nanoparticle-bound CPG was interfering with BDCA2 targeting, the experiment was repeated using soluble CPG. In this case, the BDCA2 targeting again decreased T cell activation from 1.43% to 0.6%.

**Conclusions:** As demonstrated for other dendritic cell subtypes, plasmacytoid dendritic cells can be targeted by antigens carried by nanoparticles. Contrary to the enhanced effect observed in those subtypes, however, targeting pDCs via BDCA2 results in inhibition of T cell activation. This is the first evidence of BDCA2 targeting as a potential strategy to induce antigen-specific inhibition of T cells. Future studies will determine which steps in BDCA2 signaling result in decreased T cell activation and investigate whether BDCA2 targeting to pDCs leads to suppression by increasing production of Tregs or IL-10 producing T cells. Finally, we propose application of this technology to systems such as autoimmunity where dampening of T cell activation by DCs would be desirable.
Background: In the United States, there are millions of visits to the emergency room with complaints of chest pain. It is important to quickly triage those patients that may be experiencing acute coronary syndrome from those that may be appropriate for safe and early discharge. Many clinicians require a normal troponin 6 hours after hospital presentation for safe discharge. We sought to determine if a normal 3-hour point of care (POC) troponin I adequately predicts a normal 6-hour POC troponin I.

Methods: This retrospective cohort study was undertaken in a single-center emergency department within an academic tertiary hospital. We evaluated 1658 consecutive patients brought to the chest pain unit (CPU) from February 2013 to February 2014. For our study, we included patients aged 18 years or older, Thrombolysis in Myocardial Infarction (TIMI) score <3, adequate renal function defined as creatinine < 1.5mg/dL, and troponin I drawn at 3 hours after presentation. The primary end point was the incidence of a positive 6-hour POC troponin I after a negative 3-hour POC troponin I.

Results: Of the 1658 patients brought to the CPU, 945 patients met inclusion criteria. Of these patients, three patients had a positive 3-hour troponin. Of the remaining 941 patients, 3 patients had a positive 6-hour troponin.

Conclusion: From this study, a negative 3-hour POC troponin I predicted a negative 6-hour POC troponin I 99.7% of the time. The next phase of this research will be to evaluate 30 day event rates.
Background
Inappropriate laboratory testing is a significant problem in U.S. hospitals, especially for those with prolonged hospital admissions. In addition to their added healthcare costs, inappropriate testing subjects patients to added blood draws and are more likely to produce false positive results, which in turn can lead to additional interventions, extended hospitalizations, and patient distress.

Objective
To compare an algorithm for less frequent blood draws with usual care in selected medical inpatients

Design, Setting, Participants
Retrospective review of all medical inpatients admitted to 9-West (Klatskin Firm, a liver subspecialty unit) with prolonged hospitalizations between January 2013 and August 2014.

Methods
Encounters with greater than 5 hospital days were extracted from the medical record. Results for designated laboratory tests were analyzed and a simple algorithm on when to obtain bloodwork was applied to each patient encounter to with the aim of reducing laboratory testing by 50%. This algorithm creates a hypothetical state of the world where a patient’s laboratory values are eliminated from the dataset every other day, emulating a strategy of ordering labs every other day. Then, the hypothetical world of every other day testing is compared to the actual state of affairs of daily testing to determine if any significant laboratory values were missed.

Main Outcome and Measures
The primary end-point was loss of clinically significant laboratory information with the novel testing strategy as compared to the standard of care. Clinically significant changes in liver enzymes (AST, ALT, alkaline phosphatase) were defined as an absolute increase of greater than 100U/ml or a greater than 50% increase from prior day’s testing. Clinically significant change in bilirubin was defined as an increase greater than 50% or greater than 1 mg/dL increase from the prior day’s testing.

Results
During the study period, there were 984 distinct admissions and approximately 10,000 liver panels ordered. Of the 984 distinct admissions, 453 admissions – resulting in approximately 8,000 liver panels – met the study criteria of having a length of stay of greater than 5 days. In the hypothetical world of every other day labs, 3800 out of 7927 (47.9%) of AST’s were not drawn with 76 instances of missing a clinically significant change (2% of all skipped AST’s), 3837 out of 7920 (48.4%) of ALT’s were not drawn with 53 instances of missing a clinically significant change (1.4% of all skipped ALT’s), 3867 out of 7952 (48.6%) of bilirubin’s were not drawn with 89 instances of missing a clinically significant change (2.3% of all skipped bilirubin’s), and 3846 out of 7926 (48.5%) of alkaline phosphatase’s were not drawn with 62 instances of missing a clinically significant change (1.6% of all skipped alkaline phosphatase’s).

Conclusions and Relevance
A simple algorithm of moving towards every other day testing of liver panels for cirrhotics with lengthy inpatient stays would have reduced laboratory testing by nearly 50% and resulted in missing only 1-2% of clinically significant changes in AST, ALT, bilirubin, and alkaline phosphatase. This could have resulted in $36,700 in annual cost savings for this patient population at Yale alone.
Title: Initial Experience with a Technician Supported Remote Interrogation System for Cardiac Implantable Electronic Devices

Resident: Eric Carpentier, Mentor: Dr Lynda E Rosenfeld

Introduction & Aims: CareLink Express is a remote interrogation system for Medtronic CIEDs (Cardiac Implantable Electronic Devices) that provides off-site, real time technical support for device interrogation. It is designed to facilitate care of patients with CIEDs in settings where those trained to perform and interpret device interrogations may not be available. In an effort to evaluate this system, we report our first year’s experience with CareLink Express. Our primary aim was to determine if Carelink Express provides more timely interrogation than the current standard of care. The secondary outcome was to describe the utilization (clinical query, location, time of day) and the incidence of clinically significant findings.

Methods: We reviewed the charts of all patients who had CareLink Express interrogations at Yale-New Haven Hospital from July 1, 2012 to June 30, 2013. We compared these to a sample of 528 interrogations by device representatives across the USA in the year prior.

Results: Of the 232 retrieved interrogations, 28 were excluded due to insufficient documentation. Thirty-two interrogations were routine interrogations, for settings only or for pre-MRI clearance. Thirty-eight (22%) of the remaining 172 interrogations had significant findings (arrhythmias, shocks or device/lead malfunction). Most of these, 24, were in the ER (Emergency Room) whereas 14 were on inpatient wards. Almost all perioperative (98%) and radiation oncology (100%) interrogations were reassuring. The average time required to obtain an interrogation interpretation was 37.8 ± 8.7 min (95% CI). This was significantly faster than in-person interrogation, which took on average 116.5 ± 15.0 min (95% CI, P-value <0.01).

Conclusions: Device interrogation is an important component of the evaluation of patients with CIEDs. CareLink Express provides more timely interpretation of CIED interrogations and can allow for appropriate triage of patients to electrophysiologists, particularly in the ER and on the medical floors, where there is a significant proportion of clinically significant abnormalities. Interrogations in the perioperative and radiation therapy settings were overwhelmingly reassuring, which supports use of a remote technology for interrogation.

<table>
<thead>
<tr>
<th>Demographics and Results. * : % abnormal interrogations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age (yrs ± SD)</td>
</tr>
<tr>
<td>Device Type</td>
</tr>
<tr>
<td>Pacemakers</td>
</tr>
<tr>
<td>Defibrillators</td>
</tr>
<tr>
<td>Time of Day</td>
</tr>
<tr>
<td>Day</td>
</tr>
<tr>
<td>Evening</td>
</tr>
<tr>
<td>Night</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>ER</td>
</tr>
<tr>
<td>Wards</td>
</tr>
<tr>
<td>OR/PACU</td>
</tr>
<tr>
<td>Radiation Clinics</td>
</tr>
<tr>
<td>Clinics</td>
</tr>
<tr>
<td>Average Response Time (mins ± 95% CI)</td>
</tr>
<tr>
<td>Reason for interrogation</td>
</tr>
<tr>
<td>Perioperative</td>
</tr>
<tr>
<td>Post Radiation</td>
</tr>
<tr>
<td>Symptom</td>
</tr>
<tr>
<td>- Syncope</td>
</tr>
<tr>
<td>- Chest pain</td>
</tr>
<tr>
<td>- Dyspnea</td>
</tr>
<tr>
<td>- Palpitations</td>
</tr>
</tbody>
</table>
Resident Applicant: Gregory Ouellet, MD  
Research Mentor: Sarwat Chaudhry, MD  
Title: Risk factors for pre-hospital delay in patients age 75 or older presenting with acute myocardial infarction  

Specific Aim: The objective of this study was to determine risk factors for pre-hospital delay in elderly patients hospitalized for acute myocardial infarction. Specifically, we aimed to elucidate whether cognitive impairment predicts pre-hospital delay. In addition, we sought to assess whether risk factors for pre-hospital delay identified in younger patients (i.e. female gender, diabetes mellitus, nonwhite race, and atypical symptoms) are predictive in patients 75 and older.  

Hypothesis: We hypothesized that the decreased cognitive function, as measured by the TICS-M, would drive risk for pre-hospital delay before admission for acute myocardial infarction in patients 75 and older. We also hypothesized that previously identified risk factors for delay in younger age groups would also be predictive in the SILVER-AMI patient population.  

Background Information: The pre-hospital period comprises two thirds of the time from symptom onset to treatment in acute myocardial infarction, and as such, remains a potential target for reducing myocardial damage. Previous studies have demonstrated that female gender, history of diabetes mellitus, older age, nonwhite race, and atypical symptoms (i.e. symptoms other than chest pain) are risk factors for longer duration of pre-hospital delay. However, the majority of studies have been performed primarily on patients younger than 75 years of age. It is critical to determine whether the same risk factors are again important in patients 75 and older. Furthermore, the effect of cognitive dysfunction on pre-hospital delay has not yet been studied.  

Methods: The study population comprises 983 patients age 75 or older with acute myocardial infarction enrolled in the multicenter SILVER-AMI study through July 2014. Non-English speakers, patients with aphasia, and comatose patients were excluded. Trained interviewers at each of the study centers collected data through patient interviews and medical record abstraction. Cognitive function was assessed using the TICS-M score (Modified Telephone Interview for Cognitive Status). Univariate and multivariate analyses of the effect of potential risk factors on pre-hospital delay (defined as symptom duration of 6 hours or greater before hospital presentation) were performed using logistic regression with significance of effect determined using the likelihood ratio test. Significance will be defined by p value less than 0.05.  

Results: In univariate logistic regression, decreasing TICS-M score was significantly associated with increased odds of pre-hospital delay (odds ratios 1.02 per unit decrease in score). In addition, atypical symptoms and transportation via private car were also significantly associated with increased odds of pre-hospital delay (OR 1.46 and 2.26 respectively). Similarly in multivariate analysis, TICS-M, atypical symptoms, and transportation via private car all made independent contributions to predicting pre-hospital delay (OR 1.03 per unit decrease in TICS-M, OR 1.47 for atypical symptoms, and OR 2.27 for transportation by private car). The multivariate model adjusted for previously reported risk factors for pre-hospital (delay age, gender, race, and diagnosis of diabetes), but none made independent contributions to the model.  

Conclusions: Decreases in cognitive function, measured by TICS-M, atypical symptoms, and transportation by private care were significantly associated with increased odds of pre-hospital delay in patients 75 and older presenting with acute myocardial infarction. It is possible that both cognitive dysfunction and atypical symptoms may result in patients failing to identify the etiology of their symptoms as cardiac. In addition, even if patients or their caregivers do identify the need for medical evaluation, waiting for a family member or friend to bring the patient to the hospital may prolong the duration of cardiac ischemia. Future studies will need to evaluate whether pre-hospital delay results in increased morbidity and mortality in this population.
Specific Aims and Hypothesis: The aim was to characterize antimicrobial susceptibility patterns of urinary isolates among participants in a pilot randomized controlled trial of cranberry versus placebo capsules. We hypothesized that overall bacterial susceptibility to oral antibiotics would be decreased due to an increased proportion of non-\textit{E. coli} \text{Enterobacteriaceae} in the cranberry group compared to placebo.

Methods: Data were collected from a double-blind, randomized, placebo-controlled trial of 80 residents from 11 nursing homes in Connecticut that compared various doses of cranberry over 1 month. The primary outcome, antibiotic susceptibility, was quantified using counts and percentages of susceptible isolates to each of 6 antibiotics (ampicillin, ampicillin/sulbactam, trimethoprim/sulfamethoxazole, ceftriaxone, ciprofloxacin, and nitrofurantoin). In addition, percentages of \textit{E. coli} and non-\textit{E. coli} were compared according to treatment group. Rao-Scott Chi Square tests accounting for the clustering of repeated isolates within individuals were used as a measure of association. A multivariate generalized estimating equations (GEE) model was used to test the association of treatment group with the total count of antibiotics to which isolates were susceptible.

Description of Results: There were no significant differences comparing antibiotic susceptibility between the cranberry and placebo groups for any of the antibiotics analyzed. Additionally, the GEE model did not show an adjusted association between treatment group and the total count of antibiotics reported as susceptible (adjusted means: cranberry 4.16 and placebo 4.20, p= 0.91). Finally, the relative proportions of \textit{E. coli} to non-\textit{E. coli} gram-negatives were also not statistically different between cranberry and placebo groups (71.2\% \textit{E. coli} in cranberry group versus 72.5\% \textit{E. coli} in placebo, p= 0.90).

Conclusion: Results did not suggest that cranberry affects antibiotic susceptibility or the proportion of non-\textit{E. coli} gram-negatives. One potential explanation for these findings is that proportions of non-\textit{E. coli} compared to \textit{E. coli} isolates were similar in both groups suggesting cranberry may not act through an \textit{E. coli}-specific mechanism. Although these data are encouraging to suggest cranberry does not foster antibiotic resistance, larger studies must be done to confirm efficacy as well as investigate the effect on antibiotic resistance over a longer period of time and in different patient populations.
Same-Day CT Colonography after Incomplete Colonoscopy is Safe and Extends Follow-Up Intervals

Heather Klavan, MD, Anil Nagar, MD

Background: Colonoscopy is the preferred method for colorectal cancer screening and diagnosis, however up to 10% are incomplete. Further evaluation of the non-visualized colon is necessary with barium enema, capsule endoscopy, double-balloon colonoscopy, computed tomographic colonography (CTC), or repeat colonoscopy. There are few published studies analyzing same day CTC after incomplete colonoscopy, however it remains an attractive option as it obviates the need for repeat colon preparation and is minimally invasive.

Aim: The aim of this study is to report the implementation of a same day CT colonography protocol following an incomplete colonoscopy and to evaluate if this strategy reduces repeat colonoscopy exams.

Hypothesis: We hypothesize that same day CTC will be executed without adverse events and reduce the number of unnecessary repeat colonoscopies.

Methods: This is a single center, IRB approved, observational study based on a protocol instituted at the West Haven Veterans Affairs Hospital from 2008 to 2013. Patients were enrolled prospectively with data extracted retrospectively from the electronic medical record. Descriptive and Fishers exact test was used for analysis. All patients with incomplete colonoscopy were given the option of same day CTC. CTC protocol included automated rectal insufflation of carbon dioxide, with supine and prone scans obtained on a 64 row multidetector CT. Interpretation of synchronized 2D and 3D images was performed on a Viatronix™ workstation. Patients with poor bowel preparation at colonoscopy were excluded.

Results: From 2008 to 2013, 13,998 colonoscopies were performed under moderate sedation. Of these 151 (1.08%) were incomplete with adequate prep. These patients were offered same day CTC and all accepted the procedure. Average age was 65 years with CRC screening the most common indication and scope looping the most common reason for incomplete colonoscopy. Colonoscopy polyp detection rate was 36% with 17% adenomas (5.3% >9 mm) and 4 cancers. Polypectomy was performed in 41 patients. Same day CTC results demonstrated an adequate quality CTC exam in 119 (78.8%), CTC polyp detection rate was 49 %, cancers in 5 and significant extra-colonic findings in 21 (13.9%). No complications were observed during CTC including patients who underwent prior polypectomy. Inadequate CTC exam was observed in 32 patients, most commonly due to insufficient colonic distention. The presence of elevated BMI ≥ 25 was associated with an inadequate same day CTC (p<0.01). Follow up recommendations based on CTC included repeat colonoscopy in 56 (37.1%), 2-3 year follow up in 44 (29%) and 5 year follow up in 46 (30.5%) patients.

Conclusion: Same day CTC following incomplete colonoscopy is feasible and safe even in the setting of polypectomy. The majority of patients (59.5%) avoid a repeat colonoscopy with an extended follow-up interval from 2 to 5 years. Increased BMI was associated with an inadequate CTC. Same day CTC is a beneficial evaluation after incomplete colonoscopy for detection of polyps, cancer, and significant extra-colonic findings.
Aim: To investigate atrial metabolism and the role of AMPK in atrial metabolism, which may lead to a better understanding of disorders such as atrial fibrillation

Method: For the glucose uptake experiments, mice were sacrificed and the right and left atria were isolated. The atria were sequentially moved through flasks of buffer in a shaking warm water bath with oxygen flowing into each flask. There were different stages of flasks, with test drugs and radioactive tracers added at different stages. Multiple trials were performed to determine the optimal duration of these stages for atrial tissue.

After the protocol was established, an experiment was performed using insulin as the test drug. Next, experiments with hypoxia were performed to simulate ischemia. For the hypoxia group, oxygen was substituted by nitrogen gas.

Then, similar hypoxia experiments were again performed, except that instead of adding radioactive tracer, the atria were freeze-clamped with liquid nitrogen and then Western blotting was performed on the tissue.

Description of Results: For the insulin experiment, it was found that insulin did not increase glucose uptake in atrial tissue as much as expected. With outliers excluded, data is as follows: RA control average glucose uptake 118.9 nmol/g/min ± 17.2, RA insulin 76.5 ± 4.7, p-value RA ctrl vs RA insulin 0.048; LA control 62 ± 8.31, LA insulin 77.9 ± 12.3, p-value not significant.

For the hypoxia experiment, the average glucose uptake was lower for the control group than the hypoxia group: RA control 86.7 ± 26.4, RA hypoxia 169.6 ± 22.8, p-value RA control vs RA hypoxia 0.015; LA control 55.4 ± 19.5, LA hypoxia 150 ± 14.9, p-value LA control vs LA hypoxia 0.001.

For the Western blotting of atria from the hypoxia experiment, the ratio of phospho-AMPK (activated AMPK) to total AMPK was higher in the hypoxia group than the control group. Ratio of density of phospho AMPK to total AMPK was as follows: RA control 0.061 ± 0.057, RA hypoxia 1.514 ± 0.451, p-value RA control vs RA hypoxia 0.001; LA control 0.296 ± 0.053, LA hypoxia 2.051 ± 0.556, p-value 0.001.

Conclusions: In the insulin experiment, insulin was expected to increase the glucose uptake in the atria. This was not seen in the experiment, which could be because glucose uptake is not significantly controlled by insulin in the atria, or it could be because the hypoxia that the atria are exposed to may have upregulated glucose uptake such that the effect of the insulin could not be seen.

For the hypoxia experiment, it was clear that hypoxia upregulated the glucose uptake of the atria. As AMPK has been previously found to be involved with protective metabolic changes in the ventricles during hypoxia, this raises the question of whether AMPK is the cause of these results. In the Western blotting experiments, it was found that AMPK appears to be activated under hypoxic conditions, as has been found previously in ventricular tissues. To determine whether glucose uptake in hypoxic conditions is regulated by AMPK, further studies could be performed using inhibitors of AMPK or an AMPK knockout model.

These experiments provide preliminary results that will guide further investigations with larger sample sizes to investigate atrial metabolism and the role of AMPK in the atria.
TITLE: Systematic Evaluation and Feedback of Resident Physician Handoffs in the Era of Duty Hour Restrictions

AUTHORS: Jessica Hu MD, Maura Le MD, David Chia MD

LEARNING OBJECTIVES:
1. Create an intervention to provide feedback to resident physicians at the time of patient care handoffs
2. Assess intern perceptions of the quality and efficiency of handoffs both before and after receiving systematic feedback
3. Monitor the effect of feedback on subjective and objective measures of patient care handoffs between residents

BACKGROUND: Patient handoffs between providers at shift changes are crucial to maintaining continuity and quality of care. Previous studies have established the necessity of duty hour restrictions to protect provider health and patient safety. However, these same restrictions have increased the frequency of handoffs. Currently, many residency training programs do not have a system in place to monitor, educate, and improve handoffs between resident physicians in order to minimize the possibility of medical error.

METHODS: Our study implemented an intervention that involved the systematic evaluation and feedback of handoffs between resident physicians on the general medical wards at an academic teaching hospital. Senior residents on the night shift would supervise the handoff between interns on the day and night shifts and use a standardized evaluation form to provide immediate feedback on verbal and written sign-outs on a weekly basis. Pre- and post-intervention surveys were completed by interns to assess perceptions of the quality and efficiency of handoffs.

RESULTS: Prior to the intervention, three fourths of interns felt they had appropriate training on safe and effective patient handoffs as well as adequate supervision. All interns reported feeling comfortable giving sign-out. However, half of interns felt that they were not given sufficient pertinent information or concrete anticipatory guidance when receiving sign-out, while a third reported being given too much irrelevant information. In the end, only three fourths of interns felt comfortable taking care of patients after the handoff.

There were statistically significant improvements in several areas when comparing handoffs evaluations comparing pre- and post-intervention. Sign-out was more likely to occur in an area free of distractions and more likely to include a brief and pertinent summary of the hospital course, a review of the task list, and sufficient anticipatory guidance. In addition, interns receiving sign-out were more likely to ask questions and confirm understanding. Lastly, written sign-outs were more concise and task lists more accurate.

After the intervention, surveyed interns perceived statistically significant improvements with regard to adequate supervision of handoffs and decreased irrelevant information given during sign-out.

CONCLUSION: Systematic evaluation and feedback of resident physicians resulted in subjective and objective improvements of handoffs between providers. However, implementation of the intervention may be challenging given time and workload constraints.
A Diagnostic Score for Insulin Resistance in Non-Diabetic Patients With Ischemic Stroke or Transient Ischemic Attack

Jin Xu, MD; Catherine Viscoli, PhD; Walter Kernan, MD

Objective:
We sought to develop two simple, reliable instruments – a Basic instrument which does not require laboratory samples, and an Enhanced instrument which uses laboratory measurements - to screen for insulin resistance in patients with a recent ischemic stroke or transient ischemic attack (TIA).

Methods:
Subjects were non-diabetic men and women with ischemic strokes or TIA within the past six months, over age 40 years of age, and enrolled in the Insulin Resistance Intervention after Stroke (IRIS) trial. The 7262 subjects were randomly divided (60%-40%) into development and validation cohorts. In the development cohort, clinical features were analyzed in bivariate analysis for their association with insulin resistance as measured by the homeostasis model assessment for insulin resistance (HOMA-IR). Abdominal obesity was defined as waist circumference >88 cm in women and >102 cm in men. Body mass index (BMI = kg/m²) was classified as <25, 25-29, 30-35, and >35. Elevated waist-hip (WTH) ratio was classified as >0.9 in men and >0.85 in women. Elevated systolic blood pressure (SBP) was defined as > 130 mmHg. Features that were significantly associated with HOMA-IR (p<0.05) were entered into a multivariable analysis. We used the magnitude of regression coefficients from the multivariable model to assign point values for a diagnostic scoring instrument. The performance of the instrument was then tested in the validation set using receiver operator characteristic (ROC) analysis.

Results:
In the Basic model, five features were retained in the multivariable regression analysis and allocated points in the model: male gender (2 points); abdominal obesity (2 points); BMI [25-29 kg/m² (2 points); 30-35 kg/m² (4 points); >35 kg/m² (8 points)]; elevated WTH ratio (2 points); and systolic blood pressure (1 point). Points for each feature were summed in the Basic model to yield a total score between 0 and 15. In the Enhanced model, four features were retained in the multivariable regression analysis: BMI [25-29 kg/m² (1 point); 30-35 kg/m² (2 points); >35 kg/m² (4 points)]; abdominal obesity (1 point); fasting glucose >100 mg/dL (4 points); and triglyceride-HDL ratio [1.6-2.3 (1 point); 2.4-3.5 (2 points); >3.6 (4 points)]. Points for each feature were summed in the complete model to yield a total score between 0 and 13. In the Basic model, the area under the curve (aROC) was 0.7057 in the development cohort and 0.73 in the validation cohort. In the Enhanced model, the area under the curve (aROC) was 0.77 in the development cohort and 0.78 in the validation cohort.

Conclusions:
In both instruments, increasing score corresponded with increasing specificity for prediction of insulin resistance as defined by HOMA-IR >3, but with decreasing sensitivity. The current versions of our instruments are not yet ready for clinical use due to the high false positive and negative rates, however we suggest several strategies for future instruments to reach higher degrees of accuracy for the prediction of insulin resistance, such as using the hyperinsulinemic euglycemic clamps method, rather than HOMA-IR, as a gold standard, and including family history of diabetes as part of the instrument.
Research Summary: Efficacy of Delta-AFP in Predicting the Development of Hepatocellular Carcinoma in Cirrhotic Patients

**Specific Aim and Hypothesis:** The aim of this study was to evaluate the utility of delta AFP in predicting the development of hepatocellular carcinoma (HCC) in cirrhotic patients.

**Methods:** This was a retrospective cohort study. The study included (1) all cirrhotic patients with a baseline AFP and two subsequent AFP measurements during 2006-2011, the first no earlier than six months from the baseline and the last no later than 2 years from the baseline measurement, and (2) the absence of HCC on dynamic imaging prior to the second serial AFP measurement. Subjects were classified according to whether they had hepatitis C (HCV) cirrhosis, or a different cirrhosis etiology (non-HCV). Statistically, longitudinal analysis with patient level random effects was used to model change in AFP between those who developed and did not develop HCC. Lastly, logistic regression analysis was used to explore the link between delta AFP and the development of HCC.

**Results:** 169 total subjects met criteria for study analysis. 91 subjects had HCV cirrhosis (53.85%), while 78 subjects had non-HCV cirrhosis (46.15%). Of the 169 subjects, 17 developed HCC (10.06%).

Using longitudinal analysis, the association between delta AFP and HCC was analyzed. At the first serial AFP measurement, the HCC negative (HCC-N) group mean delta AFP was 0.20, while the HCC positive (HCC-Y) group mean delta AFP was 8.75 (p = 0.0362, 95% CI: 0.56-16.55). At the second serial AFP measurement, the HCC-N group mean delta AFP was 1.72, while the HCC-Y group mean delta AFP was 85.73 (p < 0.0001, 95% CI: 43.86-124.16). These results show that there is a significant difference in the delta AFP between the HCC-N and HCC-Y at both the first and second serial AFP measurements. After controlling for ALT, platelets, age of cirrhosis diagnosis and HCV status, there was a significant difference in delta AFP between the HCC-N and HCC-Y groups at the time of the first serial AFP measurement (0.24 v. 8.75, respectively; p = 0.038; 95% CI: 0.48-16.54) and second serial AFP measurement (1.77 v. 85.73; p < 0.0001; 95% CI: 43.77-124.16).

Using logistic regression analysis, subjects were divided into groups based on whether they experienced a delta AFP greater than 20 between their baseline and second serial AFP measurement. Subjects with delta AFP < 20 were classified as variable 0, whereas subjects with delta AFP > 20 were classified as variable 1. Odds ratio analysis demonstrated that variable 1 was 5.342 times more likely to develop HCC as compared to variable 0 (p= 0.0067; 95% CI: 1.593-17.919).

Lastly, both variable 0 and 1 groups were broken down based on their etiology of cirrhosis (HCV v. non-HCV). Of the subjects with HCV cirrhosis (n=91), 15 were classified as variable 1. Four of these subjects developed HCC (26.67%), showing an association between delta AFP > 20 and HCC development in HCV cirrhotic patients (p=0.0376). Of the non-HCV cirrhotic subjects (n=78), only 1 subject belonged to the variable 1 classification, and this patient developed HCC (100%), showing significance (p = 0.0029). Due to the small sample size and the association between variable 1 and HCC development in both groups, the moderating effect of HCV could not be statistically tested.

**Conclusion:** This study demonstrated that there was statistically significant differences in the delta AFP in cirrhotic subjects who developed HCC versus cirrhotic subjects who did not develop HCC. Importantly, this difference in delta AFP was seen at the first serial AFP measurement, at least 6 months prior to the development of HCC. Additionally, the risk of developing HCC for subjects with a delta AFP > 20 over a 2 year span was significantly increased. Due to limited sample size, HCV as a moderator could not be analyzed. This study was weakened by its small sample size and wide confidence intervals, which limits the power and precision of its results. Despite these weaknesses, the study findings are remarkable and should warrant a larger investigation to determine if delta AFP can serve as an early, sensitive marker for the development of HCC.
BACKGROUND: In 2010, as part of developing the infrastructure of a dedicated liver cancer program, a Cancer Care Tracking System (CCTS) was implemented at VACT. Designated radiology codes and a natural language processor (NLP) were used to conduct automated reviews of all relevant radiology reports and generate flags for manual review of findings suspicious for hepatocellular carcinoma (HCC). We aimed to evaluate the clinical impact of this system for patients with HCC in regards to BCLC stage at diagnosis.

METHODS: This study was a retrospective cohort design with research data collected by chart review from years 2003-2013. Two primary groups were compared: patients diagnosed with HCC prior to CCTS implementation in 2010, and those diagnosed after. The primary outcome was BCLC stage at diagnosis, which was analyzed by Chi-squared Test (χ² test) to assess for difference in proportional distributions.

RESULTS: 78/78 patients with diagnosed HCC from 2003-2009 and 96/104 patients from 2010-2013 had sufficient data on chart review for BCLC staging. In the pre-CCTS group, stages at diagnosis were BCLC-0 1.3%, BCLC-A 33%, BCLC-B 7.7%, BCLC-C 32%, and BCLC-D 25.6%. In the post-CCTS group, stages at diagnosis were BCLC-0 9.4% BCLC-A 42.7%, BCLC-B 18.8%, BCLC-C 16.7%, and BCLC-D 12.5%. The proportional distribution was significantly different between the two groups (p<0.001) with a shift observed toward earlier stage disease.

CONCLUSION: There is a statically significant difference in distribution of BCLC-staged HCC at diagnosis pre- and post- implementation of a cancer care tracking system at VACT. The observed shift towards earlier stage disease suggests that such a system is beneficial in the earlier diagnosis of HCC in patients with cirrhosis.
Matthew Drew  
Mentor: Sofia Jakab

The Impact of a focused educational intervention about management of decompensated cirrhosis for internal medicine residents rotating through a subspecialty hepatology service. Part 1: Creating the Survival Guide.

Aims/Hypotheses
The purpose of the study is to evaluate the effectiveness of a focused educational intervention using an evidence-based “survival guide” to increase the knowledge of decompensated cirrhosis management for internal medicine residents rotating through a subspecialty hepatology service (Klatskin Liver Service). Exposure to hepatology varies in medical school. Our goal was to show that a reference guide improved housestaff knowledge of managing patients with decompensated cirrhosis.

Methods
The survival guide is a 5-page document that is based on the American Association for the Study of Liver Diseases guidelines. It was created by Matthew Drew and Sofia Jakab and was then approved by the Department of Hepatology leadership. The guide discusses management of patients with ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, and esophageal varices. It is written in a “how-to,” conversational format, for example, “How do I approach ascites?” and “What should I do when my patient’s kidney function worsens?” We also developed two separate quizzes, each consisting of 8 questions. Each question was written as a clinical vignette, often asking for the next best step(s) in management. We provided a large answer sheet from which the housestaff had to choose answers. They received 1 point for every correct answer and lost a point for including an incorrect or inappropriate answer. No points were lost for omitting a correct answer. Losing points for inappropriate answers was a way to reward evidence-based medicine and judicious testing.

Results
Initial data gathering proved difficult and the “roll-out” period took an unforeseen amount of time. 8 participants were recruited, 4 from each group. The mean number of answers correct in the control group was 9.5. For the experimental group, the mean number of correct answers was 15.0. However, the p value between the two groups was 0.14, not meeting statistically significant.

Conclusion
In its current iteration, the study is planning on recruiting more help to administer the quizzes. There was a clear trend towards improved knowledge in the experimental group. However, recruitment issues only left a 8 total participants, 4 per group. Thus, the study was very underpowered for its primary end point. Current housestaff who will be working in the Internal Medicine department will be spearheading the project for the next academic year. Verbal feedback for the guide has been positive and we hope to provide better data in the coming year.
Multifocal Lung Cancer: Description of an Adenocarcinoma Subtype
Michael Cecchini, M.D., Lynn Tanoue, M.D.

Background: The term “Multifocal Lung Cancer” (MLFC) is used variably in the lung cancer literature. While a definition of MFLC has recently been proposed, it is as yet without definitive diagnostic criteria. Previously, “bronchioloalveolar carcinoma” contained a multifocal subtype, but this term has been retired altogether. The identification of characteristics that differentiate multiple independently arising lung cancers from intrapulmonary metastases has significant implications for staging and treatment. This promising area of research requires a unified nomenclature in order to advance, and therefore we sought to characterize a population of patients meeting the currently proposed criteria.

Specific Aim: Identify clinical and pathological characteristics including eGFR status for patients with MFLC compared to unifocal lung cancer.

Hypothesis: MFLC patients will be younger, more frequently female, non-smokers, have a higher eGFR mutation rate than unifocal lung cancer.

Methods: The Yale Lung Cancer Biorepository was used to identify patients with MLFC defined as 3 or more primary lung cancers in the absence of metastases, and a control group of stage I adenocarcinoma in a 3:1 control to cohort ratio. The study was designed as a nested case control study, and the cohort group was identified as “multifocal lung cancer” after case review by an experienced thoracic surgeon and pulmonologist. Controls were selected by filtering the biorepository for unifocal stage I unifocal adenocarcinoma. Continuous variables were analyzed by t-test, and binary or ordinate variables were analyzed by Pearson’s χ2.

Results: The cohort group identified 27 individuals with multifocal lung cancer and was compared to 90 patients with a single primary lung adenocarcinoma (Table 1). The acinar subtype was present in 13 (48.0%) of multifocal tumors and 43 (48%) of controls.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Multifocal (n=27)</th>
<th>Unifocal (n=90)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>69</td>
<td>67</td>
<td>0.54</td>
</tr>
<tr>
<td>Female sex</td>
<td>24 (89%)</td>
<td>56 (62%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>26 (96%)</td>
<td>84 (93%)</td>
<td>0.27</td>
</tr>
<tr>
<td>ECOG 0</td>
<td>20 (74%)</td>
<td>74 (82%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hormone Replacement</td>
<td>13 (54%)</td>
<td>17 (30%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>History of other cancer</td>
<td>12 (44%)</td>
<td>25 (27%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cancer in Family</td>
<td>21 (78%)</td>
<td>55 (61%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Smoking (pack years)</td>
<td>30</td>
<td>37.6</td>
<td>0.19</td>
</tr>
<tr>
<td>Never Smoker</td>
<td>3 (11%)</td>
<td>16 (18%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Suzuki Type 1-4</td>
<td>19 (70%)</td>
<td>45 (50%)</td>
<td>0.054</td>
</tr>
<tr>
<td>Spiculation</td>
<td>11 (41%)</td>
<td>55 (61%)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Conclusions: Patients identified with MFLC were more likely to be female, have history of previous cancer, received hormone replacement therapy, and were less likely to be associated with spiculation on imaging. A family history of cancer and lower Suzuki classification approached but did not reach statistical significance. Acinar is the most common adenocarcinoma subtype for both groups, which suggests that left untreated MFLC will progress to metastatic disease. These differences support the concept that MFLC represents a unique subset of adenocarcinoma.
Title: Association Between Weight Loss and 30-day Readmission Risk in Heart Failure Inpatients

Resident: Michael G. Nanna MD  Mentor: Robert L. McNamara MD, MHS

I. Specific Aims and Hypothesis: Adequate weight loss as a reflection of fluid balance in patients hospitalized for heart failure (HF) is considered essential for high quality care. However, the association with short-term clinical outcomes is unclear. We proposed that weight loss in HF patients admitted to Yale-New Haven Hospital would be associated with 30-day HF-specific and all-cause readmission.

II. Methods: We conducted a retrospective observational cohort study of adults admitted to a single center from June 2012 to February 2013 with decompensated HF (N = 658). We collected demographic, clinical, laboratory, imaging and weight data on all patients. We performed bivariate and multivariable logistic regression analyses to determine the association between inpatient weight loss and two outcomes: 30-day HF specific readmission and 30-day all-cause readmission.

III. Results: Admission and discharge weights were documented 72.8% (479 of 658) of the time, though admission (10.6%) and discharge (36.8%) standing weights were far less common. Admission, daily and discharge weights were infrequent (33.1%) and only a small minority of patients had standing admission and discharge weights along with daily weights (3.6%). Average weight loss among patients was 2.8 kilograms (kg) (3% of initial weight). Weight loss, both absolute and as a percentage of initial body weight, was not significantly associated with 30-day all-cause or HF-specific readmission (Table). Although not meeting statistical significance, there was a trend toward an association between increasing absolute weight loss and lower 30-day all-cause readmission (OR = 0.88, CI = 0.76-1.01, P = 0.08).

IV. Conclusion: In our single-center study, measurement of admission, discharge and daily weights among HF inpatients was inconsistent. A small minority of patients received daily weights and even fewer received ideal assessment - standing weights on admission and discharge with daily weights. Although considered a valuable assessment of treatment effect, in hospital weight change was not significantly associated with 30 day readmission among HF inpatients in clinical practice. Further study is needed to determine whether the quality of weight measurement seen in this study is generalizable to other institutions, to identify potential barriers to consistent inpatient weight measurement, and to perform a more robust assessment for the association of weight change with short-term clinical outcomes while controlling for weight measurement quality.

<table>
<thead>
<tr>
<th></th>
<th>30-day all-cause readmission</th>
<th>30-day HF-specific readmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute Weight Loss (kg)</td>
<td>OR: 0.88 CI: 0.76-1.01 p: 0.08</td>
<td>OR: 0.89 CI: 0.74-1.08 p: 0.23</td>
</tr>
<tr>
<td>Weight Loss (percentage of initial weight)</td>
<td>1.08 CI: 0.96-1.20 p: 0.17</td>
<td>1.06 CI: 0.92-1.23 p: 0.41</td>
</tr>
</tbody>
</table>

Based on results of a Multivariable Logistic Regression Model that included Age, Sex, Race, left ventricular ejection fraction, pro B-type natriuretic peptide (ProBNP), Troponin T, history of chronic kidney disease, admission serum sodium level, discharge serum blood urea nitrogen level, discharge serum creatinine level, discharge serum sodium level, the patient’s calculated Yale Center for Outcomes Research & Evaluation (CORE) score, presence of a documented standing weight on admission and discharge, weight loss as a percentage of measured initial weight, and absolute weight loss in kilograms.
A Randomized Trial of Endoscopic Simulator Training in First Year Gastroenterology Fellows
Pichamol Jirapinyo, M.D., Avlin B. Imaeda, M.D. Ph.D.

Background: Training in endoscopy has traditionally relied upon clinical hands-on experience. Simulators may now allow the development of endoscopic skills in a non-clinical environment. Specific Aim: To assess the effect of an endoscopic simulator on trainees’ endoscopic performance. Hypothesis: Fellows who routinely practice on an endoscopic simulator will perform better on clinical colonoscopy than those who only receive traditional hands-on clinical training. Methods: Simulator: An endoscopic part-task training box consisting of 5 modules (snare polypectomy, retroflexion, torque, knob control and loop reduction/navigation) and a validated scoring system. Subjects: First year gastroenterology fellows. Design: Fellows were randomized into 2 arms. The study arm practiced on the simulator for at least 45 minutes a week for the first 3 months of training, in addition to receiving traditional hands-on clinical training. The control arm received only hands-on clinical training. Outcomes: All fellows were assessed for their endoscopic skill performance using the Mayo Colonoscopy Skills Assessment Tool (MCSAT) and the simulator at month 0, 1 and 3. Results: Ten first year gastroenterology fellows participated in the study. Five were randomized into the study arm and five into the control arm. Average numbers of prior EGDs and colonoscopies are shown in Table 1. There was no difference in total MCSAT hands-on skill scores between the two groups at month 1 (p>0.05), however, there was a trend for fellows in the simulator group taking less time (p=0.09) to reach a farther landmark (hepatic flexure in simulator group vs. splenic flexure in control group (p=0.22). Additionally, fellows in the study arm performed significantly better on the simulator at month 1 (Table 2; p<0.01), and showed significant improvement in training box performance from month 0 to month 1, compared to the control group (p<0.05). At month 3, the control group eliminated this difference as reflected by similar MCSAT hands-on skill scores, time spent reaching the maximal insertion site, location of the farthest landmark reached without assistance and absolute simulator scores, compared to the simulator group (p>0.05 in all variables). Conclusion: The part-task endoscopic simulator provides a non-clinical environment for trainees to practice fundamental endoscopic maneuvers and become familiar with accessories prior to initiation of clinical cases, and during ongoing clinical training. This small sample size suggests that routine use of the simulator may improve technical endoscopic performance during the early phases of training, and larger studies are now needed.

Table 1. Average numbers of esophagoduodenoscopies (EGDs) and colonoscopies (colons) performed

<table>
<thead>
<tr>
<th></th>
<th>Month 0</th>
<th>Month 1</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EGDs</td>
<td>Colons</td>
<td>EGDs</td>
</tr>
<tr>
<td>Study arm (n = 5)</td>
<td>4</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Control arm (n = 5)</td>
<td>4</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 2. Average simulator scores

<table>
<thead>
<tr>
<th></th>
<th>Training box score at month 0</th>
<th>Training box score at month 1</th>
<th>Training box score at month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study arm (n = 5)</td>
<td>62 ± 41</td>
<td>284 ± 105</td>
<td>303 ± 84</td>
</tr>
<tr>
<td>Control arm (n = 5)</td>
<td>52 ± 16</td>
<td>140 ± 51</td>
<td>331 ± 113</td>
</tr>
<tr>
<td>P-value</td>
<td>&gt; 0.05</td>
<td>0.0067</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>
Research Summary: Efficacy of Delta-AFP in Predicting the Development of Hepatocellular Carcinoma in Cirrhotic Patients
Ross Mund, Mentor: Dr. Tamar Taddei

Specific Aim and Hypothesis: The aim of this study was to evaluate the utility of delta AFP in predicting the development of hepatocellular carcinoma (HCC) in cirrhotic patients.

Methods: This was a retrospective cohort study. The study included (1) all cirrhotic patients with a baseline AFP and two subsequent AFP measurements during 2006-2011, the first no earlier than six months from the baseline and the last no later than 2 years from the baseline measurement, and (2) the absence of HCC on dynamic imaging prior to the second serial AFP measurement. Subjects were classified according to whether they had hepatitis C (HCV) cirrhosis, or a different cirrhosis etiology (non-HCV). Statistically, longitudinal analysis with patient level random effects was used to model change in AFP between those who developed and did not develop HCC. Lastly, logistic regression analysis was used explore the link between delta AFP and the development of HCC.

Results: 169 total subjects met criteria for study analysis. 91 subjects had HCV cirrhosis (53.85%), while 78 subjects had non-HCV cirrhosis (46.15%). Of the 169 subjects, 17 developed HCC (10.06%). Using longitudinal analysis, the association between delta AFP and HCC was analyzed. At the first serial AFP measurement, the HCC negative (HCC-N) group mean delta AFP was 0.20, while the HCC positive (HCC-Y) group mean delta AFP was 8.75 (p = 0.0362, 95% CI: 0.56-16.55). At the second serial AFP measurement, the HCC-N group mean delta AFP was 1.72, while the HCC-Y group mean delta AFP was 85.73 (p < 0.0001, 95% CI: 43.86-124.16). These results show that there is a significant difference in the delta AFP between the HCC-N and HCC-Y at both the first and second serial AFP measurements. After controlling for ALT, platelets, age of cirrhosis diagnosis and HCV status, there was a significant difference in delta AFP between the HCC-N and HCC-Y groups at the time of the first serial AFP measurement (0.24 v. 8.75, respectively; p = 0.038; 95% CI: 0.48-16.54) and second serial AFP measurement (1.77 v. 85.73; p < 0.0001; 95% CI: 43.77-124.16).

Using logistic regression analysis, subjects were divided into groups based on whether they experienced a delta AFP greater than 20 between their baseline and second serial AFP measurement. Subjects with delta AFP < 20 were classified as variable 0, whereas subjects with delta AFP > 20 were classified as variable 1. Odds ratio analysis demonstrated that variable 1 was 5.342 times more likely to develop HCC as compared to variable 0 (p= 0.0067; 95% CI: 1.593-17.919).

Lastly, both variable 0 and 1 groups were broken down based on their etiology of cirrhosis (HCV v. non-HCV). Of the subjects with HCV cirrhosis (n=91), 15 were classified as variable 1. Four of these subjects developed HCC (26.67%), showing an association between delta AFP > 20 and HCC development in HCV cirrhotic patients (p=0.0376). Of the non-HCV cirrhotic subjects (n=78), only 1 subject belonged to the variable 1 classification, and this patient developed HCC (100%), showing significance (p = 0.0029). Due to the small sample size and the association between variable 1 and HCC development in both groups, the moderating effect of HCV could not be statistically tested.

Conclusion: This study demonstrated that there was statistically significant differences in the delta AFP in cirrhotic subjects who developed HCC versus cirrhotic subjects who did not develop HCC. Importantly, this difference in delta AFP was seen at the first serial AFP measurement, at least 6 months prior to the development of HCC. Additionally, the risk of developing HCC for subjects with a delta AFP > 20 over a 2 year span was significantly increased. Due to limited sample size, HCV as a moderator could not be analyzed. This study was weakened by its small sample size and wide confidence intervals, which limits the power and precision of its results. Despite these weaknesses, the study findings are remarkable and should warrant a larger investigation to determine if delta AFP can serve as an early, sensitive marker for the development of HCC.
Screening with diabetes-specific questionnaires can assist in timely detection of psychological problems in young adults with type 1 diabetes transitioning to adult care

Quinn SM, Ambrosino JM, Weyman K, Doyle EA, Tamborlane WV, Jastreboff AM

BACKGROUND a & AIMS: The coexistence of type 1 diabetes (T1D) with mental health conditions such as disordered eating, depression, and anxiety contributes to poor glycemic control and increased morbidity in young adults (YA). In this study, we tested the hypothesis that screening for these problems would aid in their early identification in young adults transitioning from pediatric to adult care.

METHODS: Forty-three YA with T1D (47% male, mean age 19.7 +/- 1.4y; mean duration of T1D 10.5 +/- 4.8y; mean HbA1c 8.5 +/- 2.0%; mean BMI 25.5 +/- 4.6 kg/m²) enrolled in the Yale T1D Transition Clinic completed the Diabetes Eating Problem Survey-Revised (DEPS-R), the Diabetes Distress Scale (DDS), and Patient Health Questionnaire (PHQ-8), a measure of depression. Each subjects’ medical records were reviewed to determine if clinicians noted similar symptoms during the 12 months prior to questionnaire completion.

RESULTS: Questionnaire results revealed 23.5% reporting disordered eating, 7.1% diabetes-distress, and 9.5% depression. Medical record review revealed 0% diagnosed with disordered eating, 11.9% diabetes-distress/anxiety, and 2.3% depression. Concordance with questionnaire responses was highest for detection of diabetes distress, lowest for disordered eating. HbA1c positively correlated with all 3 indices. Even though HbA1c levels were higher in patients with vs. without disordered eating (p<0.001), BMI did not differ between the two groups (p=0.51).

CONCLUSION: In the transition from pediatric to adult care, screening with diabetes-specific measures may assist in earlier detection of psychological symptoms, especially disordered eating, thus potentially creating opportunity for timely intervention contributing to improved metabolic control.
1. Restatement of the specific aim and hypothesis: My hypothesis is that IL-22 is an important cytokine in the pathogenesis of human atopic dermatitis (AD) and my aim is to further investigate the pathological and immunological effects of IL-22 in vivo using a skin-specific transgenic mouse model to examine the clinical AD/itch scores, inflammatory cell infiltration, and the pro-inflammatory cytokine profiles in the skin.

2. Brief review of methods actually used in the project: The generation of the K5-tTA-Tight-IL-22 mouse model of atopic dermatitis was accomplished by crossbreeding K5-tTA mice and TRE-Tight-IL-22 mice. The K5 promoter is a keratinocyte derived promoter that allows for IL-22 to be selectively expressed in the skin. The tTA (tetracycline transactivator) is controlled externally using doxycycline (Dox) in the drinking water. Transgenic positive (Tg(+)) mice and their Tg(−) littermate controls received water with doxycycline to turn off the IL-22 transgene in vivo, until they are 6 weeks old. Dox withdrawal activates the IL-22 transgene in the skin. Tg(+) mice and Tg(−) mice were sacrificed at designated stages of AD. RT-PCR with gel electrophoresis was performed on mRNA from different tissues to show that only skin tissue expressed IL-22. Gross and histological examination of the mice was performed and the clinical scores for AD severity and itch-mediated scratching scores were recorded. Infiltration and cell differential of eosinophils, CD4+, CD8+, and F4/80+ cells in the skin was compared in Tg(−) and Tg(+) mice using immunohistochemistry (IHC) and toluidine blue staining was used for mast cells. The cytokine profile and cell differential were examined by measuring the cytokines using ELISA in the skin after protein preparation. Total serum IgE was determined by ELISA.

3. Description of Results: After generation of the K5-tTA-TRE-Tight-IL-22 mice, RT-PCR showed that IL-22 was expressed in the skin, but not in other tissues such as lung and heart. ELISA showed significant differences in IL-22 protein in the Tg(+) as compared to Tg(−) mice (p<0.0001). H&E staining showed that epidermal and dermal thickness was significantly increased in Tg(+) mice as compared to Tg(−) mice (p<0.0001). Itch-scratch count was significantly increased in Tg(+) mice (p=0.0007) that correlates with the AD severity. Staining with IHC/IF for eosinophils, CD4+, CD8+, F4/80+ cells (activated Langerhans’ cells/macrophages) and toluidine blue staining for mast cells all showed significantly increased cellularity in Tg(+) mice with p<0.001 for all cell types. IL-22 induced chronic pruritic dermatitis was associated with significantly altered cytokines in the skin of Tg(+) compared to Tg(−) mice as follows: IL-4 (p=0.04), IL-13 (p=0.0003), INF-γ (p=0.01), IL-17A (p=0.03), IL-17F (p=0.01), and TSLP (p=0.04). In Tg(+) mice, decreased Th1 and enhanced Th2 cytokines were found in activated draining lymph node lymphocytes as well as from activated splenocytes. Total serum IgE and IgG1 were significantly elevated in Tg(+) mice compared to Tg(−) with p=0.01 and p=0.005, respectively, but no significant change for IgG2a.

4. Conclusion: Cutaneous expression of IL-22 causes chronic pruritic dermatitis characterized by eczematous lesions with thickening of the epidermal and dermal layers, dermal infiltration of inflammatory cells including eosinophils, CD4+ cells, CD8+ cells, F4/80+ cells and mast cells, elevated cytokines including IL-4, IL-13, INF-γ, IL-17A, IL-17F, and TSLP. Tg(+) mice showed decreased Th1 but enhanced Th2 cytokines from activated draining lymph node lymphocytes and from activated splenocytes. Given these results, dermal expression of IL-22 appears to cause a chronic inflammatory pruritic dermatitis with features resembling human atopic dermatitis and provides a model for further exploring the pathogenesis of atopic dermatitis and offers a potential future target for directed therapies.
The purpose of the Research Summary is to document the final results of the project. This should consist of a one page summary (12 point font, 1” margins) highlighting the following areas:

1. Restatement of the specific aim and hypothesis.
2. Brief review of methods actually used in the project.
3. Description of Results.
4. Conclusion.

Deadline for submission of the Research Summary is April 10, 2015 and it must be signed by the Resident and Faculty Mentor. Or, an email from the mentor, indicating approval of the final summary, will also be acceptable. Please submit proposal, and approval email(s) to Lynn Gambardella at (lynn.gambardella@yale.edu). Please call Lynn at 203-785-4140 or email her if you have any questions.
Abstract

Is there Seasonal Variation in Nursing Home Acquired Pneumonia?
Shelli Farhadian, M.D., Ph.D., Peter Van Ness, Ph.D., M.P.H., Vincent Quagliarello, M.D.

Background: Pneumonia is a leading cause of hospitalization among elderly adults, and particularly among nursing home residents. The seasonal variation in nursing home acquired pneumonia is not yet known. Studies to date on seasonal variation in pneumonia have focused exclusively on community dwelling adults. These studies find that the peak month for community acquired pneumonia (CAP) admissions was January (43% of cases), and that the months of March to May had relatively high rates of CAP admission. It is difficult, though, to extrapolate this information to a population of elderly, nursing-home residing adults.

Specific Aim: To investigate the seasonal pattern of pneumonia in a cohort of older nursing home residents

Hypotheses:
1. There is evidence of seasonal variation in the occurrence of the first pneumonia in a study nursing home cohort

Methods:
This is a secondary analysis of a cohort in which participants are nursing home residents in the New Haven area. We utilized a database already collected for a recently completed clinical trial which tested the role of a multicomponent protocol targeting oral hygiene and swallowing difficulty in an attempt at preventing nursing home acquired pneumonia. The study participants were residents of nursing homes in the New Haven area, where the average annual pneumonia incidence rate is approximately 18.9%. All study participants were observed for an average of 1.13 years (up to a maximum of 2.5 years). Pneumonia was defined by the presence of a compatible radiographic infiltrate on chest x-ray plus at least two clinical features. Subjects were considered to be at risk for pneumonia from the time they enrolled in the study until death or until the study ended. Given a fixed sample size of 12 outcome data points in the time series, no statistical tests were performed, due to lack of adequate power.

Results: Of 213 total first pneumonias, 43 (20%) occurred in Fall, 55 (26%) in Spring, 60 (28%) in Summer, and 55 (25%) in Winter. There were likewise no seasonal trends in nursing home acquired pneumonia when participants were stratified according to control or intervention arm of the original clinical trial.

Conclusion: Although this study was not powered to find statistical significance, our results suggest that nursing home acquired pneumonia does not follow the familiar seasonal trend of pneumonia in community dwelling adults. This suggests that modes of acquisition and transmission of pneumonia are unique in the nursing home population, and this may provide a basis for future intervention to decrease nursing home acquired pneumonia.