Program

Noon - 1:00 pm  Plenary lecture - SON Auditorium G013

“Past, present and future of EBM”
Dr. Gordon Guyatt, MD, FRCP(C), OC,
Distinguished Professor in the Departments of Medicine
and Health Research Methods, Evidence, and Impact at
McMaster University

Poster Sessions - Ad Astra Room, 5th Floor HEB

1:00 - 2:00pm  Poster Session 1

2:00 - 3:00pm  Poster Session 2

3:00 - 4:00pm  Poster Session 3

4:30 - 6:30 pm Awards Ceremony & Reception
2019 Research Day Abstracts
Stroke Volume Guided Resuscitation in Patients Presenting to the Emergency Department with Sepsis and Septic Shock
Amanda Jobe¹, Steven Q. Simpson², Kelsey M. Bakalar³, Nancy Doane³, Joseph M. Leoni³, Emily Burgen⁴, G. John Chen⁴, Heath E. Latham²

¹Department of Internal Medicine, ²Department of Internal Medicine, Division of Pulmonary and Critical Care, ³Department of Nursing, ⁴Department of Internal Medicine, Division of Health Services Research, The University of Kansas Medical Center, Kansas City, KS

Introduction: Sepsis and septic shock are leading causes of hospital morbidity and mortality. The Surviving Sepsis Campaign recommends 30ml/kg of IV crystalloid as initial resuscitation in all patients with sepsis-induced hypotension. However, there are no data demonstrating that all patients are fluid responsive on presentation and limited data on how stroke volume (SV) guided strategies impact initial resuscitation. Therefore, we studied the impact of SV-guided strategies on septic patients presenting to the emergency department (ED) and hypothesized that SV-guided strategies would be associated with reduced IV crystalloid infusion without impacting outcomes.

Methods: We conducted a chart review of patients from October 1, 2017 to December 31, 2017 who presented to the ED with sepsis or septic shock. All patients were evaluated with a non-invasive cardiac output bioreactance monitor. Patients were divided into two groups depending on whether or not IV fluids were stopped by ED providers prior to 30ml/kg based on SV data, i.e. SV failed to increase ≥10% with a passive leg raise or with the previous bolus. The primary outcome was initial fluid received, and secondary outcomes included length of stay (LOS), mortality, and need for vasopressors, mechanical ventilation, and/or acute hemodialysis.

Results: Only sixty-three percent of patients were fluid responsive on initial SV assessment. The patients in whom IV fluids were stopped based on SV received less total fluid within the first three hours. There was no statistically significant difference in NEWS score, LOS, mortality, or need for vasopressors, mechanical ventilation, and/or acute hemodialysis in comparing patients whose fluids were stopped based on SV data versus not (Table 1).

Table 1:

<table>
<thead>
<tr>
<th>Were fluids stopped before 30 ml/kg based on SV?</th>
<th>Yes (n=50)</th>
<th>No (n=70)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total IVs in 3 hours (ml)</td>
<td>1678.0</td>
<td>2200.7</td>
<td>0.0051</td>
</tr>
<tr>
<td>Volume in ml/kg</td>
<td>19.98</td>
<td>29.47</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NEWS score</td>
<td>7.2</td>
<td>6.9</td>
<td>0.3958</td>
</tr>
<tr>
<td>Vasopressors Required (%)</td>
<td>22/50 (44%)</td>
<td>21/70 (30%)</td>
<td>0.1146</td>
</tr>
<tr>
<td>Vasopressor Duration (hr)</td>
<td>37.18</td>
<td>44.35</td>
<td>0.2715</td>
</tr>
<tr>
<td>Mechanically Ventilated (%)</td>
<td>1/50 (2%)</td>
<td>6/70 (8.6%)</td>
<td>0.2987</td>
</tr>
<tr>
<td>Acute Hemodialysis (%)</td>
<td>1/50 (2%)</td>
<td>2/70 (2.9%)</td>
<td>1.0000</td>
</tr>
<tr>
<td>Hospital LOS (days)</td>
<td>6.73</td>
<td>7.30</td>
<td>0.3956</td>
</tr>
<tr>
<td>Hospital Mortality (%)</td>
<td>4/50 (8%)</td>
<td>9/70 (12.9%)</td>
<td>0.3917</td>
</tr>
</tbody>
</table>

Conclusion: Stroke volume guided resuscitation may lead to lower volumes of IV crystalloid administered to patients presenting with sepsis and septic shock, avoiding over resuscitation which may be associated with increased morbidity and mortality. Additionally, SV-guided strategies did not negatively impact patient outcomes. While there was a trend towards a higher proportion of vasopressor use in the SV-guided group, vasopressor duration was shorter and there was a trend towards decreased LOS and mortality. Further studies are needed to determine the impact of SV-guided resuscitation on outcomes.

Funding Sources: None
30-year-old Female with Chronic Cough: A Presentation of Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH)

Amanda Jobe, MD¹, Wei Cui, MD², Laura A Thomas, MD³

¹Department of Internal Medicine, ²Department of Pathology, ³Department of Internal Medicine, Division of Pulmonary and Critical Care, The University of Kansas Medical Center, Kansas City, KS

Introduction: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) is a rare, female-predominant pulmonary disorder. We present a case of a 30-year-old, non-smoking female diagnosed with DIPNECH, younger than nearly all cases noted in the literature.

Case Report: A 30-year-old female presented to the pulmonary clinic for chronic cough of 5-6 years duration with associated dyspnea on exertion. Her initial work up including chest x-ray, PFTs, and methacholine challenge was normal. A CT chest showed numerous small pulmonary nodules, as well as mild air trapping on expiratory images. Laboratory testing revealed a negative ANA and ANCAs. Bronchoscopy with bronchoalveolar lavage was unremarkable. Due to persistent pulmonary nodules on follow up imaging, she was referred for open lung biopsy. The pathology specimens revealed >3 foci of neuroendocrine tumorlets, 2 foci of pulmonary neuroendocrine cell hyperplasia (NECH), and one bronchiole with constrictive bronchiolitis. Immunohistochemical studies noted foci of synaptophysin and chromogranin positive tumorlets. A serum chromogranin level was normal. A diagnosis of DIPNECH was made and she was started on octreotide with significant improvement in her cough.

Discussion: DIPNECH is a rare disorder that usually affects non-smoking, middle age females. It may be discovered incidentally on lung biopsy or present as a clinical syndrome in patients with chronic respiratory symptoms. Traditionally, the diagnosis has been made based on histologic criteria; however, recent publications have highlighted the importance of combining the clinical, radiographic, and histologic features into diagnosis. While our patient did not meet all proposed histologic criteria (≥3 bronchioles with NECH and ≥3 carcinoid tumorlets), the findings were suggestive of early DIPNECH and potentially reflective of her young age at diagnosis as compared to the usual demographic. Based on the combination of her symptoms (chronic cough and dyspnea), characteristic radiographic findings (innumerable nodules and air trapping), and histologic findings, the diagnosis of DIPNECH was ultimately made. Due to her degree of symptoms and potential for progressive airflow obstruction and bronchiolitis obliterans, she was started on octreotide. In conclusion, our case represents one of the youngest published cases of DIPNECH and illustrates the importance of incorporating clinical, radiographic, and histologic features into the diagnosis.
Exploring Interprofessional Advocacy: a Learner-Centered Experience for Beginning Student Nurses

Elizabeth Young, MSN, RN, CNE, Clinical Assistant Professor, University of Kansas School of Nursing
Branden Comfort, MD, MPH, Assistant Professor of Medicine, University of Kansas School of Medicine
Nelda Godfrey, PhD, ACNS-BC, RN, Professor and Associate Dean, Innovative Partnerships and Practice, University of Kansas School of Nursing.

No conflicts of interest.
No funding source.

Background: Comparing and contrasting roles and perspectives of the nursing profession with other professionals is an important learning goal for student nurses. While collaboration among health care professionals has long been a theme within education and practice, advancing the idea of interprofessional advocacy is new and currently unexplored. This in-class learning activity is the first step to exploring the concept with healthcare learners.

Purpose: The purpose is to analyze movement in nursing students’ thinking when exposed to the novel idea of interprofessional advocacy in a first-year nursing class.

Methods: A SON faculty member (nurse) and a SOM faculty member (physician) created a two-hour interactive class on interprofessional advocacy. Students completed reflective writing assignments before and after class. We used content analysis to examine 10 randomly selected paired student responses (N=113).

Results: Prior to this class session, students had not been thinking about interprofessional advocacy in a concrete manner. Written student responses at the end of the class expressed a deeper understanding. Two examples are below:

- I think interprofessional advocacy is saying to a member of another profession “I see your unique skills and you are a valuable aspect of this patient’s care team” while also not discrediting, undermining, or devaluing the work of one’s own profession. After further discussion during class today, I don’t believe I would change that definition. I really enjoyed Dr. Comfort’s insights!

- Looking back on my definition of professional advocacy, it has changed from today’s discussion. Not only do you need to have your interprofessional team’s back, but you need to understand their struggles, values, and daily duties to advocate for them and for health professions.

Discussion: Interprofessional advocacy is difficult to achieve in many healthcare environments. This research confirms that deliberately exploring other professions’ knowledge, skills, beliefs, and motivations can lead to reflection and more knowledge and more thoughtful consideration regarding others on the healthcare team.

Conclusion: The competency categories of interprofessional collaborative practice—values and ethics, roles and responsibilities, interprofessional communication, and teams and teamwork—can be enhanced and made more ‘real’ when the notion of interprofessional advocacy is added to the learning environment.
**Cardiac Amyloidosis**

Ethan Hacker, MD (PGY-2)  
Branden Comfort, MD, MPH

**Introduction:** AL amyloid cardiomyopathy is a rare, but serious disease caused by abnormal deposition of amyloid protein within the heart leading to heart failure with significant mortality.

**Case:** A 53 year old female presented with complaint of enlarging neck lump over the past 2 months. She also had gagging for several weeks, difficulty with swallowing, and weight loss. She had no stridor, but had exertion shortness of breath. On examination, she had thyromegaly, moderate tachycardia, 3/6 holosystolic murmur, and 1+ pitting edema. A CT neck showed an enlarged thyroid with evidence of compression on the esophagus. An echocardiogram was obtained for her systolic murmur which showed significant obstructive hypertrophy with diastolic dysfunction. Her thyroidectomy was delayed, and she was transitioned from a diuretic to a beta blocker in order to avoid decreased preload that could lead to further obstructive cardiac physiology. She then underwent evaluation with cardiac MRI and stress testing. After being cleared by cardiology, she underwent thyroidectomy, and was found to have significant deposition of amyloid on surgical pathology. Her cardiac MRI showed a prominent basal interventricular septum, as well as diffuse infiltration of myocardium consistent with amyloid cardiomyopathy. Serum free light chain analysis revealed an elevated free lambda light chain, and a significantly decreased kappa/lambda light chain ratio. SPEP revealed a monoclonal spike of beta/gamma immunoglobulins. Fat pad biopsy confirmed AL amyloidosis on Congo red staining, and bone marrow biopsy revealed 5% monoclonal plasma cells. The patient was diagnosed with multiple myeloma and initiated on cyclophosphamide, bortezomib, and dexamethasone chemotherapy.

**Discussion:** This case highlights the importance of physical exam findings, and the heterogenous array of diagnoses possible from relatively common findings. In this case, findings of a murmur and goiter led ultimately to diagnoses of multiple myeloma and cardiac AL amyloidosis. Had clinical evaluation of her murmur not been undertaken, she would have remained on dangerous pre-load depleting diuretic therapy with obstructive cardiomyopathy during surgical resection of her thyroid. While her AL amyloid cardiomyopathy carries a poor prognosis, early recognition and treatment likely led to significantly improved quality and quantity of life.

**References**

Out-of-Pocket Costs for Patients with Type 2 Diabetes Mellitus

Christian David, Emily Burgen, GJ Chen

OBJECTIVE: Type 2 diabetes mellitus is a growing epidemic in the United States. In 2015 alone, it affected 30.2 million people. Additionally, the cost of managing type 2 diabetes continues to rise. This condition requires long-term management, and the out-of-pocket costs for type 2 diabetes are not well-characterized. The objective of this study was to understand the magnitude of out-of-pocket costs for type 2 diabetes patients can help better inform healthcare policy decision-making.

METHODS: We identified studies in the PubMed databank that were published between 2000 and 2017. From these studies, we examined the amount spent on out-of-pocket costs by type 2 diabetes patients.

RESULTS: Across the ten studies examined, we found a cost range of $143 per year to $2210 per year, a mean cost of $2063 per year and a median cost of $435 per year. There is a wide range in cost of out of pocket costs for people with diabetes.

CONCLUSION: It is clear that there is not a consistent cost measurement through all of the studies. Some of the variation is accounted for by different definitions of out of cost across the studies. To help better inform patients and healthcare policy decision-makers, accurately assessing out-of-pocket cost per year in patients with diabetes, there needs to be a consistent definition of out of pocket costs, as well as a consistent way to measure out-pocket costs.
Reaffirmation of the PREMM$_5$ Model for prediction of Lynch Syndrome

Christian Davis, Jack Harrigan, Rashna Madan, Daniel Buckles, Kevin Kennedy, Amit Rastogi, Mojtaba Olyaee, Anwaar Saeed, Ajay Bansal

Introduction: The Prediction Model for Gene Mutations (PREMM) is a widely used tool for predicting the probability of Lynch syndrome but the predictive power of various cutoffs for the risk scores is unclear.

Aim: To determine the performance of various PREMM risk score cutoffs for prediction of Lynch syndrome.

Methods

In this retrospective, single-center study, all patients with a diagnosis of colon cancer between January 1, 2016 and June 30$^{th}$, 2018 were included. The patients were identified using search in the pathology database for SNOMED codes. Additionally, the search results of SNOMED codes were tallied with the cancer center database to capture all patients with colon cancer. A structured RedCap electronic database was created to systematically abstract data about demographics, location and stage of colon cancer, PREMM$_5$ scores, genetic testing and a detailed 3-generation family pedigree. All patients underwent genetic testing using well-established commercial assays. The yield of Lynch syndrome was compared across three categories of PREMM$_5$ scores: <2.5%, 2.5-5%, >5%. These scores reflect pre-test probability of Lynch syndrome. Statistical comparisons were performed using ANOVA.

Results

Of a total of 258 patients, the final diagnosis of Lynch syndrome was made in 5% (13/258). The mean age across the three PREMM categories (<2.5%, 2.5-5%, >5%) was progressively lower: 69.8 ± 9.9 vs. 55.1 ± 9.4 vs. 46.4 ± 18.1, $P<.001$ suggesting that stronger the family history, younger is the age of onset of cancer. The location or the stage of cancers was not different across the three groups. The yield for a final diagnosis of Lynch syndrome was highest at the 5% cutoff (Table 1). The sensitivity, specificity, positive predictive value, negative predictive value of the 5% cutoff were 53.85%, 86.18%, 17.07% and 97.25%. The sensitivity, specificity, positive predictive value, negative predictive value of the 2.5% cutoff were 61%, 69%, 8.6% and 97%. Four of 13 (30%) patients with Lynch syndrome were missed even at the 2.5% cutoff.

Table 1

<table>
<thead>
<tr>
<th>PREMM Score</th>
<th>&lt;2.5%</th>
<th>2.5-5%</th>
<th>&gt;5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Scores (SD)</td>
<td>1.6 ± 0.5</td>
<td>3.6 ± 0.8</td>
<td>14.1 ± 14.1</td>
</tr>
<tr>
<td>Final diagnosis of Lynch syndrome*</td>
<td>2.6%</td>
<td>3.2%</td>
<td>17.1%</td>
</tr>
<tr>
<td>Age (Mean ± SD)</td>
<td>69.8 ± 9.9</td>
<td>55.1 ± 9.4</td>
<td>46.4 ± 18.1</td>
</tr>
<tr>
<td>First Degree Relative with Colon/Uterine Cancer</td>
<td>29 (18.8%)</td>
<td>16 (25.4%)</td>
<td>19 (46.3%)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (1.5%)</td>
<td>1 (1.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>IA</td>
<td>8 (6.0%)</td>
<td>3 (5.1%)</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td>IB</td>
<td>I</td>
<td>II</td>
<td>IIA</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>2 (1.5%)</td>
<td>24 (17.9%)</td>
<td>31 (23.1%)</td>
<td>3 (2.2%)</td>
</tr>
</tbody>
</table>

| Piercing | 17 (12.7%) | 11 (18.6%) | 5 (3.7%) | 6 (10.2%) | 4 (1.3%) | 10 (15.9%) |

<table>
<thead>
<tr>
<th>Cecum</th>
<th>Ascending Colon</th>
<th>Hepatic Flexure</th>
<th>Transverse Colon</th>
<th>Splenic Flexure</th>
<th>Descending Colon</th>
<th>Sigmoid Colon</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 (14.9%)</td>
<td>26 (16.9%)</td>
<td>4 (2.6%)</td>
<td>13 (8.4%)</td>
<td>4 (2.6%)</td>
<td>7 (4.5%)</td>
<td>27 (17.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rectum</th>
<th>Unknown</th>
<th>17 (15.7%)</th>
<th>5 (3.7%)</th>
<th>6 (10.2%)</th>
<th>4 (1.3%)</th>
<th>10 (15.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42 (27.3%)</td>
<td>3 (1.9%)</td>
<td>0 (0.0%)</td>
<td>18 (28.6%)</td>
<td>7 (11.9%)</td>
<td>17 (27.8%)</td>
<td>1 (2.4%)</td>
</tr>
</tbody>
</table>

*P*<.001

**Conclusion**

PREMM$_5$ scoring system aids in selection of patients for Lynch syndrome screening but may fail to suspect at least 1/3 of the proven cases. With costs of genetic testing rapidly decreasing, universal population-based testing in appropriate cohorts may be the solution.
Barney 3.0: A Bicampus Interprofessional Hospital Discharge Simulation

Kalender-Rich, Jessica L.1,2 Coffey, Candice1,2, Jernigan, Stephen3, Sabata, Dory4, Jackson, Susan5, Burkhart, Crystal6, Hughes-Zahner, Laura1, Rucker, Jason3

1 Landon Center on Aging, University of Kansas Medical Center, Kansas City, Kansas
2 Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas
3 Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center, Kansas City, Kansas
4 Department of Occupational Therapy Education, University of Kansas Medical Center, Kansas City, Kansas
5 Department of Hearing and Speech, University of Kansas Medical Center, Kansas City, Kansas
6 University of Kansas School of Pharmacy, Lawrence, Kansas

Background:
Interprofessional (IP) education is a core competency across all healthcare disciplines and educators continue to seek innovative ways to engage IP learners. Barney 3.0 is an IP simulation during which teams of medicine, physical therapy (PT), occupational therapy (OT), and pharmacy students practice collaborative patient care in a hospital discharge encounter followed by a simulated outpatient pharmacy encounter. The patient, Barney, is an older adult who is ready to discharge home from the hospital with home health.

Methods:
The simulation occurs in the Neis Clinical Skills Lab with nearly 100 students each session. All students are on site except pharmacy learners. On-site learners perform a group chart review followed by a discharge encounter with standardized patient actors as Barney and his wife. This is followed by the outpatient pharmacy encounter using video conferencing, and then a debrief session with all students and faculty. Data is collected using a five-point scale ranging from strongly agree to strongly disagree via a post-encounter REDCap survey with questions focused on IP collaboration.

Results:
Since February 2018, 247 students participated, including Medicine (118), PT (60), OT (37), and Pharmacy (32). The overall response rate was 52%. Of survey respondents, 95.4% reported Barney 3.0 would improve future patient care, 88.5% felt more equipped to communicate with other professions because of the simulation, 81.6% reported they learned something new about the roles of their IP team members, and 99.3% felt it was important to trust other healthcare professionals on the IP team.

Conclusions:
Barney 3.0 is a meaningful, IP activity to practice IP skills and encourage collaborative practice for the future.
Intern Bootcamp: Differentiating Level of Intervention Code Status Orders

Kalender-Rich, Jessica L,1,2 Olson, Lori,2,3 Porter-Williamson, Karin3

1Landon Center on Aging, University of Kansas Medical Center, Kansas City, Kansas
2Division of General and Geriatric Medicine, University of Kansas Medical Center, Kansas City, Kansas
3Division of Palliative Medicine, University of Kansas Medical Center, Kansas City, Kansas

Background: The University of Kansas Health System recently adopted new code status designations that specify discrete levels of intervention (LOI) desired by the patient in the event of health status decline. They expand the previous options of Full Code and DNAR to further delineate the patient’s goals of care in a concise and accessible way. These LOI are based on the Transportable Physician Orders for Patient Preferences (TPOPP), which is the regional adaptation of the POLST paradigm. Rolling out new language related to code status designations requires education at all levels and this project sought to design and evaluate education presented to incoming residents as a pilot for future broader education.

Methods: As part of the required Intern Bootcamp, all incoming residents attended a large group session focused on an overview of the LOI, TPOPP, and illness trajectory. Those in fields other than ophthalmology and dermatology participated in small group sessions led by Geriatric and Palliative Medicine faculty which used rapid-fire case studies to highlight distinctions between LOI designations. This was integrated with a demonstration of how to input and locate this information in the Electronic Medical Record (EMR). Participants answered a REDCap survey prior to the initial session and after the small group discussion focused on comfort and knowledge.

Results: 108 residents participated in the small group session. Response rate was 80.5%. Resident-rated understanding of the LOI increased for “most situations” from 21.3% to 95.4%. Confidence interpreting LOI in the EMR increased from 35.9% to 94.3% and inputting the order increased from 24.3% to 86.2%. 87.4% felt the smaller session was more helpful than the larger session. Knowledge assessment post-intervention indicated accurate interpretation (Full Code 100%, DNAR-Full Intervention 94%, DNAR-Comfort Measures Only 97%, DNAR-Limited Intervention 98%).

Conclusion: Incoming residents had improved understanding, confidence and knowledge of a unique code status designation system following this educational intervention. More opportunities exist to expand this education to other members of the healthcare team.
IMPACT OF NURSE OR TRAINEE PARTICIPATION AS AN ADDITIONAL OBSERVER ON ADENOMA DETECTION RATE: A META-ANALYSIS

Venkat Nutalapati, Sravan Jeepalyam, Madhav Desai, Ajay Bansal, Mojtaba Olyaee, Amit Rastogi

Background:
Adenoma detection rate (ADR) has been established as an important quality metric of colonoscopy. ADR is variable between endoscopists and tandem colonoscopy studies have shown a significant adenoma miss rate even for experts. Several factors like withdrawal time, inspection technique have been shown to affect the ADR. Participation by nurse or trainee serving as a second observer of the monitor in the endoscopy room has been shown to improve the ADR.

Aim:
We performed a meta-analysis to assess the impact of nurse or trainee participation as an additional observer on ADR during screening colonoscopies.

Methods:
A comprehensive search of MEDLINE, EMBASE, Scopus, Cochrane Database was conducted from each database’s inception to search for comparative studies on the impact of nurse or trainee participation (study arm) vs no participation (control arm) on ADR. The primary outcome of interest was ADR. Outcomes were reported as pooled odds ratio (OR) with 95% confidence intervals (CI) with statistical significance (p <0.05). RevMan 5.3 software was used for statistical analysis.

Results:
A total of 7 studies were included in our analysis. There were a total of 2992 and 4213 patients in the study and control arm respectively. Mean age was 59.1 years in study arm and 59.2 years in control arm. There were 77% males in study arm vs 61.2 % males in control arm. The ADR in study arm was 45.9% and it was significantly higher than the 32.09% ADR in the controls - pooled OR 1.29; 95% CI 1.16-1.44; p<0.01). There was no heterogeneity in the inclusion studies (I²=0%); Figure 1

3 studies included in this analysis had trainee participation, while 4 studies had nurse participation. In the trainee participation studies, the ADR was significantly higher in the study arm with a pooled OR 1.30; 95%CI 1.03-1.63; p<0.005). Similarly, in the nurse participation studies also the ADR was higher in the study arm compared to control arm – pooled OR 1.32; 95%CI 1.11-1.57; p<0.005 – Figure 2

Conclusion:
In conclusion trainee or nurse participation serving as an additional observer during colonoscopy improves the ADR. This is a simple way to improve the ADR and thereby decrease the miss rate and should be encouraged.
### Forest Plots

**Figure 1 - ADR Combined**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Askarian</td>
<td>119</td>
<td>253</td>
<td>102</td>
<td>249</td>
<td>9.6%</td>
<td>1.28 [0.90, 1.82]</td>
<td></td>
</tr>
<tr>
<td>Buchner</td>
<td>95</td>
<td>318</td>
<td>549</td>
<td>2112</td>
<td>17.5%</td>
<td>1.21 [0.94, 1.57]</td>
<td></td>
</tr>
<tr>
<td>Chalifoux</td>
<td>362</td>
<td>724</td>
<td>156</td>
<td>331</td>
<td>17.7%</td>
<td>1.12 [0.86, 1.46]</td>
<td></td>
</tr>
<tr>
<td>Chalifoux (b)</td>
<td>389</td>
<td>667</td>
<td>173</td>
<td>339</td>
<td>16.3%</td>
<td>1.64 [1.25, 2.14]</td>
<td></td>
</tr>
<tr>
<td>Kim</td>
<td>74</td>
<td>192</td>
<td>57</td>
<td>191</td>
<td>6.7%</td>
<td>1.47 [0.96, 2.25]</td>
<td></td>
</tr>
<tr>
<td>Lee</td>
<td>196</td>
<td>407</td>
<td>166</td>
<td>384</td>
<td>15.3%</td>
<td>1.22 [0.92, 1.61]</td>
<td></td>
</tr>
<tr>
<td>Turner</td>
<td>50</td>
<td>185</td>
<td>82</td>
<td>316</td>
<td>7.1%</td>
<td>1.06 [0.70, 1.59]</td>
<td></td>
</tr>
<tr>
<td>Wang</td>
<td>90</td>
<td>296</td>
<td>67</td>
<td>291</td>
<td>8.5%</td>
<td>1.46 [1.01, 2.11]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 2992 4213 100.0% 1.29 [1.16, 1.44]
Total events: 1379 1352
Heterogeneity: Tau² = 0.00; Chi² = 6.23, df = 7 (P = 0.51); I² = 0%
Test for overall effect: Z = 4.33 (P < 0.0001)

![Forest Plot](image)

**Figure 2 – ADR Fellow Participation**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buchner</td>
<td>95</td>
<td>318</td>
<td>549</td>
<td>2112</td>
<td>33.7%</td>
<td>1.21 [0.94, 1.57]</td>
<td></td>
</tr>
<tr>
<td>Chalifoux</td>
<td>362</td>
<td>724</td>
<td>156</td>
<td>331</td>
<td>33.6%</td>
<td>1.12 [0.86, 1.46]</td>
<td></td>
</tr>
<tr>
<td>Chalifoux (b)</td>
<td>389</td>
<td>667</td>
<td>173</td>
<td>339</td>
<td>32.7%</td>
<td>1.64 [1.25, 2.14]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 1659 2782 100.0% 1.30 [1.04, 1.63]
Total events: 846 878
Heterogeneity: Tau² = 0.02; Chi² = 4.34, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 2.32 (P = 0.02)

![Forest Plot](image)

**ADR Nurse participation**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Intervention Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Askarian</td>
<td>119</td>
<td>253</td>
<td>102</td>
<td>249</td>
<td>23.8%</td>
<td>1.28 [0.90, 1.82]</td>
<td></td>
</tr>
<tr>
<td>Kim</td>
<td>74</td>
<td>192</td>
<td>57</td>
<td>191</td>
<td>16.5%</td>
<td>1.47 [0.96, 2.25]</td>
<td></td>
</tr>
<tr>
<td>Lee</td>
<td>196</td>
<td>407</td>
<td>166</td>
<td>384</td>
<td>37.8%</td>
<td>1.22 [0.82, 1.61]</td>
<td></td>
</tr>
<tr>
<td>Wang</td>
<td>90</td>
<td>296</td>
<td>67</td>
<td>291</td>
<td>21.0%</td>
<td>1.46 [1.01, 2.11]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 1148 1115 100.0% 1.32 [1.11, 1.57]
Total events: 478 392
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 3 (P = 0.83); I² = 0%
Test for overall effect: Z = 3.18 (P = 0.001)

![Forest Plot](image)
NO ASSOCIATION BETWEEN LONG TERM PROTON PUMP INHIBITOR (PPI) USE WITH COGNITIVE DECLINE AND DEMENTIA: A SYSTEMATIC REVIEW AND HAZARD RATIO META-ANALYSIS

Madhav Desai, Jihan Fathallah, Abhiram Duvvurri, Chandra Dasari, Viveksandeep Thoguluva Chandrasekar, Ramprasad Jegadeesan, Tarun Rai, Anjana Sathyamurthy, Prashanth Vennalaganti, Divyanshoo Kohli, Michael Vaezi, Prateek Sharma

Introduction: Recently published studies have reported conflicting results on the association between long term PPI use and cognitive decline and dementia.

Methods: An extensive literature search was performed in Pubmed, google scholar and Cochrane for studies examining the risk of cognitive decline and dementia among PPI users to that of non-users. Case reports, case series, editorials, uncontrolled cohort studies, cross sectional studies and review articles were excluded. Primary outcome was pooled estimate of hazard of development of cognitive decline and any dementia among PPI users compared to non-users. Secondary outcome was pooled hazard ratio (HR) of PPI use and Alzheimer dementia. Generic inverse variance method was used to analyze pooled estimates with 95% confidence interval. Meta-analysis and heterogeneity (I2) was calculated by statistical software review manager.

Results: Seven studies with 347,391 patients (average age 75.5 years) met the inclusion criteria and were included in the final analysis. This included 3 prospective, 2 retrospective and 2 case-control studies with follow up ranging from 1.5 to 10 years (no randomized control studies). A total of 94,739 PPI users were compared to 105,492 control subjects. Pooled estimate of HR was 1.09 (95% CI: 0.89 to 1.34) suggesting no statistically significant difference (p=0.40) between patients using PPI compared to those who did not use PPI (Figure 1). There was substantial heterogeneity among inclusion studies (I2=95%). When analysis was restricted to cohort studies alone, outcomes did not change (pooled HR 1.11; 95% CI 0.79-1.56, p=0.54). In addition, PPI use was not associated with an increased risk of Alzheimer’s dementia with pooled HR of 1.02 (95% CI 0.73-1.43, p=0.91; Figure 2).

Conclusion: Findings of this meta-analysis are in line with poor biological plausibility for such an association between PPI use and risk for dementia. Large scale controlled trials with long term data will be required to confirm these findings.

Figure 1. Pooled Hazard ratio of PPI use and risk of incident dementia

Figure 2. Pooled hazard ratio of PPI use and Alzheimer’s dementia
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Hazard Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein 2017</td>
<td>-0.1956712</td>
<td>0.0735750</td>
<td>48.0%</td>
<td>0.62 [0.71, 0.55]</td>
<td></td>
</tr>
<tr>
<td>Gray 2018</td>
<td>0.10436002</td>
<td>0.21428571</td>
<td>28.9%</td>
<td>1.11 [0.73, 1.60]</td>
<td></td>
</tr>
<tr>
<td>Haensel 2014</td>
<td>0.36464001</td>
<td>0.26785714</td>
<td>23.1%</td>
<td>1.44 [0.85, 2.43]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.02 [0.73, 1.43]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0.06$; $Q = 5.45$, df = 2 ($p = 0.06$); $I^2 = 64$

Test for overall effect: $z = 0.11$ ($p = 0.91$)
Balancing deliberate practice and reflection: A randomized comparison trial for simulation-based cardiopulmonary resuscitation training

Emily Diederich, MD*; Matthew Lineberry, PhD*; Michael Blomquist, RN; Vanessa Schott, PhD; Chelsi Reilly, RN; Megan Murray, MHSA; Pooneh Nazaran, RN; Meghan Rourk, OTD; Julie Broski, MA

* ED and ML contributed equally as primary authors on this manuscript.

Zamierowski Institute for Experiential Learning
University of Kansas Medical Center and Health System, Kansas City, KS

Background: A key question in simulation-based education is how to maximize learning within time and resource limits, including how best to balance hands-on practice versus reflective debriefing. Several instructional design frameworks suggest setting the balance according to the type of learning objective(s); however, broad professional activities like team-based cardiopulmonary resuscitation include several interrelated component skills. This study experimentally manipulated hands-on practice versus reflective debriefing for cardiopulmonary resuscitation skills, hypothesizing that the former best supports learning taskwork (e.g., compression quality) while the latter best supports learning teamwork.

Methods: The study was a randomized comparison trial with pre- and post-tests. Twenty-six teams of 5-6 first-year residents underwent either “drill” practice of key resuscitation phases, designed to maximize deliberate practice opportunities for individual and team skills, or “scrimmage” practice, designed to maximize full-scenario rehearsals and reflective debriefs. Key taskwork and teamwork behaviors were coded, and compression quality was collected and analyzed from an accelerometer.

Results: Most performance parameters improved considerably from pre- to post-test for both taskwork (e.g., percent correct compression depth from 62% to 81%, p=.01) and teamwork (e.g., role leadership, 47% to 70%, p=.00). Only two parameters improved differently by condition, favoring “drill” training: checking “Do Not Actively Resuscitate” wristband (odds ratio=14.75, p=.03) and use of compression adjuncts (estimated marginal means=75% versus 67%, p=.03).

Conclusions: Consistent with the notion that component skills in resuscitation do not clearly and exclusively constitute “taskwork” versus “teamwork”, both instructional designs led to similar improvements despite differences in the balance between hands-on practice versus reflection.
A computable phenotype for PKD

Mohamad A Kalot, MD; Mohammed Al Khatib, MD; Nedaa Husainat, MD; Kerri Mcgreal, MD; Alan Yu, MD; Reem Mustafa, MD, PhD, MPH.

Background

Polycystic kidney disease (PKD) is an irreversible life-threatening inherited disease that causes chronic kidney disease (CKD) and permanent worsening in kidney function. Autosomal dominate polycystic kidney disease (ADPKD), a form of PKD, is a rare disease with typically a small number of patients in any healthcare system. A computable phenotype is an algorithm used to identify a certain set of patients within an electronic medical record system. Developing a computable phenotype that can accurately identify patients with ADPKD in administrative databases will assist researchers in designing studies and clinical trial recruitment within this population.

Methods

We reviewed of a random sample of 538 patients' medical records who are at least 18 years old and who visited the University of Kansas Medical Center (KUMC) nephrology clinic between October 2015 and October 2018. The sample had 250 patients with no ICD 9 and/or ICD 10 codes for ADPKD but who have a code for renal cysts and 283 had ICD 9 codes 753.12 and 753.13, and ICD10:Q61.2 and Q61.3 to identify patients with ADPKD. Then, we compared the extracted data from electronic medical records to the internationally accepted diagnostic criteria for ADPKD to judge about the diagnosis of PKD.

Results

In the 283 patients who had positive ICD codes, ADPKD was confirmed in 236 patients. In four charts the diagnosis of ADPKD was unclear due to missing information. A sensitivity analysis was performed to determine whether classifying the excluded patients as having ADPKD, or as not having ADPKD, and it did not meaningfully change the results. Algorithm 1 using the ICD codes for ADPKD provided a positive predictive value of 83.4 % and a negative predictive value of 99.2%. The algorithm has a sensitivity of 99.2%, and the specificity of 84.1%.

Conclusion

Our results suggest that the developed algorithm using the ICD9 and 10 codes can correctly identify those with ADPKD in 99.2% of the cases, and can correctly identify those without the disease in 84.1%. This suggests that this algorithm identifies most patients with ADPKD, and these codes can be used by researchers to collect ADPKD patients’ cohorts and hospital encounters.

<table>
<thead>
<tr>
<th></th>
<th>PKD</th>
<th>No PKD</th>
<th>Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD codes Positive</td>
<td>236</td>
<td>47</td>
<td>283</td>
</tr>
<tr>
<td>ICD codes Negative</td>
<td>2</td>
<td>248</td>
<td>250</td>
</tr>
<tr>
<td>Totals</td>
<td>238</td>
<td>295</td>
<td>533</td>
</tr>
<tr>
<td>Result</td>
<td>Point Estimate</td>
<td>Lower C.I.</td>
<td>Upper C.I.</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>99.16%</td>
<td>97.00%</td>
<td>99.90%</td>
</tr>
<tr>
<td>Specificity</td>
<td>84.07%</td>
<td>79.38%</td>
<td>88.05%</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>83.39%</td>
<td>79.43%</td>
<td>86.72%</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>99.20%</td>
<td>96.89%</td>
<td>99.80%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Point Estimate</th>
<th>Lower C.I.</th>
<th>Upper C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>90.81%</td>
<td>88.03%</td>
<td>93.12%</td>
</tr>
<tr>
<td>Likelihood Ratio Positive</td>
<td>6.22</td>
<td>4.79</td>
<td>8.09</td>
</tr>
<tr>
<td>Likelihood Ratio Negative</td>
<td>0.01</td>
<td>0.00</td>
<td>0.04</td>
</tr>
<tr>
<td>Disease prevalence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6/10 000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Assessing patients’ beliefs and attitudes about renal cysts: A survey

Introduction
Renal cysts are a common incidental finding on cross-sectional radiographic imaging. While most cysts are indolent, individuals with such cysts are frequently monitored for interval growth and potential malignant transformation, which is ultimately rare. We aim to assess patients’ values and preferences (believes and attitudes) about renal cysts.

Methods
We deployed a cross-sectional survey to a random sample of patients who have the diagnosis of renal cysts. This study utilized the Greater Plain Collaborative (GPC) de-identified dataset. This study is a collaborative effort between the University of Kansas Medical Center (KUMC), the University of Texas Southwestern Medical Center (UTSW), University of Minnesota Medical Center, and the University of Iowa (UI). We developed and pilot tested the survey. We collected data about the demographics and characteristics of patients with renal cysts. We performed a binary regression analysis to determine anxiety predictors in patients with renal cysts. Patients with renal cysts were identified by billing code and self-identification.

Results
We present the results of 301 respondents who had agreement on both billing code and self-identification: 138 with renal cysts, and 163 without renal cysts. The mean age was 61 years. Women constituted 62% of the respondents and the majority are employed (45%) or retired (32%). Regarding the insurance status, 97% reported having a health insurance. While a majority (72%) reported no family history of kidney disease, 5% reported having a family member on dialysis. The results of the characteristics of patients with renal cysts are described in table 1. In an adjusted regression analysis, patients with a clear treatment plan tend to have no anxiety (OR=0.49, 95% CI [0.22 - 1.11]) and patients with family history of renal disease tend to have anxiety with OR= 1.94, 95% CI [0.76 - 4.94].

Conclusion
There is wide variability in patient values regarding renal cysts and their follow-up. While one third of participants with renal cysts expressed concerns about the risk of progression to cancer, others were not worried. Guidance on this topic is needed and could help physicians and patients with shared decision making regarding renal cyst management.
Table 1. Characteristics of patients with renal cysts.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cysts positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=138*</td>
</tr>
<tr>
<td>How many renal cysts have you had?</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>1-4</td>
<td>90</td>
</tr>
<tr>
<td>&gt;4</td>
<td>8</td>
</tr>
<tr>
<td>Unsure</td>
<td>34</td>
</tr>
<tr>
<td>What is the approximate size of your renal cyst(s)?</td>
<td></td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>42</td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>11</td>
</tr>
<tr>
<td>Unsure</td>
<td>48</td>
</tr>
<tr>
<td>Do you have a specific treatment of follow-up plan for your renal cyst?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40</td>
</tr>
<tr>
<td>No</td>
<td>96</td>
</tr>
<tr>
<td>No renal cyst</td>
<td>2</td>
</tr>
<tr>
<td>If you receive specific treatment (N=43), what treatment have you been offered?</td>
<td></td>
</tr>
<tr>
<td>Repeated imaging</td>
<td>32</td>
</tr>
<tr>
<td>Surgery</td>
<td>9</td>
</tr>
<tr>
<td>Would you worry more about the renal cyst(s) if there was not follow-up (N=43)?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>36</td>
</tr>
<tr>
<td>Undecided</td>
<td>2</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>Are you satisfied with the management plan (or lack of a management plan) for your renal cyst(s)?</td>
<td></td>
</tr>
<tr>
<td>Satisfied</td>
<td>87</td>
</tr>
<tr>
<td>Neutral</td>
<td>30</td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>17</td>
</tr>
<tr>
<td>No renal cyst</td>
<td>3</td>
</tr>
<tr>
<td>Do you have important questions to ask a doctor about renal cysts?</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35</td>
</tr>
<tr>
<td>No</td>
<td>81</td>
</tr>
<tr>
<td>Unsure</td>
<td>21</td>
</tr>
<tr>
<td>Do you agree or disagree with this statement: I feel fully informed about renal cysts and the risk of progression.</td>
<td></td>
</tr>
<tr>
<td>Agree</td>
<td>66</td>
</tr>
<tr>
<td>Undecided</td>
<td>21</td>
</tr>
<tr>
<td>Disagree</td>
<td>48</td>
</tr>
<tr>
<td>In your opinion, what is the risk of progression to cancer for a renal cyst?</td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>45</td>
</tr>
<tr>
<td>Low risk</td>
<td>47</td>
</tr>
<tr>
<td>Undecided</td>
<td>43</td>
</tr>
<tr>
<td>What sources informed your opinion on the risk of progression to cancer?</td>
<td></td>
</tr>
<tr>
<td>Doctor</td>
<td>70</td>
</tr>
<tr>
<td>Family/Friends</td>
<td>7</td>
</tr>
<tr>
<td>Internet</td>
<td>22</td>
</tr>
<tr>
<td>No sources</td>
<td>43</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
<tr>
<td>How easy or hard is it to understand the</td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>57</td>
</tr>
<tr>
<td>risk of renal cyst progression?</td>
<td>Undecided</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Hard</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What type of doctor is involved in your kidney cyst care?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care physician</td>
</tr>
<tr>
<td>Nephrologist or urologist</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do you agree or disagree with this statement: My doctor considers my values and opinions regarding follow-up imaging for my renal cyst(s).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agree</td>
</tr>
<tr>
<td>Undecided</td>
</tr>
<tr>
<td>Disagree</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Would you like to receive more information about renal cysts?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Unsure</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do you agree or disagree with this statement: I am anxious about my renal cyst(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agree</td>
</tr>
<tr>
<td>Undecided</td>
</tr>
<tr>
<td>Disagree</td>
</tr>
</tbody>
</table>

*N=138 unless specified otherwise in the question.
Von Willebrand Disease: International Scoping Survey Study.

Mohamad A. Kalot, MD; Mohamad Al Khatib, MD; Reem A. Mustafa, MD, MPH, PhD.
Outcomes and Implementation Research Unit, The Jared Grantham Kidney Institute. University of Kansas Medical Center.

Background: Von Willebrand disease (VWD) is a rare inherited hemorrhagic disorder caused by dysfunction of a clotting factor, which leads to prolonged bleeding after an injury. The American Society of Hematology, the International Society on Thrombosis and Haemostasis, the World Federation of Hemophilia, and the National Hemophilia Foundation are collaborating to develop guidelines on the diagnosis and management of VWD.

Purpose: To prioritize main areas to be covered in the VWD guidelines.

Methods: A multi-disciplinary team led by researchers at KUMC designed and distributed a scoping survey to different stakeholders (patients, caregivers, clinicians, and allied health) worldwide. The primary analysis was based on the rating of different scoping areas using a 7 points Likert-scale. The survey was conducted in English, French and Spanish. We performed a descriptive analysis of demographics and baseline characteristics and a stratified analysis of patients and caregiver vs. clinicians and allied health. Additionally, we performed a conventional content data analysis utilizing a combination of deductive and inductive coding process to allow for in depth exploration of the comments.

Results: 601 stakeholders responded to the survey (51% patients/caregivers, and 49% clinicians/allied healthcare teams). Of the respondents, 54% were females and 21% were males. In the part assessing diagnosis areas, diagnostic criteria/classification and bleeding assessment tools were rated highest, while screening for anemia and iron deficiency was rated lowest. In the part assessing management areas, treatment options for women and for surgical patients were rated highest, while plasma-derived therapy vs. recombinant therapies was rated lowest. Figure 1 and 2 summarize the findings.

Discussion/Conclusion: Our study represents an collaborative effort between clinicians, methodologists, allied health, and patients. This effort helped in understanding different stakeholders’ views (patients, clinicians, methodologists, patients, caregivers) and guiding the decision on the most important areas to be covered in a guideline effort for VWD. Involving the broader stakeholder community from an early stage is essential to ensure that the areas prioritized in the guideline are in line with the stakeholders’ priorities in VWD care. We believe that this interdisciplinary approach is the drive behind the international responses despite the rarity of VWD.
Figure 1: Scoping priorities: the vWD diagnosis

Figure 2: Scoping priorities: the vWD management
An Interactive Introduction of the I-PASS Patient Handoff Curriculum to a Residency Program

Abebe Abebe, M.D., Erica E Howe, M.D.
University of Kansas Medical Center

Introduction

Patient handoffs are a crucial aspect of patient care and have become even more important in the setting of resident work-hour restrictions in recent years, new ACGME requirements, and new evidence that poor handoffs are directly related to medical errors.\(^1\)\(^-\)\(^2\)

Methods

In August 2015, all new categorical interns (n=24) attended a session introducing the I-PASS Handoff Model that started with a short lecture followed by role-playing and group reflection. For each role-play, the interns were paired up and alternated roles as the “handoff giver” and “handoff receiver.” A large group reflection took place after each role play.

A pre-session self-assessment survey was provided at the start of the class to evaluate frequency (never, rarely, sometimes, often, always) with which the I-PASS characteristics were used in practice. Approximately one month later, a post-session survey reassessed the intern’s use of the characteristics of new I-PASS model. Two-tailed T-test statistical analysis was used to compare the results.

Results

Overall, our findings noted no statistical significance between pre- and post-I-PASS surveys by dividing frequency as “never/ rarely/ sometimes” verses “often/always”. However, we remark on two notable findings:

1. A large increase in situation awareness and action planning frequency from “often/always” 58% of the time before the I-PASS session to 86% of the time following the I-PASS session was found.
2. A small decrease in frequency of synthesis by the receiver was noted from 33% of the time pre-session to 27% post-session when I-PASS surveys were compared.

Discussion

We suspect the increase in situation awareness and action planning following the I-PASS Friday School session is due to the interactive role playing with reflection. The lack of change in frequency of other I-PASS components was not surprising given that these components are consistent with our school’s traditional handoff practice. We also noted a small decrease in frequency of a novel aspect of the I-PASS model—synthesis by receiver, likely because this is a novel aspect of the handoff model that requires a more significant change in behavior for the learners. We suspect this data will increase with intermittent reminders of handoff expectations throughout the year.

References

Formative Research with Internal Medicine Trainees on Workplace Violence to Inform and Guide Decisions About Curriculum Development

Howe EE, Lowry B, Gibson C, Eck L.

Background:
With 2017 ACGME common program requirements in place highlighting the need to evaluate and address workplace safety, our program set out to understand the impact of workplace violence on our resident trainees and then use that data to develop a curriculum.

Methods:
All Internal Medicine residents were asked to complete a survey to better understand their previous exposure and response to violent patients in the workplace. A Violent Patients in the Workplace (VPW) curriculum was subsequently developed and includes violent patient simulations with small group discussions, a review of de-escalation strategies and hospital policies and resources, and pre-and post-testing to evaluate new knowledge mastery.

Results:
88.5% (69/78) of residents completed the survey. 36.2% (25/69) were female. 28.4% (19/67) self-reported as a member of a minority ethnic group. 63.8% (44/69) of residents are “not worried at all” or “a little worried” about workplace violence. 20.9% (14/67) of residents have witnessed physical violence in the workplace in the past 12 months. None of the residents verbally, physically, or sexually abused sought counseling, reported the incident to the GME office, completed an incident form, nor reported the incident to the police or the residency program.

Of those who did not report sexual abuse, the most common reasons were “it was not important” (66.7%; 2/3) and “useless” (33.3%; 1/3). The most common reasons for not reporting a violent event were "it was not important" (62.5%, 15/24) and "did not know who to report it to" (29.2%, 7/24). None of the residents who reported physical abuse completed the question on reporting.

Discussion:
Our survey results reveal the startling prevalence of learner exposure to violent patients in the workplace throughout their training, but perhaps more startling is the under-reporting of these incidents to authorities and under-utilization of hospital resources to assist them.

Our survey underlines the importance of educating our learners on workplace violence resources and de-escalation techniques.

References:
Quantification of cyst ventilation using $^{129}$Xe MRI correlates with pulmonary function tests in patients with LAM

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Introduction: Lymphangioleiomyomatosis (LAM), a rare lung disease characterized by the infiltration of smooth-muscle-like cells, leads to progressive cystic destruction and loss of lung function. CT imaging is the current imaging gold standard in monitoring cystic lung disease progression and treatment efficacy. $^{129}$Xe MRI has been utilized in assessing ventilation defect percentages (VDP) in several obstructive lung diseases. From these studies, VDP has been shown to correlate with lung function measurements such as FEV1, FEV1/FVC, and DLCO. However, it is unknown if cysts ventilate and how the presence or absence of that ventilation contributes to lung function.

Methods: We obtained $^{129}$Xe MR ventilation images in eight LAM patients (ages 51.6±12.6 years) using a 2D multi-slice gradient echo sequence on a 3T Philips scanner (TR/TE 8.0/4.0ms, FA 10-12°, FOV 300x300mm, voxel size=3x3x15mm); CT images of the same patients were acquired clinically ±1 year of MRI. The volume percentage of abnormally low-density lung (cysts, putatively) were quantitatively assessed using an established threshold (attenuation <-900 HU). For $^{129}$Xe MR images, ventilation was classified into no/low ventilation, normal ventilation, and hyper-ventilated areas. To assess if cysts ventilate, ventilation images were registered to each patient’s corresponding cyst labeled CT images using Advanced Normalization Tools (ANTs). Ventilated cyst volumes were quantified as a percentage of the whole lung volume and were compared to the clinical standards of LAM severity (FEV1% predicted, FEV1/FVC, and DLCO).

Results: Figure 1A displays representative examples of cyst labeled CT image, registered $^{129}$Xe ventilation image, and color-coded cyst labeled $^{129}$Xe ventilation images. Figure 1B displays the percentage of cystic lung volume breakdown for each patient. There was a significant correlation between an increase in percent cyst volume with no/low ventilation and a decrease in FEV1% predicted (n=8, r=0.85, p=0.007), FEV1/FVC (n=8, r=0.90, p=0.002), and DLCO% (n=6, r=0.89, p=0.016). There was no significant correlation between normal or hyper-ventilated cysts and lung function parameters.

Conclusions: Through image registration, cystic lung ventilation was assessed in a small cohort of LAM patients. It was determined that cyst ventilation could be heterogeneous, however, increased percentage of lung volume with no/low ventilated cysts correlated to lower lung function.
Regional Ventilation Changes in Severe Asthma After Bronchial Thermoplasty

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Background: Hyperpolarized 129Xe MRI can provide safe and high-resolution ventilation images. Subjects with severe asthma have more and larger ventilation defects when evaluated by 129Xe MRI than those without severe asthma. Bronchial thermoplasty (BT), which decreases airway smooth muscle, may decrease the ventilation abnormalities in bronchopulmonary segments when assessed by 129Xe MRI. We sought to quantify regional lung ventilation before and after BT.

Methods: Thirty subjects with uncontrolled severe asthma (ATS/ERS Workshop criteria) were imaged once with multi-detector CT (MDCT) and twice with 129Xe MRI (MagniXene™) at baseline, three weeks apart, prior to BT. A segmental airway mask was generated from the CT images using Apollo (VIDA). The thoracic cavity was segmented from the proton MRI using a custom trained convolutional neural network and used to define the ventilation boundaries. After bias correction, the ventilation images were then segmented using Advanced Normalization Tools (ANTS/ITK) into four ventilation categories (non-ventilated, poorly-ventilated, normal, and well-ventilated) and registered to the segmental airway mask. 129Xe MRI was repeated 12 weeks after the third BT and compared to the baseline MRIs. Linear mixed model analysis was used to examine the mean differences in ventilated volume percentage for each ventilation category in all segments and the whole lung before and after BT.

Results: Our cohort was predominantly Caucasian (93%) females (80%) with uncontrolled severe asthma (Mean PC20 of 1.67+/−3.55 mg/mL and ACT score 9.63 +/- 3.61) with 43% on biologic therapy and reduced FEV1 (70.61+/−24.72% predicted) at baseline. There were no significant differences in segmental or whole lung ventilation between the two baseline 129Xe MRI scans. There was a reduction in the percentage of poorly-ventilated lung (-4% p=0.008) and an increase in the percentage of well-ventilated lung (+6% p=0.002) 12 weeks after BT. Results at individual bronchopulmonary segments varied, but most trended towards improved ventilation.

Conclusion: 129Xe MRI can be used to determine segmental and whole lung ventilated volume percentages. Regions of poorly-ventilated lung are decreased with BT. This information may be useful in targeting only segments with poor-ventilation for treatment, potentially eliminating the need for multiple treatment sessions and decreasing adverse effects.

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Computed Tomography Fractional Flow Reserve: An appropriate low-risk screening tool for coronary disease

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Introduction: Left heart catheterization for direct visualization of coronary vessels has been common practice for many years. The decision to perform percutaneous coronary intervention (PCI) is often based upon the observed percent stenosis in each vessel, and vessels with 70% or greater stenosis often have intervention performed. Over the last decade, fractional flow reserve (FFR) has gained traction in determining if a lesion is hemodynamically significant [1]. FFR uses direct measurement of pressure and flow to determine if the stenosis is truly causing significant ischemia—thus giving a more approachable and objective measurement to assist with making the decision to intervene[2]. More recently Computed Tomography fractional flow reserve (CT FFR) imaging has allowed physicians to obtain an FFR value without requiring an invasive left heart catheterization. As this is a relatively new technique, there is limited data comparing CT FFR with direct visualization of left heart catheterization.

Methods: 71 patients received CT FFR during their care at Kansas University. Of those 71 patients, 19 patients had a diagnostic left heart catheterization as part of an ischemic workup. Seven of those patients had to be excluded due to misalignment, motion artifact, or previous stents obscuring the results. The 12 remaining patients had their CT FFRs compared with their catheterization results. An FFR result of less than 0.8 was considered to be hemodynamically significant, while a stenotic lesion of 70% or more was also determined to be significant.

Results: Using the guidelines noted previously for determining significant lesions, five of the patients were found to have FFR values that were less than 0.8. Three of those patients were then found to have significant stenosis on catheterization. The remaining seven patients receiving CT scans all had non-significant FFR values. All seven of those patients had negative left heart catheterizations as well. For purposes of screening or diagnostics, CT FFR was found to have a sensitivity of 100% and specificity of 77.8% when compared to gold standard left heart catheterization.

Conclusion: Fractional flow reserve is a technique that has been gaining attention to help distinguish whether a stenotic lesion has hemodynamic significance. With this small cohort of patients, CT FFR was found to be a potentially useful screening tool for stenotic lesions requiring PCI. This could help prevent unnecessary left heart catheterizations which carry risks of bleeding and infection.

Inflammasome-mediated cleavage of the trafficking adaptor protein RILP regulates exosome cargo specificity

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Exosomes secretion plays an important role in cell-cell communication and responses to disease states. While details continue to emerge describing exosome effects on target cells, there is still little understanding of mechanisms responsible for stimulus-specific increases in exosome secretion. We previously reported that HCV-infection increases exosome production by inflammasome-mediated caspase-1 activation which cleaves the trafficking adaptor protein RILP. Cleaved RILP (cRILP) cannot bind dynein and this enhances trafficking of Rab7-containing vesicles towards the plasma membrane. How cRILP-dependent processes affect exosomes and whether they alter exosomal cargo is unknown. The aims of this study were to determine the effect of inflammasome-activated RILP cleavage on exosome cargo specificity and determine how RILP interacts with multivesicular bodies (MVBs) and the ESCRT pathway. We first examined cargo specificity. Inflammasome activation by LPS/ATP increased exosome production 4-fold but the effect on cargo miRNAs was highly selective. While total cellular abundance of individual miRNAs did not change, exosomal content of pro-inflammatory miRNAs such as miR155 increased 150 fold. Many other miRNAs either showed no change or actually decreased after inflammasome activation. The effects on exosome miRNA selectivity was blocked by a non-cleavable RILP mutant (ncRILP) and could be duplicated by expressing cRILP in the absence of inflammasome activation. We next determined whether RILP directly associates with components of the exosome secretion machinery. Since exosomes originate from MVBs, we examined localization of this structure by immunostaining for CD63. cRILP redistributed MVBs away from the nucleus and moved them toward the periphery of the cell, while ncRILP completely sequestered the MVB near the mitotic center. We further determined if cRILP associates with the ESCRT machinery, the complex responsible for internal vesicle budding within the MVB. Immunoprecipitation of cRILP-associated intracellular vesicles pulled down ALIX, an ESCRT-related adaptor protein. In addition, cRILP bound Rab 27a, a key component in the docking of the MVBs to the plasma membrane. We therefore conclude that inflammasome activation and subsequent cleavage of RILP not only increases exosome secretion, it interacts with the machinery of exosome formation, repositions the MVBs, and changes the miRNA selectivity of exosome cargo loading.
Educating Residents on Health Disparities: A Model Curriculum for Identification and Action

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Introduction: An understanding of social determinants of health is critical in addressing health disparities and plays a pivotal role in patient care. The American College of Physicians (ACP) recently called for the integration of health disparities into all levels of medical education. Furthermore, the Clinical Learning Environment Review (CLER) program emphasizes residents identify and address health care disparities unique to their institution. The 2018 CLER Report described few centers with comprehensive approaches towards identification and reduction of health care disparities. While our health system maintains health disparity initiatives, a formal resident curriculum has not previously existed to provide structured education on their importance in patient care.

Methods: A systematic curriculum was formed to educate and enable categorical internal medicine residents to address health disparities. To solidify core concepts, residents completed an online learning module. Subsequently, small group sessions investigated the role of physicians in addressing health disparities and reviewed system resources in both the ambulatory and inpatient settings of our health system. Residents were surveyed pre- and post-small group discussion on their understanding of institutional health disparity priorities and their comfort to address them. Responses were recorded on a five-point Likert scale with scores of five indicating the highest level of understanding. Additionally, residents’ subjective assessments of their patient panel’s three most common health disparity-related concerns were reported.

Results: Fifty-two residents completed the intervention and pre-survey with 51 of those completing the post-survey (98.1%). Following the intervention, residents improved their understanding of institutional priorities for addressing health care disparities (2.6 vs. 4.3, p < 0.001) and how to address them in both the outpatient (2.7 vs. 4.3, p < 0.001) and inpatient settings (2.9 vs. 4.3, p < 0.001). Residents most frequently reported transportation (58.8%), mental health (51.0%), and prescription assistance (49.1%) as their patients’ most common health disparities.

Conclusion: Creating a health disparities curriculum based on ACP-CLER priorities was feasible for our program. Following participation in the curriculum, residents reported increased understanding in institutional health disparity priorities and how to address them in both outpatient and inpatient settings.

Funding Source: None
Development and validation of a new measure of adherence to cystic fibrosis care

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Introduction/Aim:
Patient adherence to cystic fibrosis (CF) treatment regimens is similar to that in other chronic diseases, with estimated adherence rates ranging 30-70%. Particularly with recent FDA approval of CFTR modulators, enhancing adherence to therapies is expected to improve both lifespan and quality of life for individuals with CF. We report on the development and validation of a new measure (CF-Care Behavior Survey; CF-CBS) to assess patient non-adherence to components of CF care.

Methods:
The CF-CBS is a self-administered survey, ascertaining data on: estimated adherence to CF therapies, barriers to adherence, motivation for changing adherence patterns, and self-assessed confidence in ability to change behavior. The survey is constructed to address individual items across treatment components (e.g., airway clearance, inhaled antibiotics). Content validation of the CF-CBS is being conducted as one key component of a broader multi-site, pilot and feasibility trial to test tele-coaching as an adherence promotion intervention. The validation sample will consist of about 40 patients (ages 14-25), and approximately 20-25 parents of these patients. Patients and parents each complete the CF-Care Behavior Survey (CF-CBS) at study enrollment and participate in an individualized, cognitive debriefing interview. All cognitive debriefing interviews are audio-recorded and transcribed verbatim by a paid third-party service. Cognitive debriefing interview transcripts are divided equally among three coders, with 30% of interviews independently coded by two coders to assess reliability. The CF-CBS measure will be revised based on aggregated data results and feedback.

Results: 38 patients completed cognitive debriefing interviews and coding was completed. Patient and parent feedback will be summarized and the revised measure will be displayed as part of the presentation.

Conclusion: The CF Care Behavior Survey (CF-CBS) is anticipated to be a unique and useful tool for measuring adherence to CF care, including volitional and inadvertent non-adherence. Because adherence often varies as a function of type of treatment, this new measure has significant potential for measuring variation in adherence across the different CF regimen components. Further, it is expected to be valuable to use during targeted interventions (e.g., tele-coaching) and in measuring outcomes for adherence promotion interventions, more broadly.

Grant Support: Cystic Fibrosis Foundation Therapeutics/Success with Therapies Research Consortium
Development of a tele coaching intervention to enhance adherence in patients with cystic fibrosis using stakeholder feedback via focus group methodology.

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Introduction/Aim: Tele-coaching has been used to successfully manage other health conditions, but has not been adopted to address non-adherence in patients with cystic fibrosis (CF). Our primary objective in this study was to gain key stakeholder (i.e., patient, parent, provider) feedback on the development of a tele-coaching intervention to enhance adherence in adolescents and young adults with CF.

Methods: Our multi-center project involved a qualitative assessment, via focus groups, with regard to feasibility, structure, and logistics of the individualized tele-coaching intervention. For this study phase, 40 participants with CF (CF Patient Cohort; age 14-25 years old), and 15-25 multidisciplinary CF care providers (Provider Cohort) are to take part in two focus groups to a) inform the development of our tele-coaching intervention, and b) review the proposed intervention. A group of 20-25 parents who live with participants age 14-18 in the Patient Cohort will participate in a single focus group (i.e., Parent Cohort) to also review the proposed telecoaching intervention. All focus groups are conducted via web-based tele-conferences, audio-recorded, and transcribed verbatim through a paid service. Transcripts are coded by independent coders using qualitative data analysis software (i.e., NVivo) to identify and analyze domain themes and categories across transcripts. Reliability of coding will be calculated via Kappa statistic.

Results: Data collection and coding is ongoing; thus far, a total of 38 patients, and 20 providers have taken part in initial focus group sessions. This presentation will include a review of findings from our full sample with respect to the acceptability of study methods, reaction to intervention plan, and feedback on structure and logistics for intervention delivery. Thus far, preliminary findings highlight the receptiveness of both patients and providers to video-call based coaching, with enthusiasm for maintaining continuity of care between clinic visits, and improving access for long-distance care/communication. Access to high quality internet connection has been listed as a concern.

Conclusion: Findings will provide stakeholder guidance in tailoring a tele-coaching intervention to enhance feasibility and acceptability. Results will further inform study procedures for a subsequent pilot randomized controlled trial to test feasibility, acceptability, and determine effect size of the tele-coaching intervention.

Grant Support: Cystic Fibrosis Foundation Therapeutics/Success with Therapies Research Consortium
Human-specific abnormal alternative splicing of the wild-type PKD1 gene induces premature termination of polycystin–1.

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Introduction:
Human PKD1 is unusual in that it contains two long polypyrimidine tracts in introns 21 and 22 (2.5kb and 602bp, respectively, 97% C+T), whereas the mouse and other species lack these C+T rich regions. Western blot analysis of polycystin-1 (PC1), using a monoclonal antibody to the extreme N—terminus indicates that humans, but not mice, have a smaller EndoH sensitive product, termed Trunc_PC1. Here we show that Trunc_PC1 is the product of differential splicing across introns 21 and 22 and that 28.8-61.5% of human transcripts undergo splicing events that lead to premature translational termination. Thus, the presence of these polypyrimidine tracts leads to decreased levels of full length functional PC1 reducing the level of PC1 signaling from normal alleles and in the context of a mutant allele may force signaling below a critical `cystogenic' threshold.

Methods:
We used RT-PCR from exons 20-24 to quantify the number of splice forms terminating early using NanoPore sequencing. We also compared the number of copies PC1 mRNA per mg total RNA at the 5’ and 3’ end of the human transcript and compared this with the copy number from normal mouse kidneys. We also created a stable cell line that produces a C-terminally FLAG tagged PC1 cDNA that terminates after exon-20, the region where Trunc_PC1 is predicted to end.

Results:
Assaying seven adult kidneys showed that 62.2±12.6% of PC1 transcripts read through and had the accepted sequence while the remainder mis-spliced and truncated. We measured the PC1 mRNA copy number in nine adult human kidneys. For the 5’ probe (exon 15) and 3’ (exon 34) probes, there were 7.38±3.47x10^5 and 1.03±0.354x10^6 copies/mg, respectively --- about 22–31 copies per cell. Mice had a similar number of total transcripts 9.59 ±2.30x10^5 copies/mg. The synthetic cDNA had an identical mass to Trunc_PC1 showing that they are the same species.

Conclusions:
About 40% of human PKD1 transcripts terminate early producing Trunc_PC1 implying that humans are dosage hypomorphs when compared to mice. Furthermore, the presence of an ER resident truncated form of the PC1 protein may interfere with the assembly of the polycystin complex.
Infectious Diseases Subspecialty Elective Curriculum: *becoming stewards of the curricular gap*

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BACKGROUND:

Both 4\(^{th}\) year medical students and Internal Medicine Residents have opportunity complete elective time in Infectious Diseases and other subspecialty rotations. However, expectations for the learner are often vague, and the curriculum is often unstructured. In smaller studies, dedicated subspecialty curriculum has been shown to improve performance on standardized examinations. The purpose of this study was to identify dedicated Infectious Disease curriculum and modifiable opportunities for improved educational experience and performance of IM residents and 4\(^{th}\) year students.

METHODS:

A SurveyMonkey\(^\circ\) survey was created and sent to IM Residency and ID Fellowship Program Directors to answer the following questions: (1) Does your program have an Infectious Diseases subspecialty education coordinator (SSEC) for IM residents? (2) Is there an official/unofficial Infectious Diseases physician coordinating education for 4\(^{th}\) year students at the core hospital site? (3) Are there well-defined learning objectives for the Infectious Diseases elective(s) for IM residents? (4) Are there well-defined learning objectives for the Infectious Diseases elective(s) for 4\(^{th}\) year students? (5) Is there a dedicated didactic curriculum for IM residents completing an elective in Infectious Diseases? (6) Is there a dedicated didactic curriculum for 4\(^{th}\) year students completing an elective in Infectious Diseases?

RESULTS:

Of the targeted program directors, 56 responses were received. 78% of Residency Programs had well defined learning objectives for the Infectious Disease electives for IM Residents. For 4\(^{th}\) year student electives, 64.3% of programs reported either "No" or no knowledge of well-defined learning objectives. 56% reported dedicated didactic curriculum for residents, with only 30.4% reporting dedicated didactic curriculum for 4\(^{th}\) year students. 71% of programs reported dedicated subspecialty education coordinators (SSEC) for residents. Only 51% of program directors reported an Infectious Disease physician coordinating education for 4\(^{th}\) year students.

CONCLUSION:

These results suggest there are opportunities for improvements in dedicated subspecialty curriculum development for both medical students and IM residents targeted at the learner’s level of training. 4\(^{th}\) year medical students in particular could benefit from simply establishing a dedicated elective curriculum with well-defined learning objectives.
Brain Effects of Renal Transplantation: Association Between Cognition and White Matter Integrity

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Background: Cognitive impairment is highly prevalent in end stage renal disease (ESRD). Diffusion tensor imaging (DTI) shows lower fractional anisotropy (FA) values in patients with ESRD. FA values measure structural integrity of white matter and are associated with cognitive impairment.

Methods: Adults were recruited from the renal transplant waiting list. Subjects were evaluated before transplantation and 3 months after transplantation with neuropsychological (NP) tests and a brain MRI. Two-tailed paired t-test was used to analyze changes in NP tests and FA values before and after transplantation.

Results: Eleven patients, aged 56.5 ± 10.7 completed the study. Cognitive measures of memory and executive function improved post-transplant, specifically on tests of logical memory I (p=0.004), logical memory II (p=0.003) and digit symbol (p<0.0001). DTI metrics also improved post-transplant with an increase in fractional anisotropy (p=0.01) and decrease in mean diffusivity (p=0.004). These changes were more prominent in tracts associated with memory and executive function.

Conclusion: Cognitive function, particularly memory and executive function, improve post-transplant with concurrent improvements in white matter integrity. These data suggest that abnormalities in cognition and brain structure seen in the ESRD population are at least partially reversible.

Supported by Kidney Institute Pilot Award
Cognitive Impairment in Kidney Transplant Recipients

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Background: Cognitive impairment is highly prevalent in end stage renal disease (up to 87%) and largely undiagnosed (only 2.9% documented). Severity of cognitive impairment is associated with the severity of renal dysfunction. Cognitive impairment influences: quality of life, employments rates, medical adherence, health care costs, hospitalizations, mortality. The prevalence of cognitive impairment after kidney transplantation and the factors associated with it are unknown.

Aims: To systematically determine the prevalence of cognitive impairment in kidney transplant recipients and elucidate the patient and clinical factors associated with cognitive impairment.

Methods:

Design: Cross-sectional, single center, observational study

Participants: Kidney transplant recipients

Procedures: Montreal Cognitive Assessment (MoCA). The MoCA is a validated, clinic-based tool that samples from various domains of cognition and is sensitive in detecting mild cognitive impairment. MoCA consists of a single page test with a maximum score of 30 (range: 0-30).

Statistical Analysis: We compared baseline covariates between patients with and without MoCA score of <26 (t-test for continuous variables and Chi-square test for categorical variables). We performed multiple linear regression analysis to study relationships between demographic and clinical factors (independent variables) with MoCA scores (dependent variable)

Results: 265 kidney transplant recipients were evaluated, age 55 ±14, 60.4% males, 74% Caucasians, and 54% college graduates. 58.5% of the patients had cognitive impairment with a MoCA score < 26. Cognitive impairment was associated with age (p<0.001), male gender (p =0.001), lower education (p=0.006), and diabetes (p=0.003). There was no association with race, body mass index, blood pressure, h/o smoking, coronary artery disease, peripheral vascular disease, stroke, serum hemoglobin, eGFR, use of prednisone, cause of ESRD, time on dialysis prior to transplant, or time since transplant.

Conclusions: Cognitive impairment is highly prevalent in kidney transplant recipients. Cognitive impairment in kidney transplant recipients is associated with increasing age, male gender, and level of education and is independent of kidney function.
Cognitive Impairment Influences Transplant Eligibility

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Background: Cognitive impairment is common in end stage renal disease and affects health outcomes. Cognitive impairment after solid organ transplants affects medication adherence and graft outcomes. Whether pre-transplant cognition influences transplant eligibility remains unknown.

Aims: To evaluate the association between cognitive impairment and transplant eligibility.

Methods: All consecutive patients referred to our center for kidney transplantation were screened for cognitive impairment using the Montreal Cognitive Assessment (MoCA). The transplant team and the transplant committee were blinded to MoCA scores while discussing listing of patients for transplant.

MoCA: The MoCA is a validated, clinic-based tool that samples from various domains of cognition and is sensitive in detecting mild cognitive impairment. MoCA consists of a single page test with a maximum score of 30 (range: 0-30). The MoCA takes less than 10 minutes to complete and assesses seven domains of cognition: visuospatial/executive, naming, memory (delayed recall), attention, language, abstraction and orientation.

Statistical Analysis: Patients were divided into three groups on the basis of their MoCA score. Baseline characteristics were compared in the three groups. A cox proportional hazards model was created to assess factors affecting listing for kidney transplant. Kaplan Meier curves were created for time to active listing by MoCA, time to active listing by MoCA and age and time to delisting.

Results: 636 patients were screened with MoCA. Only patients who had a MoCA at their first evaluation visit were included in the analysis. Patients with different MoCA scores differed in age, race, and history of smoking (Table 1). A higher MoCA score was associated with a higher likelihood for listing (Table 2). If MoCA score was removed from the model, younger age had a higher likelihood for listing. Within the same age ranges, patients with a higher MoCA score were listed sooner (Fig 2). Conversely, patients with a lower MoCA score were delisted sooner (Fig 3).

Conclusion: Cognitive impairment influences kidney transplant eligibility of patients with end stage renal disease

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Long-term impact of head and neck cancer (HNC) and treatment on financial distress and employment of HNC survivors

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Introduction: Increasing HNC survival highlights the importance of understanding late biopsychosocial outcomes. Financial and occupational impacts of HNC remain unexplored, thus we undertook a qualitative analysis to identify themes and explore the impact of HNC/treatment on survivors’ financial health.

Methods: Eligibility: Locally-advanced HNC who participated in an R0-1, NED, and > 1 year post treatment. Ten of 12 eligible patients were interviewed. Topics queried: financial issues related to HNC/treatment, financial/insurance matters affecting treatment, impact of treatment on fiscal responsibilities, financial counseling, and late impact of HNC/treatment on work. Frequency distributions were used to summarize patient characteristics. Interviews were transcribed verbatim, double-coded, and organized into themes and subthemes.

Results: 50% male, 100% Caucasian, 60% married, median age 64 years, and median time since treatment of 64 months. Most denied ongoing financial strain from HNC/treatment, citing mitigating factors of preparedness (e.g. preexisting savings), health/disability insurance, and marital status. Those with financial distress noted an income limited by savings or disability. None reported financially-related delays in care. However, 2 patients used free healthcare. Most denied impact of HNC/treatment on financial obligations, but a minority reported subsequent delays in dental care, paying credit card bills, and travel. Financial counseling was used by 4 patients; benefits included decreased stress, access to financial programs, and education. Healthcare providers were considered an important source of financial counseling. Not all patients returned to work; late effects (fatigue, cognitive changes) impaired work capacity for those who did. Limitations: Population may have been skewed by loss to follow-up of patients with financial toxicity that precluded ongoing medical follow-up.

Conclusion: Long-term financial distress was limited in this cohort of HNC survivors. Preparedness, adequate insurance, marital status, and financial counseling attenuated financial impacts of HNC. For those returning to work, late effects may affect capacity to work.
Colonic Histoplasmosis Mimicking Metastatic Colon Cancer in a Patient with Ulcerative Colitis On Infliximab

Jonathan Henke MD, Jihan Fathallah MD, Daniel Hinthorn MD, Louis Wetzel MD, Da Zhang MD, and John A. Bonino MD. University of Kansas Medical Center, Kansas City, KS.

Introduction:

*Histoplasma capsulatum* is a dimorphic fungus that may cause a self-limited respiratory infection in immunocompetent individuals. Immunosuppressed individuals, however, are at increased risk for disseminated disease. We report a case of a patient with UC, on chronic anti-TNF therapy, presenting with colonic ulcers and CT imaging suggesting omental disease.

Case Summary:

A 43 year old man, with 12 year history of ulcerative colitis, was referred to the university hospital with progressive abdominal pain and distention. He underwent an outside colonoscopy showing segmental inflammation in the ascending colon with a discrete ulceration. Biopsies were non-diagnostic. Laboratory studies showed normal leukocyte count but marked monocytosis. Cross-sectional imaging demonstrated enlarged mesenteric lymph nodes and omental soft tissue thickening. Findings were reported by the radiologist as concerning for omental metastatic disease. Chest imaging was unremarkable.

A colonoscopy was repeated and revealed a single 2 cm ulcer with heaped-up edges in the distal ascending colon. The lesion was biopsied and sent for histology, flow cytometry, and immunohistochemical stains. Histology disclosed active colitis and cryptitis with mucosal ulceration and epithelioid granulomas. There was no evidence of malignancy, dysplasia, or viral inclusions.

Serum fungal cultures and (1→3)-β-D-glucan fungal assay were negative. Serum and urine Histoplasma antigens were reported as “weakly positive, but below level of quantification.” Percutaneous CT-guided omental biopsies were obtained, showing no evidence of lymphoma or malignancy. Fungal stains (GMS) of the colonic ulcer biopsies were requested, confirming diagnosis of histoplasmosis. Patient was treated with 2 weeks of intravenous amphotericin, then oral itraconazole for one year. Follow-up imaging showed complete resolution of the abdominal lymphadenopathy and inflammatory stranding. Subsequent colonoscopy showed total resolution of the ulcer.

Discussion:

GI histoplasmosis from disseminated disease is not well characterized in the immunosuppressed IBD population. Atypical features of our case included absence of abnormal chest imaging, which is estimated to occur in ~70% of immunocompromised patients with dissemination. Associated serologic and urinary testing were also unhelpful in diagnosis. Disseminated histoplasmosis should be considered in immunocompromised IBD patients presenting with malignant-appearing colonic ulcerations and nodular omental thickening, even in the absence of strong supporting laboratory and radiologic data.

Funding Sources:

None
Implementation of a Standardized Sign-Up Process to Increase MyChart® Enrollment among HIV-Positive Patients

Rachel Sigler DO¹, Ryan Kubat MD², Angie Lopez RN², Jessica R. Newman DO²; University of Kansas Medical Center, Department of Internal Medicine¹, Division of Infectious Diseases²

Introduction:
Patient portals have an ability to engage patients in their own healthcare like never before. Patients using electronic portals have cited scheduling appointments, visualizing medication lists, and requesting refills as benefits. While further research on the advantages of patient portals in health care outcomes is necessary, they have been shown to improve control of chronic diseases and medication adherence as well as reduce rates of hospital admissions in prior studies. The aim of this project was to increase MyChart® enrollment among HIV-positive patients receiving care within Infectious Diseases clinic by 15% over 3 months with education efforts and a standardized enrollment protocol.

Methods:
Pre-implementation MyChart® enrollment status was extracted from Epic (O2) Electronic Medical Record of HIV-positive patients actively receiving care through our Infectious Diseases outpatient clinic. A standardized protocol for enrollment of HIV-positive patients was initiated for a 3-month study period enacted during routine clinic visits. MyChart® enrollment data for the clinic HIV patients was extracted from Epic 3 months, then 7 months following implementation of the intervention.

Results:
Well-controlled HIV- patients are routinely scheduled every 6 months; poorly-controlled patients are seen more frequently at the discretion of their physician. Over the initial 3-month study period there was a rise in total HIV clinic patients from 527 to 568. In this time frame, total actively-enrolled patients increased by 6.43%. At 7 months, the total HIV clinic patients were 591, and there was an increase in portal enrollment of 9.5% from baseline.

Conclusion:
Despite benefits of patient portals, uptake and use of these services remains an issue. Low enrollment is common in some of the most vulnerable patient populations, with ethnic minorities, those with lower education levels, and those with lower incomes being less likely to register. We aimed to overcome this barrier by describing the portal and enrolling patients face-to-face during clinic visits. Given the potential for patient portals to improve control of chronic diseases such as HIV and support medication adherence, which is of concern in viral load suppression in HIV, more research is needed on methods of engaging patients to enroll in and utilize patient portals.

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Prosthetic joint infection secondary to Mycobacterium avium complex presenting as FUO

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Introduction:
Non-tuberculous mycobacterium (NTM) are commonly pathogenic in the HIV/AIDS population and in patients with chronic lung disease such as cystic fibrosis and bronchiectasis. NTM are ubiquitous in the environment. Mycobacterium avium complex (MAC) is the most common NTM infection in the United States. Those who have symptomatic infection generally present with progressive lung disease, characterized by bronchiectasis. Localized disease is rare.

Case:
A 56-year-old male with rheumatoid arthritis on abatacept, hydroxychloroquine and sulfasalazine presented to clinic with a 3-month history of malaise and low-grade fever. He returned from a mission trip to Honduras 3 months previously. He developed low-grade fever, unintentional weight loss and night sweats. White blood cell count was 6.3 with hemoglobin of 12.4, chest radiograph was normal. Blood cultures were negative and echocardiogram was normal. He developed progressive right hip pain (in the setting of remote right hip arthroplasty). A temperature of 103 degrees prompted admission. On examination, extremities were atraumatic without synovitis; decreased active range of motion of the right hip. ESR was 25. An MRI of the right hip joint showed fluid collections and joint aspirate was grossly purulent. Patient was taken to the OR for a prosthetic explant with antibiotic spacer placement. Culture grew acid-fast bacteria at 10 days, identified as MAC. Initial broad-spectrum antibiotics were adjusted and he was discharged on intravenous amikacin three times weekly with oral rifampin, ethambutol, and azithromycin. Amikacin was discontinued after 4 weeks of treatment. The remainder of therapy was continued for 12 months. His immunosuppression for rheumatoid arthritis was lowered. Eleven months after treatment initiation, repeat joint aspiration culture was negative. He underwent repeat right hip arthroplasty and tissue cultures were negative.

Discussion:
NTM prosthetic joint infections are a rare presentation of NTM infection. Few case reports of MAC prosthetic joint infection exist in the literature, most in post-transplant patients. Future increased use of biologics and other immune-modulating therapy in rheumatoid disease and malignancy the will increase the incidence of NTM infection. Optimal therapy for non-pulmonary NTM is unclear. Investigation on the appropriate choice, interval, and duration of treatment for NTM prosthetic joint infections is imperative.
Title: Adult Case of Partial Anomalous Pulmonary Venous Return Corrected with a Transcatheter Approach

Authors: Farhad A Sami, Reza Masoomi, Peter Tadros, Uzair Mahmood

Introduction:
Partial Anomalous Pulmonary Venous Return (PAPVR) is an uncommon cause of right heart failure in adults. It is characterized by abnormal connection of pulmonary veins with either superior vena cava, right atrium or inferior vena cava. The incidence in general population is reported to be around 0.7 percent. We present a rare case of a 77 year old patient with PAPVR with dual drainage to superior vena cava and left atrium associated with a childhood history of Ventricular Septal Defect (VSD) corrected with a transcatheter approach.

Case Presentation:
77 year old male with long standing persistent atrial fibrillation and surgically repaired VSD at age 15 years old progressively developed palpitations, paroxysmal nocturnal dyspnea, exertional dyspnea and lower extremity edema. Echocardiography revealed normal left ventricular ejection fraction of 55%, enlarged right ventricle and right atrium and pulmonary arterial pressures up to 60 mmHg. He was referred to heart failure clinic as symptoms progressed to NYHA Class III and IV. The etiology of his pulmonary hypertension and RV enlargement remained intriguing considering his remarkable asymptomatic course of 50 years post VSD repair. Right heart catheterization to classify PH showed PA pressures of 57/19 and uncovered a shunt physiology with step up in atrial level and mixed venous saturation of 83 with QP:QS of 2:1. Cardiac CTA revealed PAPVR with dual drainage of a large right superior pulmonary vein to the distal Superior Vena Cava and Left Atrium. For correction, we opted for transcatheter occlusion of the anomalous return of the right superior pulmonary vein into the SVC utilizing a 39 mm CP stent, deployed utilizing a 22 mm BIB balloon, post dilated to 24 mm.

Discussion:
PAPVR is a rare cause of RHF in adults and can be a diagnostic challenge. Noninvasive imaging modalities for definitive anatomical delineation include Cardiac MRI and CTA. RHC is also a useful modality to detect shunt physiology albeit a more invasive one. Transcatheter correction is described in pediatric population, not in adults. The use of transcatheter approach provides a good alternative to surgical repair in elderly patients who may benefit from a less invasive technique.
NASAL TRANSCRIPTOMIC AND GENOMIC ANALYSES IDENTIFY GENE NETWORKS ASSOCIATED WITH CYSTIC FIBROSIS LUNG DISEASE SEVERITY


RATIONALE: Cystic fibrosis (CF) lung disease severity is highly variable, even among Phe508del homozygotes, and heritability studies show that ~50% of this variability reflects non-CFTR variation. Recent CF genome-wide association studies (GWAS; n=6,365 CF participants) demonstrate 5 loci significantly associated with a quantitative phenotype of CF lung disease severity. We hypothesized that analysis of nasal epithelial transcriptomic data, plus genomic data, would elucidate modifier genes and mechanisms of GWAS loci associated with CF lung disease severity.

METHODS: We tested the association of CF lung disease severity and differential gene expression in nasal mucosal RNAseq data from 134 CF GWAS participants. We also performed a pathway analysis of genomic data in 5,659 unrelated CF GWAS participants to determine single nucleotide polymorphism (SNP) association with lung disease severity. Finally, we assessed the correlation between risk alleles at significant GWAS loci and differential gene expression.

RESULTS: We identified differentially expressed genes in pathways relevant to airway mucosal host defense, including those involved in: viral infection, inflammation/inflammatory signaling, lipid metabolism, apoptosis, ion transport, and innate immune responses (including HLA genes) with most pathways demonstrating increased gene expression associated with worse lung disease. In genomic/GWAS pathway analyses of 5,659 patients, we observed genes previously identified at (or near) 5 significant CF GWAS loci, and genes in respective pathways were associated with viral infection, inflammation, innate immunity (HLA genes), ion transport, cilia trafficking, and CFTR processing. The top-ranked SNP at chr11p12-13 (a CF GWAS locus determined predominantly by Phe508del homozygotes) revealed gene networks involved in other chronic obstructive airways diseases (COPD, asthma), and CFTR processing. Candidate modifier genes (e.g., MUC4, HLA genes) were observed in some pathways across analyses.

CONCLUSION: Our analyses demonstrate that a heritable host response to environmental stimuli plays a key role in CF lung disease severity. Findings provide new insight into mechanisms of action for genes near significant GWAS loci; for example, increased expression of genes in the methionine salvage pathway, leading to pro-inflammatory signaling, (i.e., MTAP, APIP) is associated with worse lung disease. Future studies should include mechanistic validation of identified candidate modifier genes, which may also be novel therapeutic targets.

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A Rare Complication of Opioid Abuse in Cystic Fibrosis

Authors: Charles Bengtson, MD, Michael Crosser, MD, Deepika Polineni, MD MPH

Case summary: A 28-year-old female with CF had a history of severe CF lung disease and CF arthopathy managed with chronic opioids. She had several catheter-associated blood stream infections with polymicrobial organism. She presented with respiratory failure and was found to have right ventricular (RV) dilation on echocardiogram (ECHO) and elevated pulmonary artery pressure without pulmonary embolism (PE) on computed tomogram (CT) angiography. A right heart catheterization (RHC) was then performed demonstrating normal hemodynamics with concurrent ECHO showing resolution of prior abnormalities. Several months later she was again admitted with respiratory failure and now CT chest showed new ground glass opacities and segmental left lower lobe pulmonary embolism. ECHO again showed RV dilation. To confirm, she underwent a pulmonary angiogram which was unexpectedly negative for PE. Shortly after she suffered a cardiac arrest believed to be related to her RV failure and was successfully resuscitated. A repeat RHC was performed which was consistent with a diagnosis of pulmonary hypertension (PH) and was started on appropriate therapy. Given that the underlying cause of her PH was still unclear attention was turned to the abnormalities on CT chest. She underwent a lung biopsy which showed talc granulomas. The patient’s underlying and previously undiagnosed depression was treated by a multidisciplinary team with pharmacotherapy and psychotherapy. Her pulmonary hypertension improved with cessation of injection although the CT chest changes persisted.

Discussion: Talc granulomatosis is caused by crushing and injecting oral medications causing transient vasospasm of the pulmonary vasculature. While limited, published data on substance misuse in subjects with CF has shown about 1 in 5 of those surveyed admitted to substance misuse. The rates of depression and anxiety are increased in CF compared to the general population and those with CF and mental illness have higher rates of substance abuse. There are current no guidelines for the treatment of pain and substance misuse in CF.

Conclusion: Although rare, recognition of surreptitious injection of opioids is important to minimizing long term complications. Additionally, adherence to CF Foundation guidelines regarding mental health screening are key to reducing co-morbid depression and anxiety that exists with substance misuse.

References
No Bones About It: An Unusual Case of Foreign Body Aspiration

Authors: Charles Bengtson MD and Lewis Satterwhite MD. University of Kansas Medical Center, Division of Pulmonary and Critical Care

INTRODUCTION: Foreign body aspiration (FBA) in adults is uncommon and can have a varied clinical presentation making diagnosis challenging\(^1\). Delay in diagnosis can lead to sequelae of recurrent infection, bronchiectasis and empyema. There have been several case reports in the medical literature of FBA mimicking malignancy\(^2\). We report a case of FBA mimicking solitary respiratory papilloma.

CASE SUMMARY: A 51-year-old man with a history of COPD and polysubstance abuse was transferred to our institution for workup of a lung mass and pneumonia. A prior CT chest showed a mass-like consolidation in the right upper lobe (RUL) with surrounding areas of consolidation and enlarged right hilar lymph nodes. He was started on broad spectrum antimicrobial coverage and cultures were obtained. Pulmonary was consulted and decided to proceed with bronchoscopy. Upon inspection there was an endobronchial lesion obstructing the RUL orifice, with significant amount of purulent material distal, and biopsies were obtained. Pathology of the endobronchial lesion was consistent with squamous papilloma, an FNA of the enlarged lymph nodes showed no carcinoma. Thoracic Surgery was then consulted for surgical management of his endobronchial lesion. The patient subsequently expectorated a foreign body which was histologically consistent with non-human bone. Retrospective evaluation of his initial CT chest showed a radiopaque density in the RUL bronchus. The patient was treated with a prolonged course of antibiotic therapy and follow up imaging showed near resolution of right upper lobe changes.

DISCUSSION: Solitary respiratory papillomas are a rare cause of endobronchial obstruction and can undergo malignant transformation\(^3\). Given the updated clinical history pathology felt this likely was reactive changes from the FBA. We surmised that manipulation of the endobronchial lesion and increased airway clearance maneuvers may have led him to cough up the foreign body. He could not recollect any aspiration event which is not uncommon in most cases of foreign body aspiration\(^1\).

CONCLUSION: High suspicion of FBA based upon the clinical scenario may help lead to earlier diagnosis and treatment. Our patient fortuitously coughed up his foreign body leading to resolution of his obstructive pneumonia.

REFERENCES:

Improving Compliance with Telemetry Guidelines

Authors:
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Introduction:
With concern for increasing healthcare costs there is a nationwide movement towards improving efficiency and reducing waste. One target of such evaluation is telemetry use given it is a limited, costly resource that is routinely incorrectly deployed and overutilized. We evaluate a provider education based intervention to reduce inappropriate telemetry use.

Methods:
Design: Retrospective chart review consisting of 3 week blocks. 3 weeks of telemetry utilization before and 3 weeks of telemetry utilization after intervention was reviewed for non ICU patients admitted to the hospitalist service.

Intervention: A handout was constructed according to American College of Cardiology (ACC) and Society of Hospital Medicine (SHM) guidelines for indication and duration of telemetry use. Handout was distributed to providers, nursing staff and posted at each nursing unit.

Outcome Measure: The number of telemetry days that were not associated with an accepted indication before and after intervention. Cost associated with inappropriate use of telemetry was calculated using the daily charge billed to patients.

Results:
In the 3 week pre-intervention period, 197 patients met inclusion criteria. They received 199 days of inappropriate telemetry monitoring, including both for incorrect indication or inappropriate duration. Inappropriate indications included COPD exacerbation, localized infection without sepsis while inappropriate duration of monitoring was seen most commonly in Sepsis, Heart Failure exacerbations and tachyarrhythmias. The charge for the 197 days was $131,340. In the post intervention 3 week period, 153 patients were found to be monitored via telemetry and 134 days of inappropriate telemetry monitoring was noted. The associated charge was $88,440. The pre and post change was found to be statistically significant with t test analysis with P<0.03.

Conclusion:
There was decrease in the number of patients on telemetry and duration of inappropriate telemetry use after intervention. This led to a nearly $43,000 decrease in charges billed to patients. We used a quasi-experimental nonequivalent group design so there are some limitations to our study. We cannot infer causality because of unmeasured secular trends that could be possibly influencing the results. The idea of regression to the mean could also be in effect as we measured only two time periods.

Funding Sources: none
Discrepancies in Perceived and Measured Cognition in Kidney Transplant Recipients

Authors: Gupta A¹,²,³, Klein J¹,², Mahnken J¹, Thomas TS¹,², Drew D⁴, Sarnak MJ⁴, Burns JM¹,³
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Background: Cognitive impairment is common in kidney transplant (KT) recipients and affects transplant outcomes. The ability of clinicians to detect cognitive impairment during routine visits without formal testing is unknown.

Aim: To evaluate the accuracy of providers’ (transplant physicians and nurse practitioners grouped together) and nurse coordinators’ perception of cognitive performance of KT recipients compared to a standard cognition test.

Methods: Adult KT recipients were screened for cognitive impairment by using the Montreal Cognitive Assessment (MoCA). The transplant provider and nurse coordinator who saw the patients the same day as the MoCA assessments were asked to evaluate the patients on the day of MoCA assessment, and to independently rate the patients’ cognitive status on a 10-point Likert scale (1=poor, 10=excellent).

MoCA: The MoCA is a validated, clinic-based tool that samples from various domains of cognition and is sensitive in detecting mild cognitive impairment. MoCA consists of a single page test with a maximum score of 30 (range: 0-30). The MoCA takes less than 10 minutes to complete and assesses seven domains of cognition: visuospatial/executive, naming, memory (delayed recall), attention, language, abstraction and orientation.

Statistical Analysis:

- MoCA scores were compared with perceived cognition scores using gamma statistics.
- Provider scores were compared with the nurse coordinator scores using weighted kappa statistics.
- Correlations were calculated for each domain of cognition assessed by MoCA
- The performance characteristics of perceived cognitive scores were calculated.

Results: 157 patients, 57% male, 74% Caucasian, 85% with at least some college education, completed the study.
Conclusions:

- Transplant providers and nurse coordinators are limited in their ability to accurately screen transplant recipients with cognitive impairment.
- Objective tests may be needed to accurately assess cognition in this population.

Supported by the NIH Clinical and Translational Science Award grant to KUMC, and by the KUMC Department of Medicine
Impact of Exercise on Cognitive Impairment in End-Stage Renal Disease

Authors: Aditi Gupta¹,³, Sandra Billinger²,³, Jason Stubbs¹, Alan S.L.Yu¹, David K. Johnson³,⁴, Jeffrey M. Burns³,⁴

¹The Kidney Institute, ²The REACH laboratory, ³The KU Alzheimer’s disease center, ⁴Department of Psychology, KU

Background: Cognitive impairment is highly prevalent in ESRD. Patients with ESRD have lower physical function and physical activity. Exercise has biologically plausible and temporal relationship with brain health

Aims:
Aim 1: Determine the feasibility of 12 weeks of structured aerobic exercise in patients with ESRD and generate initial estimates of its effect on cognition.
Aim 2: Aim 2: Examine if 12 weeks of exercise attenuates markers of systemic inflammation and endothelial dysfunction in patients with ESRD

Methods:
Randomized cross over design
- Plan to recruit 15 patients, 5 in control group and 10 in exercise group.
- After 12 weeks, the exercise group will complete study and the control group will cross over to the exercise intervention.
- All 15 subjects will eventually receive 12 weeks of aerobic exercise.

Procedures:
- Cognitive testing
- Laboratory analysis for inflammatory markers (IL-6, TNF-α, ADMA)
- Assessment of physical function
- Assessment of body composition (by DEXA)

All procedures done at baseline, 12 weeks and/or end of study

Inclusion Criteria:
- Patients with ESRD on dialysis
- Age 40-70 years
- Have transportation
- Speak English

Exclusion Criteria:
- Acute medical issues
- Select musculoskeletal abnormalities
- Frequent hospitalizations
- Current use of antipsychotics or anti-epileptics
- Inability to hear, read or write

Results: About 200 patients were screened, 9 were enrolled and 2 completed the study. The other 7 patients could not complete the study due to emergent surgery, withdrawal from the study, uncontrolled BP and blood sugars, travel burden and failure to remember study visits despite reminders.

Conclusions:
Exercise can improve cognition in ESRD.
Exercise interventions are feasible in dialysis patients.
Patients with ESRD have medical, socioeconomic and transportation barriers to recruitment.
- Future exercise trials should minimize travel for the dialysis patients.
- Cognitive testing in the dialysis unit and exercise intervention during dialysis should be considered.

Supported By the Frontiers Pilot Award
Sustained Improvement in Depression after Renal Transplantation

Authors: Gupta A$^{1,2,3}$, Polshak T$^{1,2}$, Johnson DK$^{3,4}$, Burns JM$^{1,3}$

University of Kansas Medical Center$^1$, The Kidney Institute$^2$, KU Alzheimer's Disease Center$^3$ and The University of Kansas$^4$

Background:
• Depression is common in end stage renal disease.
• Depression in renal transplant recipients is associated with decreased medical adherence and increased mortality.
• Whether renal transplantation improves depression is unexplored.

Aim:
• To determine the trajectory of symptoms of depression before and after renal transplantation.

Methods:
• We evaluated patients with ESRD and followed them prospectively for one year after their renal transplantation.
• We assessed depression using Beck Depression Inventory at baseline (pre-transplant), 12 weeks post-transplant and one year post-transplant.

Beck Depression Inventory (BDI-II)
• Beck Depression Inventory is a 21-question multiple-choice self-report inventory for measuring the severity of depression.
• Higher total scores indicate more severe depressive symptoms.
• BDI has been validated in chronic kidney disease.
• The standardized cutoffs are:
  0–13: minimal depression
  14–19: mild depression
  20–28: moderate depression
  29–63: severe depression

Statistical Analysis: We used paired t test for analyzing the change in BDI scores pre-transplant to 12 weeks post-transplant, pre-transplant to one year post-transplant and 12 weeks post- transplant to one year post- transplant.

Results: 31 patients participated. 21 were transplanted and had their 12 week post-transplant evaluation. Of these, 11 patients also completed the one year post-transplant assessment.
Conclusions:
• Depression is common in end stage renal disease.
• Symptoms of depression improve after renal transplantation.
• This improvement in depression after transplant persists one year after transplantation.

Supported by the Kidney Institute Pilot Award
Alterations in the miRNA cargo of HIV-infected and cocaine treated macrophage-derived Extracellular Vesicles promote pulmonary smooth muscle proliferation

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Introduction: The prevalence of HIV-related pulmonary arterial hypertension (HIV-PAH) is commonly associated with the history of intravenous drug abuse (IVDU). Our previous studies demonstrate enhanced pulmonary vascular remodeling in HIV-1 infected IVDUs, simian immunodeficiency virus (SIV)-infected macaques and in HIV-transgenic rats exposed to opioids and/or cocaine. Although we earlier reported significant perivascular inflammation including infiltration of macrophages around the remodeled vessels, exact role of these inflammatory cells in development of pulmonary vascular remodeling remains unknown. Our recent in-vitro findings revealed HIV-1 infected and cocaine-(H+C) treated human monocyte derived macrophages (MDMs) secrete higher number of extracellular vesicles (EVs) compared to HIV-infected or un-infected cocaine treated MDMs with significant increase in 51-150nm sized particles. Additionally, we observed increased proliferation of human pulmonary arterial smooth muscle cells (HPASMCs) when exposed to EVs from H+C treated macrophages. Hence now we hypothesized that dual hit of HIV-1 and cocaine may alter miRNA cargo of macrophage-derived EVs that promotes smooth muscle proliferation on its uptake.

Methods: EVs were isolated from supernatants collected from HIV-1_Bal (5ng/ml) infected and cocaine (1µM) treated MDMs at 4-days post-infection and used for analysis of miRNA expression by quantitative RT-PCR. We selected five PI3/AKT signaling associated miRNAs (miR-130,-27a,-10a,-181 and miR200) for analysis based on small RNAseq findings.

Results: We observed significant increase in expression of miR130a and-27a in EVs derived from H+C treated MDMs compared to untreated group with significantly elevated miR130a levels in H+C EVs when compared to only HIV-1 or only cocaine mono-treatments. No significant changes observed in other miRNA expression in any of the groups. Further we found that both mRNA and protein expression of PTEN, TSC-1 and-2 were significantly reduced in HPASMCs exposed to H+C-EVs and this corresponded to activation of PI3K-AKT signaling. Inhibition of miRNA130a in HPASMCs with antagomir-130a blocked the EV-mediated decrease in PTEN mRNA expression, confirming direct role of miR130a in modulating PTEN expression and therefore potentiating the PI3/AKT signaling mediated cell proliferation.

In conclusion, findings suggest pivotal role of EVs derived from HIV-1 infected and cocaine treated macrophages in modulating pulmonary smooth proliferation and may play a crucial role in development of HIV-PAH.

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Mitochondrial dynamics and HIV/opioids mediated pulmonary endothelial dysfunction: Implications in HIV-related pulmonary arterial hypertension

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Introduction: HIV related pulmonary hypertension is a “multiple-hit” phenomenon with intravenous drug use (IVDU) as one of the major risk factors. We previously demonstrated increase in the severity of angio-proliferative remodelling of the pulmonary vasculature on SIV/HIV infection in the presence of opioids (morphine). This was associated with increased oxidative stress leading to enhanced autophagy that may be involved in switching pulmonary endothelial cells from early apoptotic state to late hyper proliferative state (Autophagy; 2016). Here now we hypothesize the involvement of mitochondrial reactive oxygen species (ROS) as a deriving factor for HIV and morphine mediated autophagy/mitophagy.

Method: Human pulmonary microvascular endothelial cells (HPMECs) were treated with morphine (M) and HIV-Tat (T) in the presence or absence of mitoTEMPOL, allopurinol and VAS-3947 followed by total ROS measurement by DCF. Mitochondrial specific superoxides were measured using MitoSOX dye. Change in mitochondrial membrane potential was measured using JC-1 dye. Expression of fission and fusion proteins: Mfn-1, Fis-1, Drp-1 and OPA-1 were analysed by western blot. Mitophagy was observed by staining for functional mitochondria (mitotracker red) and autophagosome (MAP1LC3B).

Results: Increase in morphine and Tat (M+T) mediated total ROS in HPMECs was observed to be more significantly preventable in the presence mitoTEMPOL, a mitochondrial ROS scavenger in comparison to NADPH oxidase (VAS3947) and Xanthine oxidase (allopurinol) inhibitor, indicating mitochondrial as the major source of oxidative stress. In corroboration to this finding we observed an increase in mitochondrial superoxide after combined treatment (M+T) for 2h to 24h. Furthermore significant accumulation of hyper-polarized non-functional mitochondria was observed following combined treatment for 1h to 6days with a peak observed at 2h post-treatment. Co-localization of mitochondria with autophagosome, an indication of mitophagy was observed in the presence of M+T. This accompanied with a decrease in fusion (Mfn-1) and an increase in the fission (Fis-1) proteins at 2h post-treatment, suggesting disequilibrium in mitochondrial fission and fusion process.

Conclusion: Overall our preliminary findings suggest mitochondrial ROS to be the major source of morphine and HIV protein mediated oxidative stress in pulmonary endothelial cells that results in induction of autophagy/mitophagy leading to enhanced proliferation of these cells.

Funding: NIH grants: R01DA034542, R01DA042715 and R01HL129875 awarded to N.K.D
Evaluation of Monocyte Count in Alcoholic Hepatitis – Implications for Severity and Prognosis

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Background: Alcoholic hepatitis (AH) is a severe inflammatory condition characterized by acutely worsening liver function in the setting of prolonged heavy drinking. Animal studies have implicated liver macrophages and circulating monocytes in the pathogenesis of AH. A few small studies suggest an elevated absolute monocyte count (AMC) in AH but this has not been confirmed, and studies have not assessed the relationship between AMC and clinical outcomes.

Methods: Patients age 18-70 admitted with acute AH were identified retrospectively through HERON (I2B2-based research data repository). The following inclusion criteria were applied: AST 50-400, AST/ALT > 1.5, bilirubin >3mg/dL. Patients with infection, immunodeficiency, or hematologic malignancy were excluded. T tests were used to compare blood counts to the reference ranges. Pearson’s correlation coefficient was used to evaluate the relationship between MELD, Maddrey Discriminant Function (MDF) and AMC. Logistic regression was used to evaluate the effect of AMC on mortality.

Results: The study population of 189 patients was 66% male and 77% white. 162 had at least 1 AMC recorded during their inpatient stay, and 40 patients had a second AMC during the follow-up period of 10±2 days after admission. The mean AMC (0.96 K/µL) and neutrophil count (8.20) were significantly higher than the upper limit of normal (P<0.0001 and P=0.003, respectively). Mean white blood cell and lymphocyte counts were not significantly elevated. AMC was moderately correlated with MELD score (R=0.328, P<0.0001) and MDF (R=0.301, P<0.0001). Patients with severe AH (MDF >32) had a significantly higher AMC (mean 1.03) than those with mild AH (0.76), P=0.0002. 30-day, 90-day, 180-day and 1-year mortality were 9.5%, 15.3%, 18.0%, 24.3%, respectively. AMC (OR 2.68, 95% CI 1.086-6.596) and HCV infection (OR 2.93, 1.012-8.494) were associated with increased odds of 90-day mortality. Day 10 AMC was associated with increased odds of mortality at 30 days (OR 6.52, 1.23-34.58), 180 days (OR 4.34, 1.14-16.49) and 1 year (OR 5.85, 1.45-23.50). Age, sex, and steroid/pentoxifylline use were not associated with increased odds of mortality.

Conclusion: Patients with AH have elevated AMC. AMC is positively correlated with disease severity as determined by MELD and MDF scores. Patients with elevated AMC have increased odds of mortality.

Funding Sources: This work was supported by a CTSA grant from NCATS awarded to the University of Kansas for Frontiers: University of Kansas Clinical and Translational Science Institute (# TL1TR002368 and # UL1TR002366). The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or NCATS.
Targeting the Vasopressin Type 2 Receptor for Renal Cell Carcinoma Therapy

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The Jared Grantham Kidney Institute, University of Kansas Medical Center, Kansas City, KS

**Background:** Arginine vasopressin (AVP) and its type-2 receptor (V2R) play an essential role in the regulation of salt and water homeostasis by the kidneys. V2R activation is also known to stimulate proliferation of renal cell carcinoma (RCC) cell lines in vitro. However, it is unclear whether V2R is expressed or is pathogenic in human RCC tumors. The current studies investigated V2R expression and activity in human RCC tumors, and the role of V2R in RCC tumor growth.

**Methods:** The effect of V2R antagonists OPC31260 or Tolvaptan on cell viability, cell cycle, clonogenicity and cell migration were determined in Caki-1 and 786-0 ccRCC cell lines. To test the effect of V2R antagonists on tumor growth, athymic nude mice were subcutaneously inoculated with Caki-1 cells. When tumor volume reached 80-100mm³, mice received vehicle, OPC31260 or Tolvaptan for 28 days.

**Results:** Analysis of the cancer genome atlas (TCGA) database, human RCC tumor tissue microarray, cDNA array and tumor biopsy samples demonstrated V2R expression and activity in clear cell RCC (ccRCC). OPC31260 and Tolvaptan reduced clonogenicity and cell viability in 786-O and Caki-1 human ccRCC cell lines, and caused G2/M cell cycle arrest. Furthermore, Tolvaptan and OPC31260 significantly suppressed RCC tumor growth in mice, while dDAVP, a V2R agonist significantly increased tumor growth. OPC31260 and Tolvaptan also reduced V2R signaling, cell proliferation and angiogenesis in tumors, while increasing apoptosis. These results provide novel mechanistic evidence for the pathogenic role of V2R signaling in ccRCC and suggest that inhibitors of the AVP-V2R pathway, including Tolvaptan, an FDA approved and repurposed drug, could be utilized as novel RCC therapeutics.
Chronic Inflammatory Arthropathy in the Setting of Levamisole-Induced Vasculitis

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(1)University of Kansas School of Medicine Internal Medicine Residency
(2)University of Kansas Department of Allergy, Clinical Immunology and Rheumatology

Levamisole, an anti-helminthic drug, is a common adulterant of cocaine with well-described auto-immune phenomena, notably complications of ANCA-associated vasculitis. Though arthralgia is a common symptom of levamisole-induced vasculitis, the association of levamisole toxicity and inflammatory arthropathy is less well-documented. This case describes the incidental findings suggestive of chronic, deforming, erosive arthropathy in the setting of a patient with inflammatory eye disease secondary to suspected levamisole-induced vasculitis.

A 46 year-old woman with remote history of levamisole-induced skin necrosis and chronic cocaine use presented with right eye foreign-body sensation, eye pain, redness and decreased vision that began abruptly four days prior. She had history of levamisole-induced skin necrosis six years prior from cocaine abuse. Her exam showed findings suggestive of chronic inflammatory arthropathy and right ankle lesion. Ophthalmologic exam demonstrated anterior uveitis, posterior scleritis, dacryoadenitis and ocular hypertension. Labs notable for cocaine on urine drug screen, elevated erythrocyte sedimentation rate and C-reactive protein; positive antinuclear antibody with a titer of 1:160, positive p-ANCA with a titer of 1:1280 and elevated anti-myeloperoxidase at 0.7. Plain films of the hands showed findings consistent with inflammatory arthropathy. CT chest without significant findings. Lacrimal gland biopsy demonstrated dacryoadenitis with foci of chronic inflammatory cells and biopsy of her right ankle lesion showed non-specific inflammation. Treatment included topical eye drops, acetazolamide, anterior chamber tap and systemic steroids with improvement in her ocular symptoms and intraocular pressure. She was counseled on cocaine cessation.

Her presentation was thought secondary to levamisole-induced vasculitis versus idiopathic ANCA-associated vasculitis. Given the pattern of autoimmune labs and history of levamisole-induced skin necrosis, levamisole was favored as the etiology of her inflammatory eye disease. Levamisole has many known immunological effects, including the induction of antibodies against various antigens resulting in a multitude of systemic complications. If levamisole can induce such manifestations as necrotic skin lesions, vasculitis, glomerulonephritis and pulmonary hemorrhage, it is possible that over time it could also lead to erosive arthritis, as in this patient. This case documents the possible relationship between levamisole and inflammatory arthropathy. Recognizing this correlation would have unique implications on treatment and prevention of associated systemic manifestations.
Novel prognostic biomarkers and their association with survival in pancreatic cancers.

Authors: Anup Kasi, Suhaib Bajwa, Stephen K. Williamson, Weijing Sun, Joaquina Celebre Baranda, Obdulia Covarrubias Zambrano, Madumali Kalubowilage, Stefan H Bossmann; University of Kansas Cancer Center, Westwood, KS; University of Kansas, Kansas City, KS; University of Kansas Cancer Center, Kansas City, KS; University of Kansas Medical Center, Kansas City, KS; University of Kansas Cancer Center, Fairway, KS; Kansas State University, Manhattan, KS

Background: Early detection of pancreatic cancer would allow for improved survival outcomes.

Methods: We retrospectively evaluated serum protease levels and the survival of 15 pancreatic cancer patient samples (6 localized and 9 metastatic) at the KU Cancer Center. Available serum protease assays measured matrix metalloproteinases (MMPs), urokinase plasminogen activator (uPA), arginase, neutrophil elastase (NE), cathepsin B (CTSB) and cathepsin E (CTSE). The assays utilize fluorescent nanoparticle-based nanobiosensors which increase fluorescence upon posttranslational modification or enzymatic cleavage of targeted compounds and were read by a Spectral scan plate reader. Survival analysis was performed using Kaplan-Meier methods.

Results: Baseline characteristics for all 15 patients are in (Table). Median OS was 18.8m in patients with high CTSB expression (mean >51968.9) vs 9.7m in low CTSB expression (p=0.04). Similarly, median OS was 20.4m in high CTSE expression (>123264.8) vs 10m in low CTSE expression (p=0.05). Whereas, median OS was 16.3m in low NE expression (mean <30293.5) vs 9.6m in high NE expression (p=0.06). MMPs, uPA, and Arginase were not associated with survival.

Conclusions: Higher CTSB expression is associated with statistically significant improvement in survival. CTSB is a lysosomal protease involved in processing antigens and overexpression could aid in immunologic cancer suppression. CTSB is also involved in the development of desmoplasia which is hypothesized to be a physical barrier to metastasis. CTSE and NE expression did not meet statistically significant association with survival, likely due to sample size. Hence, we identify CTSB as a potential prognostic biomarker in pancreatic cancer. However, these findings need to be validated in a larger study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>High CTSB</th>
<th>Low CTSB</th>
</tr>
</thead>
<tbody>
<tr>
<td># of patients</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Median Age</td>
<td>65 (41-78)</td>
<td>62.5 [54-79]</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>5 (56%)</td>
<td>4 (67%)</td>
</tr>
<tr>
<td>F</td>
<td>4 (44%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>8 (89%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>2</td>
<td>1 (11%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Tumor Location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>6 (67%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Body</td>
<td>0 (0%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Tail</td>
<td>3 (33%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>CA19-9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (&lt;34 U/L)</td>
<td>2 (25%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>6 (75%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Localized</td>
<td>5 (50%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>4 (44%)</td>
<td>5 (63%)</td>
</tr>
<tr>
<td>1st line treatment for metastasis</td>
<td>No treatment (~25%) Gemcitabine based 75%</td>
<td>No treatment –40% Gemcitabine based – 40% FOLFRINOX – 20%</td>
</tr>
</tbody>
</table>
Implementation of an Audience Response System in a Case Conference Curriculum: Results of a Placebo Controlled Trial.

Ghulam Rehman Mohyuddin MBBS; Katherine Lester MD; Laura Thomas MD; Leigh M Eck MD; Jessica Newman DO

Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

INTRODUCTION:
Resident presented case conferences are commonly integrated into internal medicine residency program didactics. An audience response system (ARS), such as Poll Everywhere, can be incorporated into case presentations to engage learners and facilitate assimilation of material. We assessed whether the incorporation of an ARS into resident case conference would increase retention of information and self-perception of attentiveness.

METHODS:
In this study, we included ten case conferences given over a three month period by internal medicine residents. Participants included residents and medical students. Two sites were included in the study, the university hospital (UH) where Poll Everywhere was incorporated into case conferences, and the Veterans Administration hospital where Poll Everywhere was not incorporated. At UH, 3 interactive Poll Everywhere questions related to the case were added to the PowerPoint presentation. A 5 item (3 MCQ’s, 2 open-ended questions), test related to the conference subject content was given prior to and immediately following the conference at both sites. The same case subject and pre and post-tests were utilized at both sites. Chief residents facilitated case discussion and ensured that the content of the tests were covered. At the conclusion of the conferences, participants rated self-perceived attentiveness using a 5-point Likert scale.

RESULTS:
At both sites, a slightly higher number of post-tests were obtained than pre-tests. Pre-testing was similar at UH (n=93) and the VA hospital (n=90), with mean scores of 2.44 and 2.27 out of 5 possible respectively (p=0.334). At both sites, there was a significant difference in pre and post test scores with mean post-test scores of 3.36 (n=124) and 3.48 (n=118) for UH and the VA respectively (p=0.0001). There was no statistically significant difference between post-test scores at either site (p=0.444).

Self-perceived attentiveness was rated highly, however there was no statistically significant difference between self-perceived attentiveness at either site, with mean scores of 4.13 (n=115) and 4.07 (n=89) at UH and the VA respectively (p=0.568).

CONCLUSION:
Use of an ARS, Poll Everywhere, did not increase retention of material or self-perceived attentiveness when incorporated into resident case conference. Other methods to enhance attentiveness and retention must be explored.
Safety of limited dose modifications for palbociclib associated neutropenia in ER+ metastatic breast cancer.

Anthony Dominick, DO, Anne O'Dea, MD, Qamar Khan, MD, Bruce Kimler, PhD

Background:

The cyclin-dependent kinase (CDK) 4/6 inhibitor, palbociclib (P), improves outcomes in metastatic breast cancer (MBC). P has a consistent side effect profile with a high incidence of neutropenia, although with low rates of febrile neutropenia or serious neutropenia-related infections. In MBC trials of CDK4/6 inhibitors, it is recommended that dose reduction occur with an absolute neutrophil count (ANC) <1000 (Grade 3 neutropenia). These guidelines result in dose interruptions/dose reductions for >50% of patients due to neutropenia, with potential negative impact on patient outcomes.

Methods:

Specialty pharmacy data was utilized to identify patients with MBC treated with P. Patient demographics, disease characteristics, and safety data was collected. Only patients who underwent limited dose modification defined as a dose reduction/interruption for ANC <500 (Grade 4 neutropenia) were included in this analysis. Primary endpoints were incidence of neutropenic fever, infection, and percentage of patients who underwent dose reduction due to neutropenia.

Results:

50 patients with MBC who received P were included. 34(68%) received P plus an aromatase inhibitor and 16(32%) received P plus fulvestrant. 31(62%) received P as first treatment for MBC. 14% had received 1 prior therapy and 8% had received 2 prior lines of therapy for metastatic disease. 16% had received ≥3 lines of prior therapy. 15(30%) had received chemotherapy for treatment of MBC. Mean duration of P treatment was 321 days.

One incidence of neutropenic fever was observed in a patient who had received >24 months of P in whom a source of fever was not identified. 7(14%) patients experienced grade 4 neutropenia requiring cycle delay/dose reduction. 14(28%) experienced infection of any grade; 10 patients received outpatient treatment for respiratory infections and 3 were treated for urinary tract infections. One patient experienced Grade 3 colitis of undetermined cause.

Conclusions:

Limited dose modification (dose reduction for Grade 4 neutropenia) of P does not result in increased infections or higher rates of neutropenic fever. Patients receiving treatment with limited dose modification experienced fewer dose reductions/interruptions. More trials are warranted to determine if limited dose modification of P in MBC will translate into improved patient outcomes.
Cold snare endoscopic resection of non-pedunculated colorectal polyps larger than 10 mm: A systematic review and pooled-analysis.

Authors
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Background and aim:
Hot snare resection (HSR) techniques, polypectomy and endoscopic mucosal resection (EMR) are the current standard of care for the removal of colorectal polyps ≥10mm. To avoid the risk of electrocautery-induced damage with HSR, cold snare resection (CSR) techniques (polypectomy and cold-EMR) have recently been advocated. There are no published RCTs comparing HSR vs. CSR for polyps ≥ 10 mm.

Materials and methods:
An electronic database search was conducted in PubMed/MEDLINE, Embase, Google Scholar and Cochrane databases to identify studies that performed CSR for colorectal polyps ≥10mm. The primary outcome was the rate of adverse events. Secondary outcomes included: rate of complete resection, rate of overall polyp recurrence and rate of recurrence for adenomas vs sessile serrated polyps (SSPs). Sub-group analyses were performed focusing on polyp size, location and cold-EMR technique.

Results:
Eight studies were included in the final analysis: 522 polyps with a mean size of 17.5 mm (range 10-60mm) were removed with CSR. Mean patient age was 60.1 years with 55.3% males. 313 polyps were resected using cold EMR and 209 polyps by cold snare polypectomy. The overall adverse events rate was 1.1% (CI: 0.2%-2%). Immediate and delayed bleeding rates were 0.7% (CI: 0%-1.4%) and 0.5% (CI: -0.1%-1.2%) respectively, with post-polypectomy syndrome of 0.6% (CI: -0.1% - 1.3%). Using CSR, the complete resection rate was 99.3 % (CI: 98.6%-100%, I²=0%, p=0.9); and the overall polyp recurrence rate was 4.1% (CI: 0.2% - 8.4%) during a follow up period ranging from 154-258 days. For polyps ≥20mm undergoing CSR, the immediate bleeding rate and post-polypectomy syndrome rates were 1.3% (CI: 0.7% - 3.3%) and 1.2% (CI: 0.7% - 3.0%), but no delayed bleeding was reported. Of 313 polyps resected using the cold-EMR technique, the total adverse event rate was 1.3% (CI: 0% – 2.5%) with no post-procedural bleeding and a polyp recurrence rate of 4.7% (CI: 0.7% - 10.1%).

Conclusions:
The results of this pooled analysis show low rates of delayed bleeding (0.5%) and polyp recurrence rates (4%) with cold snare resection of polyps ≥ 10 mm, lower than rates reported with conventional EMR and hot snare polypectomy.
Table 1. Cold Endoscopic Mucosal Resection (EMR) outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Cold snare Endoscopic Mucosal Resection (cold EMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies</td>
<td>5</td>
</tr>
<tr>
<td>Number of polyps</td>
<td>313</td>
</tr>
<tr>
<td>Number of polyps ≥ 20 mm</td>
<td>132</td>
</tr>
<tr>
<td>Mean polyp size (mm)</td>
<td>19.3</td>
</tr>
<tr>
<td>Mean follow up</td>
<td>6.3 months</td>
</tr>
<tr>
<td>Adenomas</td>
<td>99/313 (31.6%)</td>
</tr>
<tr>
<td>Sessile serrated polyps</td>
<td>200/313 (63.9%)</td>
</tr>
<tr>
<td>Overall adverse events rate</td>
<td>1.3% (CI: 0% – 2.5%, I² – 0%, p=0.909)</td>
</tr>
<tr>
<td>Perforations</td>
<td>0</td>
</tr>
<tr>
<td>Immediate bleeding</td>
<td>0.8% (CI: 0% - 1.8%, I²-0%, p= 0.925)</td>
</tr>
<tr>
<td>Delayed bleeding</td>
<td>0</td>
</tr>
<tr>
<td>Post-polypectomy abdominal pain</td>
<td>0.7% (CI: 0% - 1.6%, I²-0%, p= 0.836)</td>
</tr>
<tr>
<td>Complete resection rate</td>
<td>99.1% (CI:98.0% - 100%, I²- 0%, p= 0.899)</td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>4.7% (CI: 0.7% - 10.1%; I²^- 65.97%, p = 0.032)</td>
</tr>
<tr>
<td>Recurrence rate (SSPs)</td>
<td>0.9% (CI: 0% - 2.3%, I²^- 0%, p = 0.651)</td>
</tr>
</tbody>
</table>

SSPs: serrated sessile polyps.
Efficacy and safety of Hot and Cold Endoscopic Mucosal Resection for resection of sessile serrated polyps: A systematic review and pooled analysis

Authors:

Viveksandeep Thoguluva Chandrasekar¹, Abhiram Duvvuri¹, Muhammad Aziz², Chandra Shaekhar Dasari³, Ramprasad Jegadeesan¹, Madhav Desai¹, Harsh Patel³, Tarun Rai⁴, Anjana Sathyamurthy⁵, Prashanth Vennalaganti³, Divyanshoo Kohli³, Maria Pellise⁶, Cesare Hassan⁵, Alessandro Repici⁶, Prateek Sharma¹.

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Background:

Endoscopic mucosal resection (EMR) with sub-mucosal injection is frequently utilized for the resection of sessile serrated polyps (SSPs) but efficacy and safety outcomes of this technique for SSPs are largely unavailable.

Methods:

An electronic database search was conducted for eligible studies using EMR for resection of SSPs ≥ 10 mm. The primary outcome was residual polyp rate at the first follow up colonoscopy. Secondary outcomes included: rate of technical success defined as complete macroscopic resection of the polyp, rate of adverse events (immediate bleeding, delayed bleeding and perforation) and recurrence rates on en-bloc vs piecemeal resection. A sub-group analysis was performed for polyps ≥ 20 mm in size and for resection by cold EMR technique. Pooled rates were expressed as proportions with 95% confidence limits.

Results:

A total of 12 studies met the inclusion criteria: 829 patients (50.2% males; mean age 60.2 years) who underwent resection of 1055 SSPs (184 SSPs ≥ 20 mm) with a mean polyp size of 20.4 mm (range: 10-60 mm). Follow up information was available for 622 patients; mean follow up duration: 14.5 months. 58.5% were resected in a piecemeal fashion. The residual polyp rate (per-patient analysis) was 5.5% (CI: 2.7%-8.4%). Secondary outcomes were as follows: technical success 99.5% (CI: 99.1%-99.9%), immediate bleed: 1.5% (CI: 0.2%-2.8%), delayed bleed: 2% (CI:0.5%-3.4%) and perforation: 0.4% (CI:0%-0.9%). Recurrence rates for polyps removed en-bloc versus piecemeal were 2.6% (CI: 0.5%-4.7%) and 3.4% (CI: 0.1% - 6.6%) respectively. For polyps ≥ 20 mm (361 patients), outcomes were: recurrence rate 7.2% (CI: 3.1%-11.3%), immediate bleeding: 3% (CI: 0.3%-5.6%), delayed bleeding: 3.6% (CI: 1.9%-5.4%) and perforation: 0.5% (CI: 0%-1.2%). Finally, 112 patients (195 polyps) underwent cold EMR with recurrence rate of 1.2% (CI: 0%-3%), immediate bleeding: 1.1% (CI: 0% - 3.1%) with no reports of delayed bleeding.
Conclusion:
This pooled analysis shows low rates of recurrence (5%) and delayed bleeding (2%) along with high technical success (99%) when SSPs > 10 mm in the colon are resected using standard EMR techniques. Cold EMR appears to have lower recurrence and bleeding rates but more data is needed comparing with conventional EMR.

Table 1. Recurrence and adverse event rates

<table>
<thead>
<tr>
<th>Events</th>
<th>≥ 10 mm polyps (n=829 pts)</th>
<th>≥ 20 mm polyps (n=361 pts)</th>
<th>Cold EMR (n=112 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence rate</td>
<td>5.5% (CI: 2.7%-8.4%)</td>
<td>7.2% (CI: 3.1%-11.3%)</td>
<td>1.2% (CI: 0%-3%)</td>
</tr>
<tr>
<td>En-bloc vs piecemeal recurrence rate</td>
<td>2.6% (CI: 0.5%-4.7%) vs 3.4% (CI: 0.1% - 6.6%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Technical success</td>
<td>99.5% (CI: 99.1%-99.9%)</td>
<td>99.1% (CI: 98.3%-99.8%)</td>
<td>98.7% (CI: 97.1%-100%)</td>
</tr>
<tr>
<td>Immediate bleeding</td>
<td>1.5% (CI: 0.2%-2.8%)</td>
<td>3% (CI: 0.3%-5.6%)</td>
<td>1.1% (CI: 0% - 3.1%)</td>
</tr>
<tr>
<td>Delayed bleeding</td>
<td>2% (CI: 0.5%-3.4%)</td>
<td>3.6% (CI: 1.9%-5.4%)</td>
<td>0%</td>
</tr>
<tr>
<td>Perforation</td>
<td>0.4% (CI: 0%-0.9%)</td>
<td>0.5% (CI: 0%-1.2%)</td>
<td>0%</td>
</tr>
</tbody>
</table>
Comparison of SIRS and qSOFA for Predicting Infection-Induced Organ Dysfunction

Author(s): S. Parashar1, K. Lembke2, S. Simpson3

1University of Kansas School of Medicine, Kansas City, United States, 2University of Kansas Institute(s): School of Medicine, Wichita, United States, 3University of Kansas, Pulmonary and Critical Care Medicine, Kansas City, United States

Introduction: The Sepsis-3 conference redefined clinical criteria for diagnosis of sepsis using measures of organ dysfunction. The qSOFA score was suggested to replace SIRS in screening for sepsis. The prognostic accuracy of suspected infection with either qSOFA or SIRS for predicting organ dysfunction, rather than mortality, has not been evaluated.

Objective: To compare prognostic ability of qSOFA with SIRS for presence of organ dysfunction within 48 hours of triage in patients admitted through the Emergency Department with suspected infection.

Methods: Single center retrospective cohort analysis of patients aged ≥18 admitted through ED with suspected infection 3/07-5/16. Presence of SIRS and/or qSOFA within 3 hours of triage were assessed. Suspected infection was defined as a combination of body fluid cultures and antibiotics within a 4-hour window, and both must have occurred within 6 hours of ED triage. Organ dysfunction was defined by both Sepsis-2 and/or Sepsis-3 criteria. Organ dysfunction at presentation was defined as presence of organ dysfunction within 3 hours of triage, and development of organ dysfunction was defined as organ dysfunction absent within 3 hours of triage, but present 3 - 48 hours post-triage. A third category included all patients with organ dysfunction either at presentation or at any time up to 48 hours after triage.

Results: 13,749 patients with suspected infection that met inclusion criteria were identified. 6,113 patients presented with only SIRS (44.46%), 427 patients presented with only qSOFA (3.11%), 3,072 patients presented with both qSOFA and SIRS (22.34%), and 4,137 patients presented with neither qSOFA nor SIRS (30.09%).

Table 1 shows area under ROC curves for organ dysfunction at presentation, development of organ dysfunction, and organ dysfunction within 48 hours, according to presence of SIRS or qSOFA at presentation.

Table 2 shows sensitivity and specificity for organ dysfunction at presentation, development of organ dysfunction, and organ dysfunction within 48 hours, according to presence of SIRS or qSOFA at presentation.

Conclusions: A majority of patients who present to the ED with suspected infection present with ≥2 SIRS. There is a substantial overlap of patients with both ≥2 qSOFA and ≥2 SIRS. qSOFA shows a significantly greater prognostic accuracy for Sepsis-2 and or Sepsis-3 Organ Dysfunction from presentation to 48 hours after ED triage. However, in each circumstance SIRS has higher sensitivity, while qSOFA has higher specificity.

References: Bone et al, Chest, 1992; 101; 1644-1655; Levy et al, Critical Care Medicine, 2003; 31; 1250-1256; Seymour et al, JAMA, 2016; 315; 762-774; Singer et al, JAMA, 2016; 315; 801-810;
Shankar-Hari et al, JAMA, 2016; 315; 775-787;
Abraham, JAMA, 2016; 315; 757-759
Grant Acknowledgements: Parker B. Francis Undergraduate Fellowship Award

<table>
<thead>
<tr>
<th>AUROC (95% CI)</th>
<th>0 - 3 HOURS</th>
<th>&gt; 3 - 48 HOURS</th>
<th>0 - 48 HOURS</th>
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<tbody>
<tr>
<td>SIRS ≥ 2</td>
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<td>0.44 (0.42 - 0.45)</td>
<td>0.63 (0.61 - 0.65)</td>
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<tr>
<td>qSOFA ≥ 2</td>
<td>0.72 (0.71 - 0.73)</td>
<td>0.33 (0.32 – 0.34)</td>
<td>0.75 (0.74 - 0.76)</td>
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[Table 1: AUROC]

<table>
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<tr>
<th>Sensitivity and Specificity</th>
<th>0 - 3 HOURS</th>
<th>&gt; 3 - 48 HOURS</th>
<th>0 - 48 HOURS</th>
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<tr>
<td>SIRS ≥ 2</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
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<tr>
<td></td>
<td>70.6%</td>
<td>44.0%</td>
<td>58.3%</td>
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<td>Specificity</td>
<td>Sensitivity</td>
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<tr>
<td></td>
<td>32.9%</td>
<td>95.5%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

[Table 2: Sensitivity and Specificity]
Faculty Research Day Abstract 2019

Modulation of Breast Volumetric Density and Proliferation as Measured by Ki-67 with Duavee in Women at Increased Risk for Breast Cancer

Carol Fabian MD
Kandy Powers NP
Jennifer Nydegger CRA
Teresa Phillips MS
Amy L. Kreutzjans CRA
Trina Metheny
Lauren Nye MD
Carola M. Zalles MD
Onalisa Winblad MD
Bruce F. Kimler PhD

Uptake of standard endocrine agents for primary prevention of breast cancer is poor due to concern about side effects, especially induction of menopausal symptoms. Duavee (20 mg of the SERM bazedoxifene and 0.045 conjugated estrogen) is FDA approved for treatment of hot flashes and prevention of osteoporosis in postmenopausal women with a uterus. Preclinical studies suggested to us that it might have a role in breast risk reduction. We undertook a pilot study to assess the feasibility of developing Duavee as a prevention agent in women at increased risk for development of breast cancer. Feasibility was to be assessed by accrual, retention, preliminary documentation of favorable effects on blood, radiographic and benign breast tissue risk biomarkers (the latter acquired by random periareolar fine needle aspiration (RPFNA). Eligibility criteria included in postmenopausal women (>12 months without menses or > 3 months with a postmenopausal FSH), hot flashes or night sweats, breast cancer risk at >2 x that of average risk woman for age group and had at least 500 cells on a baseline random periareolar fine needle aspiration (RPFNA). Women were not eligible if they had LCIS or DCIS, or were known to have a BRCA1/2 germline mutation, prior hysterectomy, or Ki-67 > 4% on RPFNA. Fasting blood draw, digital mammography with Volpara software, and DXA scan for body composition was performed at baseline along with QOL questionnaires and all women then received Duavee daily for 6 months, followed by repeat of baseline tests. There were 2 cohorts; cohort A with Ki-67 < 1% and cohort B with Ki-67 1-4% at baseline. 28 women were accrued in 28 months prior to study closure. Accrual was slower than anticipated primarily due to the strict eligibility requirements. All 28 women have completed the 6-month intervention with > 85% adherence and are evaluable; 13 in cohort A and 15 in cohort B. Women in cohort B with baseline Ki-67 of 1% or more exhibited a significant reduction in Ki-67 from baseline (p=.017) but not from cohort A (p=.44) Two/28 exhibited a protocol-defined significant increase in proliferation (to greater than 2% Ki-67 positive cells by immunocytochemistry for cohort A or doubling of Ki67 for cohort B). There a significant decrease (p=.043) in fibro-glandular volume on digital mammography from baseline as assessed by Volpara completely automated software. Concomitant non-randomized controls showed no change over the same time period (p=.66)
[See figure]. There were significant decreases in the risk biomarker IGF-1 (p=0.0011) and the molar ratio of IGF-1/IGFBP3 (p=0.022) as well as increases in estradiol, SHBG, bioavailable estradiol and decreases in bioavailable testosterone (P<0.01). Hot flash frequency and intensity dramatically improved (p<0.001) as median baseline score (average daily frequency and intensity went from 15 to 0). Menopause specific quality of life total scores and vasomotor and sexual domains also dramatically improved (P<0.001). There were no serious adverse events due to drug. A primary prevention trial in symptomatic women appears feasible given the favorable initial results. A grant has been submitted to the department of defense to support a multi-institutional Phase IIB trial of Duavee vs placebo in high risk women.

Financial support was provided by grants from Frontiers, the Breast Cancer Research Foundation (BCRF-16-049, BCRF-17-049). Duavee was provided to the study by Pfizer, Inc. which was otherwise not involved in the design, conduct, or analysis of the study.
Hyponatremia: Cardiac Salt Wasting Syndrome

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Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS
Department of Cardiovascular, University of Kansas Medical Center, Kansas City, KS

Introduction:
The association of hyponatremia with pericardial effusion and its improvement following therapeutic pericardiocentesis has been described in some previous case reports. However, the severity of hyponatremia described is usually mild. This case highlights new onset of severe hyponatremia (<110) in patient with pericardial tamponade.

Case presentation
A 70 years old female with past medical history of hypertension, coronary artery disease, diabetes, schizoaffective disorder, and chronic kidney disease presented to the emergency department (ED) with altered mental status. One day prior to presentation, she had several recurrent mechanical falls resulting in a head injury. In the ED, she was hypotensive, tachycardic, and hypoxic. Pertinent examination findings included confusion, head contusion, very distant and muffled heart tones. CT head was negative for acute intracranial process. Chest x-ray showed mild cardiomegaly. Bedside transthoracic echocardiogram demonstrated large pericardial effusion with tamponade physiology. Laboratory evaluation showed sodium concentration: 109 mmol/L (baseline 137), serum creatinine: 4.09 mg/dl (baseline 1.6), leukocytosis:15.6 k/ul, hemoglobin: 8 gm/dl (baseline 11). Other significant labs included normal TSH, serum osmolality: 257 mosm/kg, urine osmolality: 134 mosm/kg, urine sodium: 23 mmol/L, FeUrea: 10.6%. There was no recent change in medication to explain the hyponatremia. She was administered normal saline (total of 2 litres) and a repeat sodium level was 107 mmol/L. She underwent emergent pericardiocentesis with immediate improvement of hemodynamics. Pericardial fluid analysis showed hemorrhagic fluid; infectious and autoimmune analysis of pericardial fluid was negative, thus reflecting likely traumatic pericardial effusion. Though the sodium correction was quite rapid, she did not suffer from any negative consequences.

Discussion:
The likely cause of her severe hyponatremia was cardiac tamponade and related acute CHF and acute renal failure. This case further consolidates the impressive reversibility of hyponatremia following pericardiocentesis. There have been few case reports suggesting the role of SIADH in hyponatremia due to pericardial effusion but definitive physiologic mechanism is still undetermined. We propose a cardiac salt-wasting syndrome, that is due to pericardial effusion and subsequent high intracardiac pressure. Tamponade should be considered in the differential diagnosis of unexplained hyponatremia.
Subsegmental Pulmonary Embolism: An Incidental or Clinically Significant Finding?

Authors: Tarun Dalia, MD, Nilay Patel, MBBS, Matthew Lippmann, DO, Ethan Hacker, MD, Alexander Robinson, DO, Nicholas Isom, MD, Tyler Buechler, DO, Michael Pierpoline, DO, Terrance Mabry, Medical Student, Christopher Janish, MD, Lewis Satterwhite, MD, Kamal Gupta, MD

Background:
There is paucity of data on predisposing factors, presenting symptoms, clinical significance and management of isolated subsegmental pulmonary embolism (SSPE).

Methods:
We conducted a retrospective study of patients with SSPE diagnosed on chest computed tomography angiogram (CTA) from 1/1/2013 to 6/30/2017 at our center. We manually reviewed the medical records for detailed information on demographics, co-morbidities, tests performed, medications (including anticoagulants) and follow up.

Results:
We identified 213 patients with SSPE (51.2% were female and 76.1% were Caucasians). Symptoms prompted the CTA in 73.7% of the patients (dyspnea in 55.7%, chest pain in 35.7% and leg swelling in 15.2%), while SSPE was an incidental finding in 18.3%. Most patients had an underlying predisposing condition for deep vein thrombosis (DVT)/PE (malignancy in 52.1%, recent surgery in 25.8% and medical immobility 18.1%). 8.9% of patients also had concomitant DVT. 85.2% of the patients were anticoagulated (64.8% for ≥ 3 months and 31.8% for > 1 year). Enoxaparin (61.2%) and warfarin (37.5%) were the most common initial and long term anticoagulant used, respectively. 70.5% of patients had a >1 year follow up. 10.4% of patients who received anticoagulation had bleeding on follow up. No statistically significant difference was observed in mortality (2.8% vs 0%), readmission due to PE (5.5% vs 0%) or worsening of SSPE on follow up (1.1% vs 9.7%) among anticoagulated and non-anticoagulated patients, respectively.

Conclusion:
To our knowledge, this is the largest clinical study of SSPE to date. We found that in most patients SSPE was not an incidental diagnosis, but rather the CTA was prompted by symptoms and in a vast majority there was an underlying condition that predisposes to DVT/PE. Physicians chose to initiate anticoagulation in most patients, though only a minority received long-term anticoagulation. Bleeding complications were minimal among anticoagulated patients. Mortality due to SSPE is low. Due to small numbers, the study was unable to assess the outcome differences in anticoagulated and non-anticoagulated patients and larger randomized controlled trials are needed.
Appropriate Utilization of Cardiac Telemetry Monitoring: A Quality Improvement Project

Ky B. Stoltzfus, MD; Maharshi Bhakta, MD; Caylin M. Shankweiler, BSN, RN; Rebecca R. Mount, MS, RD, LD; Cheryl A. Gibson, PhD

For hospitals located in the United States, appropriate use of cardiac telemetry monitoring can be achieved resulting in cost savings to healthcare systems. Our institution has a limited number of telemetry beds, increasing the need for appropriate use of telemetry monitoring to minimize delays in patient care, reduce alarm fatigue, and decrease interruptions in patient care.

This quality improvement project was conducted in a single academic medical center in Kansas City, Kansas. The aim of the project was to reduce inappropriate cardiac telemetry monitoring on intermediate care units. Using the 2004 American Heart Association (AHA) guidelines to guide appropriate telemetry utilization, this project team sought to investigate the effects of two distinct interventions to reduce inappropriate telemetry monitoring, huddle intervention and mandatory order entry. Telemetry utilization was followed prospectively for two years.

During our initial intervention, we achieved a sharp decline in the number of patients on telemetry monitoring. However, over time the efficacy of the huddle intervention subsided, resulting in a need for a more sustained approach. By requiring physicians to input indication for telemetry monitoring, the second intervention increased adherence to practice guidelines and sustained reductions in inappropriate telemetry use.
Building and validating predictive models for acute kidney injury using electronic health records from multiple institutions: lessons learned from initial execution

Xing Song, PhD; Lemuel R. Waitman, PhD; Mei Liu (presenting author)
Division of Medical Informatics, Department of Internal Medicine, The University of Kansas Medical Center, Kansas City, KS 66160

Introduction: Acute kidney injury (AKI) is a common and highly lethal health problem, affecting 10-15% of all hospitalized patients and >50% of the intensive care unit patients and is associated with a significantly increased risk of morbidity and mortality. Predictive models would help clinicians identify high risk patients early and modify pathways accordingly to prevent AKI events. Overall aim of this project is to build and validate AKI prediction models using electronic health records (EHR) from multiple institutions.

Methods: The project proposed to utilize de-identified EHR data from 11 academic medical centers across the Midwest region through the Patient Centered Outcomes Research Network (PCORnet) using their defined common data model. A retrospective cohort will be constructed at each institution by including all adult patients who stayed for more than one day and have at least two serum creatinine measurements during the stay, and excluding patients with prior kidney disease. AKI was staged using the KDIGO serum creatinine definition. For automated cohort extraction at other participating sites, we implemented a software in R. A preliminary machine learning based prediction model was implemented on the University of Kansas Medical Center (KUMC) data with 70% for training and 30% for testing.

Results: Final analysis cohort constructed at KUMC consisted of 96,422 patients with 13,239 AKI patients (14%). Although numerous issues were encountered during the deployment of the cohort extraction software, we observed important variations in cohort characteristics, showing significant differences in patient demographics, medical history, laboratory test, and medication across institutions. The prediction model validated on the KUMC testing data achieved an area under the receiver operating characteristics curve (AUC) of 0.82 for at least AKI-stage-1, 0.88 for at least AKI-stage-2, and 0.91 for at least AKI-stage-3 for 24-hour advanced prediction; 0.76 for at least AKI-stage-1, 0.82 for at least AKI-stage-2, and 0.85 for at least AKI-stage-3 for 48-hour advanced prediction.

Conclusion: Externally validated prediction models would demonstrate true model reliability and generalizability for clinical application. The cohort characteristics variation found across institutions is expected to affect model performance, which prompted us to develop novel machine learning techniques to address the challenge.

Funding Source: The project is supported by the Patient Centered Outcome Research Network (PCORnet) Kidney Health Collaborative Research Group (CRG) Pilot Award.
TITLE: Modern IPE Implementation Challenges and Barriers: A Scoping Review

AUTHORS: Nedaa Husainat, Mohamad A. Kalot, Laith Numan, Reem Mustafa

Background: The importance of interprofessional learning and the superior outcomes when it is successfully carried out is well proven in the literature. Studies have shown, that creating a collaborative environment was associated with improved clinical outcomes and a reduction of costs. The World Health Organization (WHO) defines Interprofessional Education (IPE) as “education that occurs when two or more professions learn about, from and with each other to enable effective collaboration and improve health outcomes.” While efforts to improve interprofessional education (IPE) are underway, implementation and planning of IPE regionally and across the globe are faced with many challenges and barriers. This review focuses on recent challenges and barriers prior to and after implementing IPE among graduate medical programs in the United States.

Methods: We conducted a search for studies assessing IPE in the United States. We searched PubMed/Medline, ERIC, and PsychINFO from 2007 to 2018. We only included IPE studies published in English that are related to medical disciplines such as medicine, nursing, psychology, dentistry and pharmacy. We excluded studies that did not assess the effect of a specific IPE program and those assessing IPE in nonmedical discipline.

Results: Out of the 187 studies identified, we included 27 studies in the final review. Challenges prior to implementing IPE include the lack of IPE trained faculty, lack of IPE curriculum, curriculum content, scheduling and curriculum integration, as well as a lack of opportunity, leadership, and financial resources. The main challenge and barriers after implementing IPE include overcoming negative attitudes towards IPE. Some programs did not achieve a change in attitude towards IPE among faculty and staff. A lack of trained faculty and time for both educators and students was commonly reported as another important barrier.

Conclusion: While IPE has shown to improve health related outcomes, communication and collaboration, the various forms of IPE continue to face many challenges. To facilitate IPE in the United States, leadership commitment and resources are required. Further studies are needed on long-term results of IPE programs and the overall effectiveness and success in implementation.
Reported outcomes in ADPKD studies: A systematic review

AUTHORS: Nedaa Husainat, Mohamad Alkhatib, Mohamad A. Kalot, Kerri McGreal, Alan Yu, Ron Perrone, Reem Mustafa

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a progressive genetic disease impacting approximately 1 in every 400 to 1000 people. ADPKD is the fourth leading cause of kidney failure in the United States. Studies of ADPKD present results using a wide variability of outcome measures. This variability in measuring and reporting of outcomes hinders efforts to synthesize the body of evidence as it results in noncomparable outcome measures among studies. In this review, we aim to identify different outcomes reported in ADPKD studies including composite outcomes.

Methods: We conducted a systematic review of published studies that included ADPKD patients as the main population and measured renal outcomes. We searched the Cochrane Central Register (CENTRAL), OVID MEDLINE, EMBASE and Pubmed (from inception to January 2018). Our review included all studies regardless of design with ten or more participants. We excluded studies that only reported dialysis or transplant outcomes in ADPKD patients, prevalence studies, test accuracy studies, risk assessment studies, conference proceedings, and abstracts. We abstracted data in duplicate about individual and composite outcome measures, the effect estimates, and patients and studies’ characteristics.

Results: We identified 401 records through database searches. We included 134 records for full text screening and 85 published papers for data abstraction. These studies were conducted across 15 countries. Eleven studies were multinational and only seven assessed pediatric population. There is considerable inconsistency in the outcomes reported and how they are measured. We identified 14 outcome domains: mortality, endstage renal disease, Worsening kidney Function, Hospitalization, pain, kidney size, Hypertension, quality of life, cardiovascular events, kidney stones and infections, proteinuria, biomarkers, safety measures, and others. We identified 13 articles that reported six different composite outcomes. Components of the composite outcomes included increase in Height adjusted Total Kidney Volume (HtTKV), Left ventricular mass index, urinary albumin excretion, time to change in estimated or measured Glomerular Filtration Rate (GFR), worsening hypertension, severe kidney pain, endstage renal disease, and death.

Conclusion: There is a need to standardize outcomes in ADPKD studies. There is also a need for guidance about the appropriate components of composite outcomes in ADPKD studies. This will help comparison of results across studies especially if individual components are well defined.
HYPERGLYCEMIA CAUSES ION CHANNEL-INDUCED MUCOCILIARY DYSFUNCTION

Michael D. Kim, Nathalie Baumlin, Makoto Yoshida, John S. Dennis, Matthias Salathe
Division of Pulmonary and Critical Care Medicine, University of Kansas Medical Center, Kansas City, KS, USA

Introduction: Cystic fibrosis (CF)-related diabetes mellitus (CFRD) is a common comorbidity of CF and a major predictor of worse lung function. Hyperglycemia in CFRD patients contributes to respiratory decline by promoting inflammation, increasing infection risk, and by likely adversely affecting ion channel function, though the mechanisms remain largely unknown. We sought to understand the effects of hyperglycemia on ion channel function in normal human and CF bronchial epithelial (NHBE and CFBE) cells *in vitro* and evaluate the role of receptor for advanced glycation endproducts (RAGE) signaling in hyperglycemia-induced ion channel dysfunction in CF.

Methods: NHBE and CFBE cells were redifferentiated at the air-liquid interface. Fully differentiated NHBE and CFBE cells grown on Snapwell filters were mounted in Ussing chambers connected to a VCC MC8 voltage clamp unit (Physiologic Instruments). ATP-induced apical K⁺ (BK) currents were measured after basolateral permeabilization and amiloride treatment. CFTR currents were recorded as changes to forskolin and CFTRinh-172 after amiloride treatment. CaCC currents were recorded after UTP stimulation. ASL volume was estimated by meniscus scanning. Gene expression was quantified by qPCR.

Results: BK and CaCC currents were significantly reduced, while CFTR currents were significantly increased, in NHBE cells cultured in high glucose (HG; 12.5 mM) compared to normal glucose (NG; 5.5 mM) media. Glucose levels had no apparent effect on ASL volume in NHBE cells, although mRNA expression levels of inflammatory markers, including IL-6, IL-8, and MMP9, were significantly elevated in NHBE cells under HG. BK currents tended to decrease in CFBE cells under HG, which showed significantly lower ASL volume compared to CFBE cells cultured in NG media. RAGE mRNA expression levels trended higher in CFBE cells under HG vs. NG. Treatment with a soluble form of RAGE (sRAGE; 100 ng/mL for 4 weeks), which functions as a decoy receptor, reduced the depletion of ASL volume observed in CFBE cells under HG.

Conclusions: BK channels play an important role in CF for airway hydration. Our data indicate that hyperglycemia causes a decrease in apical K⁺ secretion through BK channels that correlates with elevated levels of RAGE mRNA expression and reduced ASL volume in CFBE cells.
Nasal inflammation is increased in cigarette smokers who switch to e-cigarettes

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\textsuperscript{1}Division of Pulmonary and Critical Care Medicine, University of Kansas Medical Center, Kansas City, KS, USA
\textsuperscript{2}Department of Medicine, Miller School of Medicine, University of Miami, Miami, FL USA

Rationale:
Vaping from electronic cigarettes (e-cigs) is generally believed to be safer than tobacco smoking and has been touted as a way to help smokers quit. Thus, we investigated the change in inflammatory parameters and mucins in the upper airways of smokers who switched to nicotine-containing e-cigs and compared these with subjects that continued to smoke.

Methods:
Inflammation marker and mucin mRNA levels were assessed in human nasal epithelial cells (HNECs) from smoking subjects and never-smoking, never-vaping subjects. MMP9 activity, MUC5AC and TGF-\(\beta\)1 proteins were analyzed from nasal fluids. Smokers (43-55 pack-year history) were recruited for the study and seen weekly over a period of 16 weeks to assure compliance. The 16 weeks were divided into two phases: 1) subjects switched from tobacco to e-cigs for 4 weeks, and 2) subjects who successfully switched for 4 weeks were asked to continue sole e-cig use for an additional 12 weeks. Subjects were trained to vape e-cigs (Joyetech e-Vic Supreme) that objectively record vaping habits. The e-liquid contained 50%/50\% w/v propylene glycol/vegetable glycerin (PG/VG) with 12 mg/mL nicotine. Exhaled CO (exCO) and venous carboxyhemoglobin (COHb) were measured weekly. Levels >6 ppm exCO and >1.6\% COHb were considered markers of active tobacco smoking and these subjects were terminated from the study. Nasal cells were collected by brushing and assayed for inflammatory marker and mucin mRNAs by qPCR. Blood samples were used for cotinine level determination in the smokers switching to e-cigs group only.

Results:
Compared to non-smokers, HNECs from smokers showed elevated TGF-\(\beta\)1, MMP-9, and MUC5AC mRNA levels with no significant difference in MUC5B mRNA. TGF-\(\beta\)1 protein expression remained unchanged in subjects that continued to smoke, but both MMP9 activity and TGF-\(\beta\)1 expression were significantly increased in smokers who switched to e-cigs. Neither group showed significant changes in MUC5AC protein expression. Cotinine levels showed no significant changes between the beginning and the end of the study for smokers switching to e-cigs.

Conclusion:
Together, our results demonstrate that smokers trying to quit using nicotine-containing e-cigs seem to show a further increase in nasal inflammation and that switching to vaping does not reduce mucin production.
Increasing Access to Expert Leukemia Care: Our Leukemia Hotline Experience

Ritika Halder, Fourth Year Medical Student, Ghulam Rehman Mohyuddin, M.D., Tara Lin, M.D.

Acute myeloid leukemia (AML) is the most common acute leukemia in adults. It has been shown that patients with AML who receive initial treatment at NCI designated cancer centers have reduced mortality as compared to those receiving treatment elsewhere.

Initiatives to facilitate referral of patients to such institutions thus have the potential to reduce mortality. At KUMC, the acute leukemia hotline is a resource that provides patients, community oncologists, emergency medicine and primary care providers access to experts if a patient presents with possible acute leukemia. This helpline is staffed by a bone marrow transplant physician at all times.

This hotline was established in July 2017 and has received 83 calls since that time. Amongst those 83 calls, 4 out of the 12 documented patients came to the KU Hospital for further evaluation. An additional 2 were taken to other high-volume centers. Final diagnosis was AML in 7, APL in 1, CLL in 1, and ALL in 1 of the patients. For additional calls, advice was provided over the phone, with no further confirmatory diagnosis obtained at high-volume centers.

9 transplant physicians were surveyed on their experiences regarding this hotline. On a 5-point Likert scale, all providers felt that this initiative provides an important service to the community with a mean score of 4.8. The physicians were also surveyed on the impact of this hotline adding to their workload and responsibilities. On a Likert scale with 5 indicating this to be a very onerous task, the median score among the providers was a 2.3, indicating that physicians felt this did not add to their workload significantly.

We systematically screened the websites of all NCI designated cancer centers to see if they had similar programs in place and did not find other programs to have such helplines.

Given the clear improvement in outcomes of patients with leukemia treated at high-volume centers we propose that our success with this hotline be replicated at other institutions to allow providers timely access to experts. Our model can be replicated by other institutions with the goal of improving outcomes for patients with acute leukemia.
The majority of recurrences post endoscopic therapy occur in the first year post treatment and occur in the distal esophagus: Results from a large multicenter Barrett’s esophagus consortium.

Authors: Viveksandeep Thoguluva Chandrasekar\(^1\), Chandra Shekhar Dasari\(^1\), Ramprasad Jegadeesan\(^1\), Rajesh Krishnamurthy\(^2\), Marco Spadaccini\(^3\), Kianoush Danboli\(^4\), Madhav Desai\(^1\), Abhiram Duvvuri\(^1\), Harsh Patel\(^1\), Tarun Rai\(^1\), Prashanth Vennalaganti\(^1\), Anjana Satyamurthy\(^1\), Divyanshoo Kohli\(^1\), Andrew Ross\(^2\), Alessandro Repici\(^3\), Irving Waxman\(^4\), Prateek Sharma\(^1\)

Affiliations:

1. University of Kansas Medical Medical Center/ VA Medical center, Kansas City, USA
2. Virginia Mason Medical Center, Seattle, USA
3. Humanitas Clinical and Research Center and Humanitas University, Rozzano, Italy
4. University of Chicago, Chicago, USA

Background:
Recurrence of Barrett’s esophagus (BE) after successful endoscopic eradication therapy (EET) has been reported but the exact location of recurrences (cardia vs distal esophagus vs proximal esophagus) and time line of recurrence is not clear.

Methods:
We report results from a multi-center consortium of BE patients with neoplasia that were treated with EET including either endoscopic mucosal resection (EMR), radiofrequency ablation, argon plasma coagulation, or multimodal therapy and achieved complete eradication of intestinal metaplasia (CE-IM). Patients who had recurrence of intestinal metaplasia and/or any dysplasia after achieving CE-IM were identified and their surveillance endoscopy data was reviewed for biopsy results and grade of dysplasia, location of recurrence and time of recurrence post CE-IM. Distal esophagus was defined as the distal 2 cm of the esophagus from the gastroesophageal junction (GEJ).

Results:
Of 455 patients who underwent EET, 73 patients had recurrences (mean age 68.9 ± 10.7 years, males 88%). Total follow up duration was 5.6 years. Recurrences were noted in esophageal biopsies in 63 (86%) patients (with 70 recurrence sites) while 10 patients (14%) had recurrences in cardia. Among esophageal biopsies, 10 recurrences were found in targeted biopsies (14%) all of which were found in the distal esophagus and 60 recurrences (in 53 patients) were from random biopsies (86%). Among those 60 random biopsies, 50 were from the distal esophagus and 10 were from the proximal esophagus. Seven patients had recurrence in more than 1 location. Majority (57%, n=42) of recurrences were noted within the first year followed by 42.4%, after the first year post CE-IM (10 recurrences in 2nd year, 8 in 3rd year and 5 in 4th year and 8 recurrences after year 4) with a mean time to recurrence of 2.9 years. Time to recurrence was similar for IM (5.8 years) vs LGD (5.2 Years) vs HGD (5.8 years).

Conclusion:
Majority of the recurrences after successful therapy occur within the 1\(^{st}\) year and probably represent residual disease versus true recurrences. Most recurrences were from random biopsies compared to targeted biopsies and the most common location was in the distal esophagus within 2 cms of the GEJ.
Table 1. Number and location of recurrences

<table>
<thead>
<tr>
<th>Target vs Random biopsies and location of recurrence</th>
<th>Recurrences total n= 73</th>
<th>Recurrences year one n=42</th>
<th>Recurrences year 1-2, n=10</th>
<th>Recurrences year 2-3, n=8</th>
<th>Recurrences year 3-4, n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>cardia recurrences</td>
<td>10(13.7)</td>
<td>4(9.5)</td>
<td>1(10)</td>
<td>1(12.5)</td>
<td>2(40)</td>
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<tr>
<td>Proximal esophagus</td>
<td>10(13.7)</td>
<td>8(19.5)</td>
<td>1(10)</td>
<td>1(12.5)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Distal esophagus</td>
<td>50(68.4)</td>
<td>29(69)</td>
<td>8(80)</td>
<td>5(62.5)</td>
<td>3(60)</td>
</tr>
<tr>
<td>Target</td>
<td>10(13.7)</td>
<td>7(16.6)</td>
<td>0(0)</td>
<td>2(25)</td>
<td>0(0)</td>
</tr>
</tbody>
</table>
Which technique is better: EUS vs ERCP guided biliary drainage for distal malignant biliary obstruction: A systematic review and meta-analysis

Authors:

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Affiliations:

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2. University of Missouri Kansas City, Kansas City, USA
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Background:

While endoscopic retrograde cholangiopancreatography (ERCP) is the current standard of care for the treatment of distal malignant biliary obstruction (MBO), the role of endoscopic ultrasound (EUS) as first line treatment of MBO has not been established.

Methods:

An electronic database search was conducted for studies comparing EUS and ERCP guided biliary drainage as first line treatment for distal MBO. Studies which included patients who had failed ERCP were excluded. The primary outcomes were: incidence of post procedure adverse events. Secondary outcomes were: rate of technical success (successful stent deployment); rate of clinical success (reduction in serum total bilirubin by > 50% within 4 weeks); mean procedure duration and need for re-intervention after clinical success. Pooled rates were expressed as proportions with 95% confidence limits.

Results:

A total of 5 studies (3 RCTs, 2 retrospective) were included in the final analysis with 157 patients in the EUS group (54% males; mean age 68 years) and 255 patients in ERCP group (53.3% males; mean age 67.8 years). The overall rate of adverse events was not significantly different between the EUS and ERCP groups: 17.8% vs 22.4% respectively (OR: 0.96, CI: 0.27 - 3.43, I²: 78%, p= 0.95). Similarly, there were no significant differences between the 2 groups for individual adverse events (Table 1). The secondary outcomes for the EUS and ERCP groups were as follows: technical success—94.9 % vs 96.9 % (OR: 0.91, CI: 0.35–2.37); clinical success—89.1 % vs 91.5 % (OR: 0.89, CI: 0.41 – 1.95), mean procedure duration—28.9 vs 27.9 minutes (SE: -1.3, 95% CI: -9.53 to 2.72) and need for re-intervention—11.8% vs 23.3% (OR: 0.49, CI: 0.13–1.90, p=0.3) respectively with no statistically significant difference between both groups. Eight patients in each group were treatment failures but eventually underwent successful stent placement with the other treatment modality.

Conclusion:

This meta-analysis comparing EUS vs ERCP guided biliary drainage for malignant biliary obstruction shows that there are no significant differences between the 2 techniques in terms of adverse events and efficacy. EUS-guided biliary drainage should be considered as a viable alternative to ERCP for this patient population.
<table>
<thead>
<tr>
<th>Events</th>
<th>EUS vs ERCP</th>
<th>OR with CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Total adverse events</td>
<td>17.8% vs 22.4%</td>
<td>OR: 0.96, CI: 0.27 - 3.43</td>
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<tr>
<td>Post-procedural pancreatitis</td>
<td>0.6% vs 8.6%</td>
<td>OR: 0.30, CI: 0.07: 1.23</td>
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<tr>
<td>Acute cholecystitis</td>
<td>2.5% vs 3.5%</td>
<td>OR: 1.21, CI:0.36–4.09</td>
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<td>Cholangitis</td>
<td>6.3% vs 4.9%</td>
<td>OR: 1.44, CI:0.38–5.93</td>
<td>0.60</td>
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<tr>
<td>Bile leak</td>
<td>2.3% vs 0%</td>
<td>OR: 3.76, CI:0.79–20.25</td>
<td>0.10</td>
</tr>
<tr>
<td>Technical success</td>
<td>94.9% vs 96.9%</td>
<td>OR: 0.91, CI: 0.35–2.37</td>
<td>0.70</td>
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<tr>
<td>Clinical success</td>
<td>89.1% vs 91.5%</td>
<td>OR: 0.89, CI: 0.41 – 1.95</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean procedure duration</td>
<td>28.9 mins vs 27.9 mins</td>
<td>SE: -1.3, 95% CI: -9.53 to 2.72</td>
<td>0.28</td>
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<tr>
<td>Stent patency duration</td>
<td>256.3 days vs 246 days</td>
<td>SE:16.5, 95% CI: -42.7 to 22.2</td>
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</tr>
<tr>
<td>Need for re-intervention</td>
<td>11.8% vs 23.3%</td>
<td>OR: 0.49, CI: 0.13–1.90</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Risk of advanced metachronous neoplasia is lower in patients with multiple diminutive vs small adenomas: systematic review and meta-analysis

Hamade, Nour; Chandrasekar, Viveksandeep Thoguluva; Desai, Madhav; Kennedy, Kevin; Dasari, Chandra; Rai, Tarun; Kohli, Divyanshoo; Sharma, Prateek

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Background: Post-polypectomy surveillance of 3-10 sub-centimeteric non-advanced adenomas requires repeat colonoscopy in 3 years without distinguishing between diminutive (1-5mm) and small (6-9mm) polyps. However, there is evidence that diminutive polyps may not carry the same risk of metachronous advances neoplasia (AN) as small polyps. We performed a systematic review and meta-analysis to evaluate the risk of metachronous AN in patients with diminutive vs small polyps.

Methods: A comprehensive electronic database (PubMed, Cochrane, and Google Scholar) search was conducted. Studies reporting risk of metachronous AN in patients with <10, sub-centimeteric non-advanced adenomas at baseline colonoscopy with at least 3 years of follow up were included. Patients were divided into three groups based on the number and size of adenomas: a '<3 adenomas' group with baseline 1-2 non-advanced adenomas, a 'diminutive' group with patients with 3-9 non-advanced diminutive adenomas, and a 'small' group with patients with 3-9 non-advanced small adenomas. Pooled rate of progression to metachronous AN in the 3 groups was calculated and compared using Odds Ratio (OR) with 95% CI with p-value <0.05 for statistical significance. Review manager 5.3 and R version 3.5 were used for statistical analysis.

Results: 3 retrospective studies (2 in South Korea, 1 in Israel) were eligible for analysis. This included 5999 patients in the <3 adenomas group, 668 in the diminutive group, and 490 in the small group. The mean age was 56.6 years (68.8% male), and overall mean duration of follow up was 36.6 months. The odds ratio of developing metachronous AN were 1.48(95% CI 1.05-2.09; p=.027) in group diminutive vs <3 adenomas, 2.79(95% CI 2.04-3.83; p<.001) in group small vs <3 adenomas, and 0.53(95% CI 0.35-0.82; p=.005) in group diminutive vs small. No study heterogeneity (I2=0%) was found.

Conclusion: These results demonstrate that in patients with 3-9 non-advanced adenomas, risk of progression to metachronous AN is significantly lower with diminutive vs small adenomas. The difference in risk of diminutive vs <3 adenomas barely reached significance. This suggests size of adenomas, independent of adenoma number, is a risk factor for development of metachronous AN and may be used for risk stratification of patients undergoing surveillance colonoscopy.
Figure 1: OR of metachronous AN in group diminutive vs group low risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95% CI</th>
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<td>Arbb 2017</td>
<td>1.25</td>
<td>1.25</td>
<td>[0.45; 3.50]</td>
</tr>
<tr>
<td>Moon 2018</td>
<td>1.36</td>
<td>1.36</td>
<td>[0.80; 3.06]</td>
</tr>
<tr>
<td>Kim 2018</td>
<td>1.55</td>
<td>1.55</td>
<td>[1.03; 2.34]</td>
</tr>
</tbody>
</table>

Random effects model
Heterogeneity $\chi^2 = 0\%, p = 0.27$

OR = 1.48 [1.95; 2.09]

Figure 2: Group diminutive vs Group small

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbib 2017</td>
<td>0.62</td>
<td>0.62</td>
<td>[0.17; 2.27]</td>
</tr>
<tr>
<td>Moon 2018</td>
<td>0.49</td>
<td>0.49</td>
<td>[0.16; 1.47]</td>
</tr>
<tr>
<td>Kim 2018</td>
<td>0.53</td>
<td>0.53</td>
<td>[0.32; 0.88]</td>
</tr>
</tbody>
</table>

Random effects model
Heterogeneity $\chi^2 = 0\%, p = 0.005$

OR = 0.63 [0.35; 0.82]
Applying the Principles of Blooms’ Taxonomy to Managing Tachyarrhythmia: Results of a Tachyarrhythmia Workshop

Ghulam Rehman Mohyuddin, Nicholas Isom, Kevin Mulhern, Laura Thomas

INTRODUCTION:
Resident physicians are routinely required to evaluate and manage patients with tachyarrhythmias. We developed a comprehensive workshop in an effort to improve resident competence and confidence at managing tachyarrhythmias.

METHODS:
A total of 55 resident physicians all were confidentially pre-tested prior to, and post tested following this workshop, in which they were asked to identify 5 different tachyarrhythmias and suggest management and describe their comfort level managing patients with arrhythmias. They then participated in an interactive 1-hour session in which a cardiologist discussed common tachyarrhythmias and their management. The residents were then divided in groups of 4-5. Using mannequins connected to heart monitors, the residents would be provided with a clinical vignette and asked to identify the heart rhythm and suggest management. A mock medication cart, and actual defibrillators/cardioversion were available. If the resident physician were to deliver cardioversion appropriately, the rhythm would change to sinus, and the patient’s hemodynamics would improve, thus providing live feedback for correct management.

RESULTS:
Amongst the 55 residents that participated in this study, the mean scores were 13.1 for pre-testing and 17.9 for post-testing respectively (p=0.0001). Residents mean comfort levels at managing tachyarrhythmias was 2.6 prior to testing and 3.6 post-testing (p=0.0001).

DISCUSSION:
We demonstrate that a 2-hour focused tachyarrhythmia workshop significantly improved residents comfort level and competence at managing patients with tachyarrhythmia. By focusing on the higher levels of Blooms’ taxonomy such as analysis, synthesis and evaluation, we were able to improve the educational experience for our resident physicians.
Development of a Simulated Patient Experience to Practice Care of the Dying Older Adult

Déon Cox Hayley, DO, Jessica L. Kalender-Rich, MD, Julie Mack, MS, Daniel Swagerty, MD, MPH

Introduction: Care of the dying older adult includes critical skills that emerging physicians should master but are not consistently taught. Simulation has been shown to be an excellent tool for teaching these skills in a standardized fashion. Simulation allows direct observation to guide ideal assessment and feedback of learner performance. We developed a hybrid simulation experience to practice and assess care of the dying older adult and identify gaps in skills wherein, in a quality improvement fashion, one can emphasize future teaching.

Methods: Learners care for a 70 year old patient (Laerdal SimMan 3G) who is actively dying in the Emergency Department and his wife (standardized patient) with a standardized nurse. Over the academic year 2012-2013, we observed and videotaped 83 fourth year medical students and 22 first year Internal Medicine residents in this setting. We assessed the learners’ completion of 15 tasks associated with good end-of-life care.

Results: All of the learners demonstrated professional activity working with the standardized nurse and all but one medical student gave narcotics appropriately for pain. Only 19% of the medical students appropriately disclosed the patient’s status to the wife using the words “death” or “dying” and only 50% of the IM residents did so.

Discussion: We successfully developed a Medical Education program in which learners can be assessed in their end-of-life skills caring for the older adult. We also determined that we can improve our educational efforts in the area of communication, especially through the use of the words “death” or “dying.”

Published:

Simulated Home Visits as a Method of Increasing Recognition of Environmental Cues about Health Status

Déon Cox Hayley, DO; James T. Birch, Jr, MD, MSPH, CMD; Dory Sabata, OTD; Jessica Kalender-Rich, MD

Background: Older adults spend most of their lives in their homes and yet are almost always observed by medical professionals in a clinical setting. Early medical school exposure to caring for older adults in their homes increases awareness, empathy and understanding of community resources. While in person home visits would be ideal for each medical student, this has not been feasible due to faculty time constraints, thus simulation may provide an acceptable alternative to teach students how to consider cues in the home environment.

Methods: In academic year 2016-17 all third year Medical Students in their Geriatrics Clerkship at the University of Kansas on alternate months either individually visit a standardized apartment or an electronic simulation of that same apartment after a web module on "Home Care & Assessment of Community-Dwelling Elderly." Each student was given 10 minutes to assess the environment for clues to the patient’s safety and well-being and then complete an on-line standardized assessment. Assessment includes Yes/No questions and options for open ended responses. Student responses were compared to standard.

Each student then made a physical house call during the Clerkship with an attending. After this house call, the student and attending separately completed the same assessment on-line and responses were compared.

Results: 77 students completed the standardized apartment visit surveys. More students noted concerns about multiple prescribers (on prescription bottles) in the virtual apartment. In both settings, the items with the lowest recognition of problems were medication organization and adherence. Most important area of discrepancy between Geriatricians and students in home visit documentation was that students underestimated caregiver stress and the physical difficulty of care.

Conclusion: There were environmental concerns in each of these settings that students did not note and students may need more detailed instructions about medication reconciliation. While the knowledge gained in an actual home visit is irreplaceable, this is limited without dedicated faculty. In this case, both physical and virtual apartments were well received and the debriefing ensured standardized content. In several cases, the virtual visit led to more detail oriented observations (e.g., safety and multiple prescribers) than the physical apartment.
TITLE: E-liquid with nicotine causes mucociliary dysfunction via TRPA1 receptors in a novel large animal model of exposure

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¹ University of Kansas Medical Center, Kansas City, KS
² University of Miami, Miller School of Medicine, Miami, FL
³ Mount Sinai Medical Center, Miami Beach, FL

RATIONALE:
E-cigarette (EC) vaping is marketed as a safer alternative to tobacco smoking. However, growing evidence of EC vapors causing chronic bronchitis in never-smoking adolescents is a concern. Chronic bronchitis is a consequence of mucociliary dysfunction. To test the effect of vaping on an intact mucociliary clearance (MCC) system, we developed a large animal model using sheep.

METHODS:
All procedures were approved by MSMC’s IACUC. Sheep were conscious and intubated using local anesthesia. Methods for measuring tracheal mucus velocity (TMV) were published previously. Aerosols with 50%/50% PG/VG were generated with an Airlife nebulizer using a dosimetry system with a piston respirator to deliver aerosols directly into the trachea during inspiration (20 breaths/min; tidal volume 500 mL; ~10% epithelial deposition). Vapor was drawn from an EC (e-Vic Supreme, Joyetech) into a 60-mL syringe and emptied into the inspiration tubing of the respirator. Serial blood cotinine levels were measured to assess nicotine uptake. Percent mucus solids from tracheal secretions was measured according to published methods.

RESULTS:
PG/VG alone and PG/VG with nicotine depressed TMV in a nicotine-dose dependent manner with a duration of ~6h to 50% of baseline after 15 or 20 mg nicotine. Repeated aerosol challenges after 6h prolonged TMV reduction for at least another 6h. Cotinine levels after aerosolized PG/VG+15 mg nicotine were high and equal to human consumption of ~3 tobacco cigarettes. Vaping PG/VG with 36 mg/mL nicotine into sheep caused reductions in TMV similar to aerosolizing PG/VG+20 mg nicotine. The decrease in TMV with aerosolized PG/VG+15 mg nicotine was blocked by pretreatment with 20 mg A967079, a TRPA1 inhibitor and prevented the increase in mucus solids concentration. Interestingly, cotinine levels did not change compared to baselines, indicating the poor nicotine delivery by vaping.

CONCLUSIONS:
EC vapor and fluid caused significant decreases in TMV and this reduction was dependent on TRPA1. This novel ovine exposure model is useful to examine the effects of EC vapor because: 1) sheep airways resemble human airways regarding MCC more closely than rodent airways; 2) exposures can be controlled and MCC measured in a non-anesthetized, awake animal; and 3) chronic exposures will be manageable.
Losartan decreases airway inflammation and mucin concentration

Nathalie Baumlin, John S. Dennis, Makoto Yoshida, Carolina Aguiar, Andreas Schmid, Eliana Mendes, Michael Kim, Matthias Salathe

**Rational:** Cigarette smoke-induced inflammation and mucus hypersecretion are distinguished features of chronic airway diseases without efficient therapeutic options available. Losartan is an FDA approved and widely used angiotensin II receptor blocker (ARB) exerting anti-inflammatory effects by inhibiting TGF-$\beta$ signaling. In this study, we investigated whether losartan can reduce inflammation and mucus hyperconcentration in human airways *in vivo* and *in vitro*.

**Methods:** Human nasal epithelial cells (HNEC) from smokers without COPD and nonsmokers taking losartan over a period of two months were analyzed by quantitative PCR for the inflammation markers TGF-$\beta$1 and MMP9 as well as mucin MUC5AC. Freshly isolated tracheal tissues from smokers and nonsmokers were stained for MUC5AC. Primary human bronchial epithelial cells (HBEC) from smokers and nonsmokers post overnight protease digestion (P0) were examined in comparison to HNEC. Fully re-differentiated HBEC (P1) from nonsmokers with and without losartan treatment, were exposed to cigarette smoke using a smoke robot to replicate and confirm *in vivo* data. *In vitro* parameters of mucociliary clearance were investigated.

**Results:** HNEC of smokers have elevated levels of MUC5AC, TGF-$\beta$1 and MMP9 mRNA levels compared to nonsmokers. Two months treatment with losartan significantly reduced these markers with no effect in nonsmokers. Immunofluorescent staining of tracheal tissues revealed increased expression of MUC5AC in smokers. HBEC P0 showed significantly increased MUC5AC expression in smokers compared to nonsmokers but no difference was recorded in HBEC P1. Cigarette smoke exposure of HBEC P1 from nonsmokers increased expression levels of MUC5AC and TGF-$\beta$1 and caused mucociliary dysfunction by decreasing CFTR and BK channel activities and ASL volumes as well as by increasing mucus solids. Losartan restored mucociliary clearance *in vitro* and markedly decreased MUC5AC expression and mucus concentrations.

**Conclusions:** This is the first report that shows the efficacy of losartan as an anti-inflammatory drug to treat airway inflammation and mucus hypersecretion, both hallmarks of many airway diseases such as COPD, cystic fibrosis, and asthma. Losartan is an affordable, FDA approved medication that could be immediately made available for the treatment of chronic airway inflammation and mucus hypersecretion in smoking-related and other airway diseases.
Low Rates of 30-day post Colonoscopy related major adverse events: Data from more than 5000 procedures in a large tertiary care medical center

AUTHORS: Poddutoori, Padma1; Gachpaz, Babak1; Duvvuri, Abhiram1; Vennelaaganti, Sreekar1; Jegadeesan, Ramprasad1; Vennelaaganti, Prashanth1; Aziz, Muhammad1; Vittal, Anusha1; Singh, Pratiksha1; Kennedy, Kevin F.1; Rai, Tarun1; Parasa, Sravanthi3; Choudhary, Abhishek1; Bansal, Ajay1; Gupta, Neil2; Sharma, Prateek1

INSTITUTIONS: 1. Department of Gastroenterology and Hepatology, Kansas City VA medical Center, Kansas City, MO, United States. 2. Department of Gastroenterology and Hepatology, Loyola University, Chicago, IL, United States. 3. Department of Gastroenterology and Hepatology, Case Western Univeristy, Kansas City, MO, United States.

Background: Un-anticipated ER visit and/or hospitalization within 30 days following outpatient screening/surveillance colonoscopy are an endoscopy quality measure, but data in the US are limited. Our aim was to determine the rates of ER visits and hospitalization in the 30-day period following colonoscopy in a large cohort of patients.

Methods: Data of the patients who underwent colonoscopy between January 2005 to November 2015 were retrospectively collected from a single tertiary care center. Data were also collected on ER visits and hospitalization in the 30 day period following colonoscopy (including number of visits, reason for the visit, primary diagnosis of the visit and length of stay). Charlson comorbidity index [CCI] score was calculated to assess the impact of comorbidity on healthcare utilization. We grouped the procedure related complications into directly associated with procedure [abdominal pain, GI bleeding and perforation] and complications from anesthesia [cardiopulmonary complications and hiccups].

Results: During the specified time frame, 2997 patients underwent 5086 procedures; mean age 64.1 years; 95% males and 68% Caucasians. The indications for colonoscopy were: screening for CRC (38%); surveillance for CRC (42%) and diagnostic (20%). The overall 30 day complication rate post colonoscopy included: 3% ER visits and 2.4% hospitalization. However, the majority of the ER/hospitalizations 102 (2%) were unrelated to procedure, whereas 98 (1.9%) of ER/hospitalizations were procedure related. Post procedure complications requiring ER visit and/or hospitalization were as follows: (1) 47 (0.9%) GI bleeding, (2) 25 (0.5%) cardiopulmonary complications (3) 20 (0.4%) abdominal pain (4) 3 (0.06%) perforation and (5) 1 (0.02%) peritonitis. The mean CCI scores were significantly higher in patients who required hospitalization (6.2 vs 5.0, p=0.010). The mean time to presentation to the ER after colonoscopy was 11.8 +/- 9.2 days, of which GI bleeding presented at 5.4+/-.5.5 and abdominal pain at 10.4+/-.9.3. Finally, for those subjects requiring hospitalization, the average length of stay was 5.9 days.

Conclusions: In a large cohort of patients undergoing colonoscopy, the overall 30-day procedure related major complications needing healthcare visits were low
Scheduled Meetings with Counseling and Educational Support Services to Promote Resident Wellness  
Jane Broxtermam, Debra Altenhofen, Amanda Jobe, Leigh Eck, University of Kansas

Description of How Program was Identified and Explored  
In the current healthcare climate, depression and burnout are significant risks for all physicians especially those in training. Unfortunately, mental health services offered to physicians are often underutilized. The University of Kansas Internal Medicine (KUIM) Residency Program has coordinated with its Counseling and Educational Support Services (CESS) Department to allow residents to receive mental health services free of charge. However, many residents have not taken advantage of this assistance. Review of other residency programs’ efforts to promote mental health wellness revealed common barriers to mental health resource utilization: scheduling conflicts, confidentiality concerns and stigma.

Description of the Innovations  
To overcome identified barriers and increase awareness of available mental health services, elective but encouraged meetings with a CESS psychologist were scheduled for KUIM residents. The CESS visits were scheduled for residents by department personnel in lieu of other clinical commitments. The intervention, modeled after a similar innovation at West Virginia University, decreased perceived stigma with universal scheduling, eliminated scheduling conflicts and assured confidentiality. Focus of the meetings was evaluation of a resident’s mental health, resiliency, and review of support systems. The primary goal of the intervention was to familiarize residents with CESS so residents could independently and comfortably attain mental health support.

Results to Date  
Thirty-five of 52 residents scheduled for meetings with CESS actively engaged with the program. Only 27% (9 out of 33) of residents utilized CESS prior to their scheduled meetings, and of those that had not, only 54% (13 out of 24) knew how to schedule an appointment. Residents felt it was helpful (mean 4.11/5) and convenient (mean 4.04/5) to have introductory meetings scheduled by the program and were less likely to have scheduled on their own (mean 2.04/5). In comparing pre- and post-meeting surveys, the perceived value of the meeting improved (48.5% answered “moderately valuable” or “highly valuable” on the pre-meeting survey as compared to 64.3% on the post-meeting survey), and the likelihood that residents would utilize CESS in time of need increased (48.5% answered “likely” or “extremely likely” on the pre-meeting survey as compared to 60.7% on the post-meeting survey).

Discussion/Reflection/Lessons Learned  
The overall attitude towards meetings with CESS was positive, and residents felt the program should continue to facilitate meetings. Scheduling residents for introductory meetings with CESS may help to eliminate barriers or stigma associated with the utilization of counseling services.
Ballon-Occluded Retrograde Transvenous Obliteration (BRTO) versus Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the management of gastric variceal bleeding: A Systematic Review and Meta-Analysis

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2 Washington University School of Medicine, St. Louis, MO, USA, Internal Medicine Department, Division of Gastroenterology and Hepatology
3 University of Kansas Medical Center, Internal Medicine Department
4 Lebanese University School of Medicine, Beirut, Lebanon

Objectives: Gastric variceal bleeding presents a clinical challenge in cirrhotic patients with portal hypertension. Compared to esophageal varices, bleeding from Gastric varices is more difficult to treat, with a higher mortality rate that can be up to 55%. Transesjugular Intrahepatic Portosystemic Shunt (TIPS) is widely used, and has been the standard of care in most centers for the management of gastric varices. However, the use of Balloon-Occluded Retrograde Transvenous Obliteration (BRTO) has been significantly increased with promising results. Due to the controversy in the literature, we aimed to perform a meta-analysis comparing BRTO versus TIPS in the management of gastric variceal bleeding.

Methods: A comprehensive search of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Scopus was performed from each database’s inception to May, 25th, 2018. Two independent reviewers systematically identified trials that compared the effect of BRTO versus TIPS in the management of gastric variceal bleeding. A meta-analysis was performed using a fixed effects model to assess the primary outcome (Mortality rate), and secondary outcomes (rebleeding rate, hemostasis, development of hepatic encephalopathy, and development of new/worsening ascites). Review Manager 5.3 software program was used for statistical analysis.

Results: Six studies met our inclusion criteria and included in the analysis, with a total of 500 patients. Our meta-analysis demonstrated a decreased mortality rate with the use of BRTO compared to TIPS (RR: 0.44, 95% CI: 0.35-0.56, p<0.01, heterogeneity I²: 0%). It also showed that the use of BRTO was associated with a decreased rebleeding risk (RR: 0.38, 95% CI: 0.24-0.59, p<0.01, heterogeneity I²: 0%), decreased hepatic encephalopathy risk (RR: 0.07, 95% CI: 0.03-0.16, p-value<0.01, heterogeneity I²: 0%), but no statistically significant difference in hemostasis (RR: 1.01, 95% CI: 0.95-1.07, p=0.73, heterogeneity I²: 19%), major complications (RR: 0.82, 95% CI: 0.24-2.77, p=0.74, heterogeneity I²: 53%), technical success (RR: 0.94, 95% CI: 0.86-1.03, p=0.18, heterogeneity I²: 73%) or worsening ascites (RR: 2.40, 95% CI: 0.97-5.95, p=0.06, heterogeneity I²: 0%).

Conclusion: Our systematic review and meta-analysis indicated that the use of BRTO appeared to be superior to TIPS in decreasing mortality, rebleeding risk, and hepatic encephalopathy in patients with gastric variceal bleeding.
Figure- 1: Forrest plots of meta-analysis comparing BRTO versus TIPS in gastric variceal bleeding and mortality risk.

<table>
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<th>TIPS Events</th>
<th>Total Events</th>
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<td>3.6%</td>
</tr>
</tbody>
</table>

Random effects model 194 119 0.44 [0.35; 0.56] 100.0%

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.79$
Test for overall effect: $z = -5.64$ ($p < 0.01$)

Figure- 2: Forrest plots of meta-analysis comparing BRTO versus TIPS in gastric variceal bleeding and risk of rebleeding.

<table>
<thead>
<tr>
<th>Study</th>
<th>BRTO Events</th>
<th>Total Events</th>
<th>TIPS Events</th>
<th>Total Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi, 2003</td>
<td>0</td>
<td>8</td>
<td>1</td>
<td>13</td>
<td>0.53</td>
<td>0.02</td>
<td>11.56</td>
<td>2.1%</td>
</tr>
<tr>
<td>Lee, 2014</td>
<td>8</td>
<td>86</td>
<td>14</td>
<td>49</td>
<td>0.33</td>
<td>0.15</td>
<td>0.72</td>
<td>23.8%</td>
</tr>
<tr>
<td>Lee, 2012</td>
<td>4</td>
<td>68</td>
<td>12</td>
<td>32</td>
<td>0.16</td>
<td>0.05</td>
<td>0.45</td>
<td>15.4%</td>
</tr>
<tr>
<td>Kim, 2017</td>
<td>3</td>
<td>25</td>
<td>3</td>
<td>27</td>
<td>1.06</td>
<td>0.24</td>
<td>4.66</td>
<td>8.2%</td>
</tr>
<tr>
<td>Lee, 2017</td>
<td>22</td>
<td>95</td>
<td>23</td>
<td>47</td>
<td>0.47</td>
<td>0.30</td>
<td>0.76</td>
<td>45.8%</td>
</tr>
<tr>
<td>Sabri, 2013</td>
<td>1</td>
<td>23</td>
<td>6</td>
<td>27</td>
<td>0.20</td>
<td>0.03</td>
<td>1.51</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

Random effects model 305 195 0.38 [0.24; 0.59] 100.0%

Heterogeneity: $I^2 = 18\%$, $\tau^2 = 0.0591$, $p = 0.30$
Test for overall effect: $z = -4.24$ ($p < 0.01$)
Figure-3: Forrest plots of meta-analysis comparing BRTO versus TIPS in gastric variceal bleeding and risk of development/worsening hepatic encephalopathy.

<table>
<thead>
<tr>
<th>Study</th>
<th>BRTO Events</th>
<th>Total Events</th>
<th>TIPS Total</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi, 2003</td>
<td>0</td>
<td>8</td>
<td>4</td>
<td>0.18</td>
<td>0.01</td>
<td>[0.01; 0.28]</td>
<td>9.2%</td>
</tr>
<tr>
<td>Lee, 2014</td>
<td>0</td>
<td>86</td>
<td>14</td>
<td>0.02</td>
<td>0.00</td>
<td>[0.00; 0.32]</td>
<td>9.2%</td>
</tr>
<tr>
<td>Lee, 2012</td>
<td>3</td>
<td>65</td>
<td>17</td>
<td>0.08</td>
<td>0.03</td>
<td>[0.03; 0.26]</td>
<td>54.2%</td>
</tr>
<tr>
<td>Kim, 2017</td>
<td>0</td>
<td>25</td>
<td>5</td>
<td>0.08</td>
<td>0.00</td>
<td>[0.00; 1.40]</td>
<td>9.0%</td>
</tr>
<tr>
<td>Lee, 2017</td>
<td>0</td>
<td>95</td>
<td>14</td>
<td>0.02</td>
<td>0.00</td>
<td>[0.00; 0.28]</td>
<td>9.2%</td>
</tr>
<tr>
<td>Sabri, 2013</td>
<td>0</td>
<td>23</td>
<td>6</td>
<td>0.09</td>
<td>0.01</td>
<td>[0.01; 1.52]</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

Random effects model

Heterogeneity: $I^2 = 0\%$, $Q = 0$, $p = 0.78$
Test for overall effect: $z = 6.21$ ($p < 0.01$)

0.07 [0.03; 0.16] 100.0%

Figure-4: Forrest plots of meta-analysis comparing BRTO versus TIPS in gastric variceal bleeding in achieving hemostasis.

<table>
<thead>
<tr>
<th>Study</th>
<th>BRTO Events</th>
<th>Total Events</th>
<th>TIPS Total</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi, 2003</td>
<td>8</td>
<td>8</td>
<td>12</td>
<td>1.08</td>
<td>0.83</td>
<td>[1.26]</td>
<td>13.4%</td>
</tr>
<tr>
<td>Lee, 2017</td>
<td>95</td>
<td>95</td>
<td>47</td>
<td>1.00</td>
<td>0.07</td>
<td>[1.03]</td>
<td>86.6%</td>
</tr>
</tbody>
</table>

Random effects model

Heterogeneity: $I^2 = 19\%$, $Q = 0.0003$, $p = 0.27$
Test for overall effect: $z = 0.34$ ($p = 0.73$)

1.01 [0.95; 1.07] 100.0%

Figure-5: Forrest plots of meta-analysis comparing BRTO versus TIPS in gastric variceal bleeding in achieving hemostasis.
Figure-5: Forrest plots of meta-analysis comparing BRTO versus TIPS in gastric variceal bleeding and major complications.

<table>
<thead>
<tr>
<th>Study</th>
<th>BRTO</th>
<th>TIPS</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi, 2003</td>
<td>8</td>
<td>13</td>
<td>1.00</td>
<td>1.00</td>
<td>[0.82; 1.22]</td>
<td>12.6%</td>
</tr>
<tr>
<td>Lee, 2012</td>
<td>59</td>
<td>68</td>
<td>0.90</td>
<td>0.90</td>
<td>[0.80; 1.00]</td>
<td>20.9%</td>
</tr>
<tr>
<td>Kim, 2017</td>
<td>22</td>
<td>25</td>
<td>0.88</td>
<td>0.88</td>
<td>[0.77; 1.02]</td>
<td>17.6%</td>
</tr>
<tr>
<td>Lee, 2017</td>
<td>95</td>
<td>95</td>
<td>1.00</td>
<td>1.00</td>
<td>[0.97; 1.03]</td>
<td>29.2%</td>
</tr>
<tr>
<td>Sabri, 2013</td>
<td>21</td>
<td>23</td>
<td>0.91</td>
<td>0.91</td>
<td>[0.81; 1.03]</td>
<td>19.6%</td>
</tr>
</tbody>
</table>

Random effects model 219 146
Heterogeneity: $I^2 = 73\%$, $t^2 = 0.0072$, $p < 0.01$
Test for overall effect: $z = -1.34$ ($p = 0.18$)

0.8 1 1.25
Technical Success

Figure-6: Forrest plots of meta-analysis comparing BRTO versus TIPS in gastric variceal bleeding and technical success.

<table>
<thead>
<tr>
<th>Study</th>
<th>BRTO</th>
<th>TIPS</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi, 2003</td>
<td>0</td>
<td>2</td>
<td>0.32</td>
<td>0.32</td>
<td>[0.02; 5.85]</td>
<td>9.8%</td>
</tr>
<tr>
<td>Lee, 2014</td>
<td>13</td>
<td>13</td>
<td>3.70</td>
<td>3.70</td>
<td>[0.87; 16.74]</td>
<td>39.5%</td>
</tr>
<tr>
<td>Kim, 2017</td>
<td>1</td>
<td>2</td>
<td>1.08</td>
<td>1.08</td>
<td>[0.07; 16.36]</td>
<td>11.2%</td>
</tr>
<tr>
<td>Lee, 2017</td>
<td>13</td>
<td>95</td>
<td>3.22</td>
<td>3.22</td>
<td>[0.76; 13.67]</td>
<td>39.5%</td>
</tr>
</tbody>
</table>

Random effects model 214 136
Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $p = 0.44$
Test for overall effect: $z = 1.89$ ($p = 0.06$)

0.1 0.5 1 2 10
Ascites

Figure-7: Forrest plots of meta-analysis comparing BRTO versus TIPS in gastric variceal bleeding and risk of worsening ascites.
Early (Pre-emptive) TIPS versus Conventional Treatment for prophylaxis of esophageal variceal bleeding: A Systematic Review and Meta-Analysis

Shadi Hamdeh¹, Osama Altayar², Mohamed Aziz¹, Jihan Fathallah¹, Mojtaba Olyaee¹, Mohammad Hassan Murad³, John Lake⁴, Michael Sorrell⁵

¹University of Kansas Medical Center, Kansas City, KS, Division of Gastroenterology and Hepatology
²Washington University School of Medicine, St. Louis, MO, Division of Gastroenterology and Hepatology
³Mayo Clinic College of Medicine, Rochester, MN, Evidence-based Practice Center
⁴University of Minnesota Medical Center, Minneapolis, MN, Division of Gastroenterology and Hepatology
⁵University of Nebraska Medical Center, Omaha, NE, Division of Gastroenterology and Hepatology

Objectives: Variceal bleeding is a life threatening complication of cirrhosis that requires secondary prophylaxis after the acute bleed. Present guidelines recommend medical therapy as the first-line treatment, and TIPS for recurrent bleeding. Results from several studies including meta-analyses comparing best medical treatment versus early TIPS (within 72 hours following Baveno consensus) have been conflicting. Moreover, some studies included studies looking for salvage TIPS or secondary prophylaxis and included inappropriate studies. In this systematic review and meta-analysis, we aimed to discern whether early-TIPS is actually beneficial over conventional therapy in terms of mortality and rebleeding.

Methods: A comprehensive search of MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus was conducted until November 20, 2018 to search for comparative studies of TIPS for variceal bleeding. The outcomes of interest included all cause mortality, rebleeding rate, hepatic encephalopathy, new or worsening ascites, and adverse effects including sepsis.

Results: Seven studies with a total of 145250 patients were included. When early TIPS was used within 72h (pre-emptively), compared to conventional therapy, it was associated with an decreased overall mortality (RR: 0.58, 95% CI: 0.34-0.99, P-value <0.01), incidence of rebleeding at 6 weeks (RR: 0.16, 95% CI: 0.06-0.45, P-value<0.01), and development of new/worsening ascites (RR: 0.41, 95% CI: 0.26-0.66, P-value <0.01), but no difference in development of hepatic encephalopathy (RR: 1.10, 95% CI: 0.91-1.34, P-value 0.09), or sepsis rate (RR: 1.05, 95% CI: 0.83-1.31, P-value 0.09).

Conclusion: The current systematic review and meta-analysis showed that early pre-emptive use of TIPS for was superior to the best medical therapy in decreasing the overall mortality risk, the risk of rebleeding at 6 weeks, and development/worsening of ascites. There was no effect on hepatic encephalopathy or sepsis.
Figure- 1: Forrest plots of meta-analysis comparing TIPS versus conventional treatment and risk of mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Early TIPS Events</th>
<th>Conventional Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monesiscilo, 2004</td>
<td>8</td>
<td>26</td>
<td>0.40</td>
<td>[0.22; 0.74]</td>
<td>14.8%</td>
<td></td>
</tr>
<tr>
<td>Garcia-Pagan, 2010</td>
<td>4</td>
<td>32</td>
<td>0.32</td>
<td>[0.12; 0.89]</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>Garcia-Pagan, 2013</td>
<td>6</td>
<td>45</td>
<td>0.40</td>
<td>[0.16; 0.98]</td>
<td>12.1%</td>
<td></td>
</tr>
<tr>
<td>Rudler, 2014</td>
<td>9</td>
<td>31</td>
<td>1.12</td>
<td>[0.50; 2.53]</td>
<td>12.9%</td>
<td></td>
</tr>
<tr>
<td>Bucscis Theresa, 2017</td>
<td>38</td>
<td>49</td>
<td>1.26</td>
<td>[0.93; 1.70]</td>
<td>17.2%</td>
<td></td>
</tr>
<tr>
<td>Njei, 2017</td>
<td>11</td>
<td>713</td>
<td>0.28</td>
<td>[0.15; 0.50]</td>
<td>15.0%</td>
<td></td>
</tr>
<tr>
<td>Lv, 2018</td>
<td>29</td>
<td>206</td>
<td>0.61</td>
<td>[0.57; 1.16]</td>
<td>16.9%</td>
<td></td>
</tr>
</tbody>
</table>

Random effects model 105 1102 7897 137353 0.58 [0.34; 0.99] 100.0%

Heterogeneity: $I^2 = 85\%$, $\tau^2 = 0.4163$, $p < 0.01$

Figure- 2: Forrest plots of meta-analysis comparing TIPS versus conventional treatment and risk of rebleeding at 6 weeks

<table>
<thead>
<tr>
<th>Study</th>
<th>Early TIPS Events</th>
<th>Conventional Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monesiscilo, 2004</td>
<td>1</td>
<td>26</td>
<td>0.33</td>
<td>[0.04; 3.00]</td>
<td>11.2%</td>
<td></td>
</tr>
<tr>
<td>Garcia-Pagan, 2010</td>
<td>0</td>
<td>32</td>
<td>0.06</td>
<td>[0.00; 1.08]</td>
<td>8.4%</td>
<td></td>
</tr>
<tr>
<td>Garcia-Pagan, 2013</td>
<td>2</td>
<td>45</td>
<td>0.67</td>
<td>[0.10; 4.48]</td>
<td>12.8%</td>
<td></td>
</tr>
<tr>
<td>Rudler, 2014</td>
<td>0</td>
<td>31</td>
<td>0.05</td>
<td>[0.00; 0.87]</td>
<td>8.5%</td>
<td></td>
</tr>
<tr>
<td>Bucscis Theresa, 2017</td>
<td>4</td>
<td>49</td>
<td>0.23</td>
<td>[0.08; 0.66]</td>
<td>18.6%</td>
<td></td>
</tr>
<tr>
<td>Njei, 2017</td>
<td>4</td>
<td>713</td>
<td>0.04</td>
<td>[0.01; 0.10]</td>
<td>19.0%</td>
<td></td>
</tr>
<tr>
<td>Lv, 2018</td>
<td>12</td>
<td>206</td>
<td>0.29</td>
<td>[0.16; 0.50]</td>
<td>21.5%</td>
<td></td>
</tr>
</tbody>
</table>

Random effects model 23 1102 21221 137353 0.16 [0.06; 0.45] 100.0%

Heterogeneity: $I^2 = 74\%$, $\tau^2 = 1.1868$, $p < 0.01$
Figure- 3: Forrest plots of meta-analysis comparing TIPS versus conventional treatment and development/worsening ascites.

<table>
<thead>
<tr>
<th>Study</th>
<th>Early TIPS Events</th>
<th>Conventional Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monesolillo, 2004</td>
<td>8 26</td>
<td>9 26</td>
<td>0.89</td>
<td>[0.41; 1.94]</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td>Garcia-Pagan, 2010</td>
<td>8 32</td>
<td>12 31</td>
<td>0.65</td>
<td>[0.31; 1.36]</td>
<td>5.8%</td>
<td></td>
</tr>
<tr>
<td>Garcia-Pagan, 2013</td>
<td>23 45</td>
<td>15 30</td>
<td>1.02</td>
<td>[0.65; 1.62]</td>
<td>12.5%</td>
<td></td>
</tr>
<tr>
<td>Rudler, 2014</td>
<td>14 31</td>
<td>16 31</td>
<td>0.86</td>
<td>[0.52; 1.47]</td>
<td>10.5%</td>
<td></td>
</tr>
<tr>
<td>Bucsis Theresa, 2017</td>
<td>12 49</td>
<td>0 34</td>
<td>17.42</td>
<td>[1.07; 284.56]</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>Njie, 2017</td>
<td>215 713</td>
<td>37123 135982</td>
<td>1.10</td>
<td>[0.99; 1.24]</td>
<td>36.6%</td>
<td></td>
</tr>
<tr>
<td>Lv, 2018</td>
<td>77 206</td>
<td>333 1219</td>
<td>1.37</td>
<td>[1.12; 1.67]</td>
<td>28.9%</td>
<td></td>
</tr>
</tbody>
</table>

Random effects model 357 1102 37508 137353 1.10 [0.91; 1.34] 100.0%

Heterogeneity: $I^2 = 46\%$, $t^2 = 0.0232$, $p = 0.09$

Favors Early TIPS  Portosystemic Encephalopathy Risk

Favors Conventional Treatment

Figure- 4: Forrest plots of meta-analysis comparing TIPS versus conventional treatment and risk of hepatic encephalopathy

<table>
<thead>
<tr>
<th>Study</th>
<th>Early TIPS Events</th>
<th>Conventional Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rudler, 2014</td>
<td>17 31</td>
<td>16 31</td>
<td>1.06</td>
<td>[0.67; 1.70]</td>
<td>23.3%</td>
<td></td>
</tr>
<tr>
<td>Njie, 2017</td>
<td>53 713</td>
<td>96565 135982</td>
<td>1.05</td>
<td>[0.81; 1.36]</td>
<td>75.5%</td>
<td></td>
</tr>
<tr>
<td>Lv, 2018</td>
<td>1 206</td>
<td>8 1219</td>
<td>0.74</td>
<td>[0.03; 5.88]</td>
<td>1.2%</td>
<td></td>
</tr>
</tbody>
</table>

Random effects model 71 950 9679 137232 1.05 [0.83; 1.31] 100.0%

Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $p = 0.95$

Favors Early TIPS  Sepsis Risk

Favors Conventional Treatment

Figure- 5: Forrest plots of meta-analysis comparing TIPS versus conventional treatment and risk of sepsis
LAG3 Promotes Acute Myeloid Leukemia-Induced Immune Suppression

Haitham Abdelhakim, MD; Neil Dunavin, MD; Meizhang Li, PhD; Mitchell Braun, BS; Tara L Lin, MD; and Andrew K Godwin, PhD
University of Kansas Cancer Center, Westwood, KS

Background: Acute Myelogenous leukemia (AML) cells can inhibit activation and proliferation of immune cells in culture. We hypothesized that irradiating AML blasts would diminish their immune suppressive capacity while maintaining antigen presentation, leading to higher activation of CD8+ T cells among peripheral blood mononuclear cells (PBMC) in co-culture.

Methods: PBMC were isolated from healthy donors. PBMC were co-cultured with live human AML K-1 cells (CRL-2724) and irradiated K-1 cells (40 Gy) at the following ratios: 1:1, 1:2, 1:4 and 1:8. Cells were cultured in RPMI complete media supplemented with 10% FBS and IL-2 20 IU/ml. On day 3 of co-culture, immunophenotypic characterization of T cells was performed on a flow cytometer using the following surface markers: CD3, CD4, CD8, CD25, CD137, CD154, PD-1, TIM3, TIGIT, and LAG3 and intracellular IFNg and FOXP3.

Results: PBMC co-cultured with irradiated AML K-1 showed significant higher IFNg expression (11.8% ± 3.1 v. 7% ± 3.3; n=7, P=0.012) and higher CD137 (4-1BB) expression (9.3% ± 1.21 v. 5.7% ± 3.4; n=7, P<0.001) on CD8+ and higher CD154 expression on CD4+ cells (44.7% ± 20.3 v. 26.3% ± 14.2; n=5, P=0.002) when compared to the live AML K-1-PBMC co-cultures. There were fewer Tregs in the PBMC co-cultured with irradiated K-1 cells (1.96% ± 0.37 v. 3.39% ± 0.58; n=4, P=0.03). There was no significant difference of PD-1, TIM3 or TIGIT expression. However, there were fewer LAG3+ CD8+ T cells in the irradiated K-1-PBMC co-cultures compared to the live K-1-PBMC co-cultures (11.8% ± 2.4 v. 17.5% ± 2.5; n=4, P=0.002). Adding anti-LAG3 antibody (3DS223H; 0.1 ng/μl) to PBMC co-cultured with live AML cells resulted in higher IFNg (Figure 1A) and CD137 (Figure 1B) on CD8+ cells and fewer Tregs (Figure 1C) compared to PBMC co-cultured with live K-1 alone. Adding anti-PD1 antibody (EH12.2HZ) did not affect IFNg expression.

Conclusion: In our in vitro model, LAG3 upregulation correlates with decreased activation of CD8+ cells and higher Tregs when healthy donor PBMC are co-cultured with AML K-1 cells. Antibody-mediated blocking of LAG3 may potentially reverse the suppression of CD8+ T cells by AML K-1 cells and produce fewer Tregs.
The Activation Marker CD137 (4-1BB) Identifies a Highly Active Subset of Donor Lymphocytes Against Acute Myeloid Leukemia

Haitham Abdelhakim, MD; Meizhang Li, PhD; Mitchell Braun, BS; Andrew Godwin, PhD and Neil Dunavin, MD.
University of Kansas Cancer Center, Kansas City, KS

Background: Donor lymphocyte infusion is a therapeutic option for AML relapse post-transplant. Isolating and expanding a subset of lymphocytes that contains antigen-specific T cells against AML antigens may increase the potential for a graft-versus-leukemia immune response. We hypothesized that irradiating AML blasts would diminish their immune suppressive capacity while maintaining antigen presentation, resulting in higher activation of antigen-specific CD8+ T cells among peripheral blood mononuclear cells (PBMC) in co-culture.

Methods: PBMC were isolated from healthy donors’ whole blood. PBMC were co-cultured with live AML K-1 (CRL-2724) cells and irradiated K-1 cells (40 Gy) separately at a 1:2 ratio in RPMI complete media supplemented with 10% FBS and IL-2 20 IU/ml. On day 3 of co-culture, CD137 positive cells were labeled and isolated by a magnetic separation column (MiniMACS; Miltenyi Biotech). PBMC Immunophenotype was evaluated on a flow cytometer using surface labels CD3, CD4, CD8, CD137, CD25, CD56 and LAG3 in addition to intracellular IFNγ and FOXP3. Both CD137-selected and unselected cells were expanded in complete media supplemented with IL-2 2000 IU/ml, IL-7 50 ng/ml and IL-15 300 ng/ml. CFSE-labeled K-1 cells were incubated with both CD137-selected and unselected PBMCs separately then viability was measured by 7-ADD on flow cytometry.

Results: PBMC co-cultured with irradiated K-1 showed significantly higher CD137 expression (9.3% ± 1.21 v. 5.7% ± 3.4; n=7, P<0.001; Figure 1A) and IFNγ expression (11.8% ± 3.1 v. 7% ± 3.3; n=7, P=0.012; Figure 1B) on CD8+ T cells when compared to the live K-1-PBMC co-cultures. After 2 weeks of in vitro expansion, CD137-selected cells expressed more CD3 (60.65% vs 22.8%; n=4, P=0.012) and CD56 (1.6% vs 0.25; n=4, P=0.01) than unselected cells. In comparison to unselected cells, CD137-selected cells showed higher killing of CSFE-labeled AML cells across AML: PBMC ratios (1:5,1:10 and 1:15) at both 24 and 48 hours (Figure 2).

Conclusion: Irradiation of AML cells prior to co-culture increases the expression of activation markers CD137 and IFNγ. The activation marker CD137 can be used to select a population of cells from healthy donor PBMC that can be expanded in vitro and induce efficient killing of AML cells.
**Figure 1**

A. CD137

- Live
- Irradiated

B. Intracellular IFNγ

**Figure 2**

A. 24 hr

- Dead AML cells (% (CFSE<7.4OD))
- AML:PBMC

B. 48 hr

- CD137-selected
- Unselected

*P<0.05
**P<0.005
Background: Gut microbiota play a role in morbidity and mortality with allo-HCT. VRE colonization is a major infection control issue in the inpatient setting as it acts as a reservoir for auto-infection or transmission of infection and changes the gut microbiome. VRE colonization is a risk factor for VRE blood stream infection which is associated with worse outcomes in autologous and allo-HCT. However, the effects of VRE colonization are not well studied independent from VRE infection.

Methods: In our allo-HCT program we monitor VRE colonization by weekly rectal swabs from pre HCT to day 100 post HCT. We reviewed patients’ charts that received allo-HCT at the University of Kansas Cancer Center from January 2013 to December 2016 and compared early outcomes after allo-HCT between patients based on VRE colonization status.

Results: 470 patients received an allo-HCT in the specified period. VRE colonization was found in 107 patients (22.8%) pre-transplant and 103 (21.9%) in the first 30 days post-transplant. Patient characteristics are listed in Table 1. There was no difference in overall survival at Day 100 with 96.2% in the VRE-colonized group vs. 93.4% in non-colonized group (P=0.31). Acute GVHD grade ≥ 2 incidence was significantly higher in the VRE colonized group (68.6% vs. 58.1% in the non-colonized group) (P=0.03). The bacteremia incidence was higher in the VRE colonized group 21.4% vs. 12.3% in the non-colonized group (P=0.005). Median time to neutrophil recovery was 17 days in both groups; while median time to platelet recovery in the VRE colonized group was 22.5 days vs. 18 days in the non-colonized group (P=0.1). The median number of transfused packed red cell units was 3 and 2 units (P=0.014), and platelet units was 3 and 3 (P=0.003) in the VRE colonized and non-colonized cohorts, respectively. (Table 1)

Conclusion: VRE colonization was associated with increased incidence of acute GVHD and blood stream infection in addition to increased transfusion requirements in our cohort. This a single center study and further studies are needed to confirm these findings.
<table>
<thead>
<tr>
<th></th>
<th>VRE colonized (n=210)</th>
<th>Non-colonized (n=270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia/MDS (%)</td>
<td>168 (80%)</td>
<td>201 (75.5%)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>30 (14.2%)</td>
<td>44 (16.3%)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (5.8%)</td>
<td>15 (8.2%)</td>
</tr>
<tr>
<td>Myeloablative regimen</td>
<td>73 (34.7%)</td>
<td>91 (33.7%)</td>
</tr>
<tr>
<td>Non-myeloablative/reduced intensity</td>
<td>137 (65.3%)</td>
<td>169 (66.3%)</td>
</tr>
<tr>
<td>Matched unrelated donor</td>
<td>103 (49%)</td>
<td>127 (47%)</td>
</tr>
<tr>
<td>Haploidentical</td>
<td>27 (12.9%)</td>
<td>30 (14.2%)</td>
</tr>
<tr>
<td>Matched related donor</td>
<td>59 (28.1%)</td>
<td>83 (31.4%)</td>
</tr>
<tr>
<td>Cord blood</td>
<td>21 (10%)</td>
<td>20 (7.4%)</td>
</tr>
<tr>
<td>Bone marrow source</td>
<td>35 (16.6%)</td>
<td>34 (12.6%)</td>
</tr>
<tr>
<td>Survival at day 100</td>
<td>202 (96.2%)</td>
<td>243 (93.4%)</td>
</tr>
<tr>
<td>Days hospital stay</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Acute GVHD G≥2</td>
<td>144 (68.6%)</td>
<td>151 (58.1%)</td>
</tr>
<tr>
<td>Acute GVHD G3</td>
<td>31 (14.7%)</td>
<td>26 (10%)</td>
</tr>
<tr>
<td>Acute GVHD G4</td>
<td>13 (6.2%)</td>
<td>6 (2.3%)</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>45 (21.4%)</td>
<td>32 (12.3%)</td>
</tr>
<tr>
<td>Staphylococcus bacteremia</td>
<td>13 (28.9%)</td>
<td>11 (34.4%)</td>
</tr>
<tr>
<td>VRE bacteremia</td>
<td>3 (6.7%)</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Days platelet recovery</td>
<td>22.5</td>
<td>18</td>
</tr>
<tr>
<td>Days Neutrophil recovery</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>PRBCs units</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Platelets units</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>
Febrile neutropenia in the nationwide inpatient sample: In-hospital outcomes and impact of comorbidities in 2007-2012.

Authors: Saqib Abbasi, Bassel Nazha, Elias Moussaly, Monika Manchanda, Jean Paul Atallah

Background: Febrile Neutropenia (FN) is associated with significant in-patient morbidity and mortality. The goal of this study is to describe the in-patient outcomes of febrile neutropenia as well as the impact of comorbid conditions through a large national dataset.

Methods: Using the Nationwide Inpatient Sample (NIS) for years 2007-2012, FN was defined as ICD-9 codes 288.0x for a primary discharge diagnosis of neutropenia in conjunction with 780.61 and 780.6 for fever in cancer patients. Linear regression analysis assessed for annual trends in in-hospital mortality, length of stay (LOS), and cost of stay (COS). Seasonal variations in admission rates were evaluated using ANOVA. We employed univariate and multivariate logistic regression analysis to elucidate the relationship between common comorbid conditions and mortality.

Results: Among 55,253 cancer patients (weighted N = 264,384) admitted with FN between 2007 and 2012, there is a mean decrease in LOS from 5.78 to 5.47 days (p < 0.0001), an increase in COS from $33,939 to $41,395 (p < 0.0001), and a 12-15% drop in hospital admissions in winter months. Mortality rate is unchanged annually (1.06-1.28%). Univariate analysis identified an increased risk of mortality associated with atrial fibrillation (OR = 4.06), coronary artery disease (OR = 2.09), congestive heart failure (OR 4.39), hypertension (1.20), COPD (OR 2.33) pancytopenia (OR 1.81), and adrenal insufficiency (OR 5.32). All remained significant on multivariate analysis, except hypertension and diabetes mellitus.

Conclusions: Between 2007-2012, FN had a slight decrease in length of stay, unchanged in-patient mortality and a 22% increase in hospitalization costs. Our results are in line with recently presented analyses of the same database (Blood 2016 128:4762, Blood 2016 128:5904). Comorbid conditions are associated with higher in-patient mortality, with up to 5-fold increase for those with atrial fibrillation, congestive heart failure and adrenal insufficiency. Clinicians should consider the significant impact of such comorbidities. Additional vigilance and potentially prophylactic antibiotics following treatment should be considered in affected patients.
Abiraterone acetate in comparison to enzalutamide in African American patients with castrate-resistant prostate cancer, A single-center retrospective study

Mohammad Telfah, Jeffrey M. Holzbeierlein, Xinglei Shen, Elizabeth Marie Wulff-Burchfield, and Rahul Parikh

Background:

African American (AA) patients with metastatic castrate-resistant prostate cancer (mCRPC) represent a high-risk population with higher mortality. Recent data suggested that abiraterone acetate (AbA) is more effective in AA in comparison to white patients. There are limited data regarding enzalutamide (Enz) use in AAs. Here, we report the outcomes of (AbA) and (Enz) in AA patients with mCRPC at our center

Methods:

A retrospective chart review included AA patients who had a diagnosis of mCRPC and were prescribed AbA and/or Enz at KUMC from 09-01-2008 through 09-01-2018. Patients were divided into two groups: those who started with AbA (abiraterone group) and those who started with Enz (enzalutamide group). Baseline characteristics were compared between the two groups using Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. The primary outcome was progression-free survival (PFS) on AbA and Enz. PFS was measured from the time of starting either of the two medications to the time of formal relapse, defined by relapse that required therapy change or prostate-cancer-related death. A stepwise Cox proportional-hazard model was used to adjust for potential confounders

Results:

During the study period, 28 AA patients with mCRPC received AbA and/or Enz. Twenty-two patients received AbA first, while six patients received Enz first. There were no significant differences in the baseline characteristics between the two groups. Median PFS for the abiraterone group was 24.3 months, while it was 11.7 months for the enzalutamide group, Log-rank test p-value 0.04. After adjusting for potential confounders, the hazard ratio of progression remained significant, favoring the abiraterone group, HR: 0.11, p-value 0.009. Median PFS on AbA after progression on previous Enz was 5.7 months, while it was 4.5 months for Enz after progression on previous AbA, p-value 0.2

Conclusions:

In this single-center retrospective study, AA patients with mCRPC who were started on AbA rather than Enz had longer PFS. More studies are needed to understand the best sequence of the two medications in this population.
**NF1 mutation is associated with worse overall survival in patients with newly diagnosed AML, A single-center retrospective study**

Mohammad Telfah, Haitham Abdelhakim, Nicole Balmaceda, Eyad Gharabeh, Andrew K. Godwin, Ziyang Y. Pessetto, Joseph McGuirk, Tara L. Lin

University of Kansas Cancer Center

**Background:**

Several recurrent genetic mutations have been described in acute myeloid leukemia (AML), which have both prognostic and therapeutic implications. Recurrent mutations in the Neurofibromin 1 (NF1) gene are reported in 1-5% of AML patients; however, there are limited data regarding its prognostic implications. Here, we report the outcomes for patients with newly diagnosed AML with a somatic NF1 mutation at our center

**Methods:**

A retrospective chart review included patients with newly diagnosed AML at KUMC from 01/2016 through 09/2018. All patients had targeted next-generation sequencing (NGS) at diagnosis. Baseline characteristics were compared between patients with NF1 mutations and those who were wild-type using Fisher’s exact test for categorical variables, and the Wilcoxon rank-sum test for continuous variables. The primary outcome was overall survival (OS), which was measured from the time of diagnosis to the time of death from any cause. A stepwise Cox proportional-hazard model was used to adjust for potential confounders

**Results:**

Data on 110 patients were included. Out of the 110 patients, 15 (13.6%) had a detectable NF1 mutation, while 95 (86.4%) patients were NF1 wild-type. The baseline characteristics of the two groups are displayed below. Median OS for patients with an NF1 mutation was 7.3 months, while it was 18.4 months for patients with NF1 wild-type, Log-rank test p-value 0.02. After adjusting for potential confounders, including age, ELN risk category, induction regimen, presence of other mutations such as TP53, the hazard of death remained significantly higher for patients with NF1 mutations, HR 2.4, CI (1.05-5.6), p-value 0.04

**Conclusions:**

In this single-center retrospective study, the presence of a NF1 mutation was associated with worse overall survival in patients with newly diagnosis AML.

<table>
<thead>
<tr>
<th></th>
<th>NF1 Positive</th>
<th>NF1 Wild-Type</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Median-years)</td>
<td>63.5</td>
<td>62.0</td>
<td>0.60</td>
</tr>
<tr>
<td>ECOG 0-1</td>
<td>9 (69%)</td>
<td>81 (86%)</td>
<td>0.21</td>
</tr>
<tr>
<td>ELN Adverse risk</td>
<td>9 (60%)</td>
<td>52 (55%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Induction regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7+3</td>
<td>8 (61%)</td>
<td>49 (54%)</td>
<td>0.77</td>
</tr>
<tr>
<td>CPX 351</td>
<td>0 (0%)</td>
<td>9 (10%)</td>
<td>0.35</td>
</tr>
<tr>
<td>HMA</td>
<td>5 (38%)</td>
<td>14 (15%)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Achiever CR</td>
<td>Achiever CR %</td>
<td>64</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------</td>
<td>---------------</td>
<td>----</td>
</tr>
<tr>
<td>Achieving CR</td>
<td>6 (40%)</td>
<td>64 (70%)</td>
<td></td>
</tr>
<tr>
<td>Transplant among CR</td>
<td>5/6 (83%)</td>
<td>39/64 (60%)</td>
<td>0.039</td>
</tr>
</tbody>
</table>
Interprofessional Geriatric Chronic Care Management Outcomes

C Burkhardt, B Melton, R Mason, J Kalender-Rich, D Hayley. Pharmacy Practice, University of Kansas, Kansas City, KS; Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Background:

Geriatric patients have a higher rate of chronic conditions and potentially preventable hospitalizations. Single profession interventions have been shown to reduce readmission rates by enhanced chronic disease management. Interprofessional teams have the opportunity to better manage chronic conditions and reduce potentially preventable hospitalizations, however evidence is limited.

Methods:

A prospective cohort study was designed to evaluate a geriatrics population enrolled in an Interprofessional Chronic Care Management (IP-CCM) service compared to standard clinic care (SCC). The IP-CCM team consisted of a pharmacist, nurse educator, social worker, and each physician/nurse team. Patient demographics, severity of comorbidity, and potentially preventable hospitalizations and/or emergency department (ED) visits were collected. Potentially preventable hospital or ED visits included fall, sepsis, hypertension, heart failure, pneumonia/respiratory infection, urinary tract infection, chronic obstructive pulmonary disease, and skin ulcers cellulitis.

Results:

A total of 288 patients were enrolled: 58 IP-CCM and 230 SCC patients. Average age was 73.5 and 74.3 years respectively for the IP-CCM and SCC patients. The diagnosis of dementia was present and 29% and 21% of patients (IP-CCM and SCC, respectively). The average Charlson Comorbidity Index (CI) was 5.66 for IP-CCM and 5.50 for SCC (p=0.602). The baseline rates of possibly preventable hospitalizations for IP-CCM and SCC were 54% and 60% (p=0.276) respectively, as compared to 53% and 50% respectively at 1 year (p=0.761). While preventable hospitalizations and ED visits were not statistically significantly reduced between groups at one-year, a clinically significant difference in absolute risk reduction in hospitalizations was noted for the IP-CCM (25%) as compared to SCC (2%).

Conclusions:

Clinically significant reductions in hospitalization rates were noted in the IP-CCM arm as compared to the SCC arm, however the difference did not reach statistical significance in this small cohort study. Further evaluation of practice models on a larger scale is needed to identify the outcomes of inter professional CCM services.
**Introduction:** Unplanned hospital readmissions are a burden on patients and cost taxpayers tens of billions of dollars annually in the United States. Multi-component interventions can be implemented to reduce readmission. But with hospital resources spread thin, it may not be necessary or even feasible to provide a multicomponent intervention for all discharging patients. Demographic and chart data have been used in prediction models to identify at-risk patients for these interventions. However, current prediction models fail to incorporate patient perceptions of their health, support systems, and readiness for discharge. To further refine and advance these models, patient-centric risk factors for readmission must be explored and identified.

**Methods:** Forty-nine patients enrolled by convenience sampling from two inpatient units at a large academic hospital were asked to fill out 19-item surveys inquiring about support at home, quality of care, and self-perceptions of health status. Patients were followed prospectively for any 30-day readmissions. Patient chart data and responses to survey items were analyzed to evaluate correlations with readmission rates. Since all variables in the data set were categorical in nature, Fisher’s exact test was used to test the association between readmission status, and variables such as (stratified) age, gender, patient’s expected return date, discharge readiness, etc. Statistical software SAS (version 9.4) was used to perform the statistical analysis.

**Results:** In our final data set of size \( n = 49 \), we observed that 8 (16.33%) subjects were readmitted within 30 days of discharge from the hospital. Using Fisher’s exact test, we found that readmission status was significantly associated with patient’s expected date of readmission. We also observed a marginally significant association between readmission status and discharge readiness. Based on the collected data, we do not have sufficient evidence to claim that readmission status is associated with age, gender, or race.
Table: *P*-values (two-sided) for Fisher’s exact test for association between readmission status and other variables

<table>
<thead>
<tr>
<th>Variable</th>
<th><em>P</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.5568</td>
</tr>
<tr>
<td>Gender</td>
<td>1.0000</td>
</tr>
<tr>
<td>Race</td>
<td>0.1333</td>
</tr>
<tr>
<td>Expected Return Date</td>
<td>0.0005</td>
</tr>
<tr>
<td>Discharge Readiness</td>
<td>0.0525</td>
</tr>
</tbody>
</table>

**Conclusion:** The preliminary data suggests that patients’ expected readmission date and their perceived readiness for discharge can help identify risk for readmission. This suggests that patients themselves can provide crucial information regarding their risk for readmission. Further study is thus needed to confirm these risk factors and incorporate them into prediction models for readmission.
Making Early Concurrent Palliative Care Happen in Advance Cancer Patients: Modeling the implementation of the American Society of Clinical Oncology clinical practice guidelines

Arash Sattarin, MD and Christian Sinclair, MD, FAAHPM
University of Kansas Health System

Background: The American Society of Clinical Oncology (ASCO) clinical practice guideline (CPG) recommends that patients with advanced cancer should be referred to palliative care within eight weeks of diagnosis. Multiple studies have shown clear benefits of early palliative care yet the current palliative care workforce is not growing fast enough to meet the expected demand.

Purpose: To analyze the current patient population with advanced cancer at a National Cancer Institute-designated cancer center to determine the number of patients that should receive palliative care based on the ASCO CPG. This denominator will then be compared to the number of patients seen by a mature palliative care program with strong inpatient and outpatient availability to estimate the current supply and future demand for palliative care services and clinicians.

Methods: Retrospective chart review of the cancer registry of the University of Kansas Cancer Center from 2016-2018 identifying patients with an initial diagnosis of advanced cancer. Definitions of advanced cancer per the ASCO CPG include those with distant metastases, late-stage disease, cancer that is life limiting, and/or with prognosis of 6 to 24 months. This population will be analyzed by treating oncologist, number of inpatient and outpatient palliative encounters, time between initial advanced cancer diagnosis and first palliative care consultation, and number of hospital or emergency department visits.

Results and Conclusion: Results are still being analyzed, but early findings suggest that our current palliative care efforts see less than 15% of patients deemed eligible by the ASCO CPG. Many patients with advanced cancer may benefit from palliative care, but are not referred or seen by palliative teams. Our review recognizes that implementing ASCO guidelines demands more palliative care clinicians. An acute shortage of palliative providers exists with a very narrow pipeline for developing more.
Bronchoscopic Features, Associations and Outcomes of Organizing Pneumonia Following Allogeneic Hematopoietic Stem Cell Transplantation

John W. Frey, DO¹ and Kyle R. Brownback, MD²
¹Department of Internal Medicine, University of Kansas Medical Center
²Department of Pulmonary/Critical Care, University of Kansas Medical Center

Rationale: Organizing Pneumonia (OP) is a well-known, but poorly understood, complication of hematopoietic stem cell transplant (HSCT). In this study we identified patients diagnosed with OP following HSCT and described their clinical course.

Methods: Patients diagnosed with OP were retrospectively identified from the records at KUMC. The patients had various hematologic diseases, but all underwent allogeneic HSCT. The records for each patient were analyzed.

Results: Fifteen patients were diagnosed with OP following HSCT, with a mean age of 48 years. Average onset for symptoms was 286 days after transplant, with most patients presenting with cough and dyspnea on exertion. CT Chest findings were remarkable for multifocal infiltrates that were predominantly ground glass opacities. Patients had an average reduction in their FVC and FEV1 of 23.1% and 22.4%, respectively, when compared to pre-transplant pulmonary function testing (PFT). Bronchoalveolar lavage (BAL) with cell differentials was performed on fourteen patients with five having lymphocytosis (>25% lymphocytes), three with eosinophilia (>5% eosinophils), three with neutrophilia (>30% neutrophils), and three with normal cell counts. Flow cytometry was analyzed on BAL fluid in thirteen patients with ten having a CD4/CD8 of <0.9. Initial treatment with 0.3-1.0 mg/kg of Prednisone resulted in improvement in symptoms as well as CT Chest findings for the majority of patients. PFTs performed at the time of steroid completion showed an increase in FVC and FEV1 of 18.4% and 20.7%, respectively, when compared to PFTs completed at time of OP diagnosis. Six patients had recurrence of OP after completing initial treatment and one patient had recurrence while taking Prednisone. Four patients died, with one patient’s death attributed to respiratory failure secondary to OP. Clinical features prior to the diagnosis of OP included history of graft versus host disease in eleven patients. Seven patients were diagnosed with an upper respiratory tract infection (URI) within eight weeks of being diagnosed with OP.

Conclusion: Patients with OP present with non-specific symptoms and laboratory findings. Most respond well to prednisone, but risk of recurrence is high after cessation of steroid treatment. Risk factors for the development of OP may include triggers such as URI.
Esophageal Plaques in a 67-Year-Old Female

Seyed Farzad Marashi nia, MD, Wei Cui, MD, Reza Hejazi, MD

Lichen planus (LP) is an uncommon disorder with unknown etiology, mostly affecting middle-aged adults with cutaneous and mucosal involvements. It may affect the skin, oral cavity, scalp, nails and esophagus. Esophageal LP (ELP) is a rare presentation of the disease that is usually under-recognized, leading to delayed diagnosis and increased morbidity related to the disease complications.

A 67 year-old female with a past medical history significant for LP presented for follow-up treatment of eosinophilic esophagitis (EOE). She had a several-year history of dysphagia to solids without odynophagia, cutaneous or vaginal LP at the time of presentation. She had been initially diagnosed as EOE based on the concentric rings and linear furrows on her esophagogastroduodenoscopy (EGD), although the biopsies had never had more than 15 eosinophils per HPF. She had been treated with Budesonide inhaler and oral steroid for several years with minimal improvements, then had to stop it, due to side effects. Several episodes of through the scope (TTS) balloon dilation up to 18 mm had failed to control dysphagia. Due to the questionable diagnosis of EOE, the patient underwent another EGD to rule out EOE and ELP, demonstrating diffuse spontaneous mucosal sclerosis of upper and middle third of the esophagus, lacy white papules and submucosal plaques. An area of abnormal mucosa, Red Island within white plagues, were found. The Biopsy specimens revealed hyperkeratosis and hypergranulosis consistent with esophageal leukoplasia. Based on the past medical history of LP and the result of the pathology, the patient was diagnosed with ELP. She underwent EGD with TTS dilation up to 16.5 mm and injection of Triamcinolone 40mg into mucosal break caused by dilation, and budesonide was discontinued. Follow up visits showed improved dysphagia. In order to keep the patient asymptomatic, serial dilations are being done every one month.

ELP is a rare disease that should be distinguished from reflux esophagitis and essentially EOE, which may have similar presentations and particularly should be considered in patients with mucocutaneous LP. ELP can cause stricture, ulceration, and squamous cell carcinoma, therefore early diagnosis is important to prevent persistent dysphagia resulting from esophagitis and stricture formation. EGD with biopsies are the main stem of diagnosis. Treatment options include topical and systemic corticosteroids, and repeated esophageal dilation.
Hyperkeratosis and hypergranulosis
Giant Esophageal Ulcer in a Patient with Acquired Immunodeficiency Syndrome
Awwadah Asalah, Seyed Farzad Marashi nia, MD, Maura F. O’Neil, MD, Reza Hejazi, MD

Esophageal ulcer is a common complication in acquired immune deficiency syndrome patients, especially in the final stages and in patients who develop an acute retroviral syndrome. Although, it can be caused by various infectious agents, such as candida, Cytomegalovirus (CMV) and herpes simplex virus 1 (HSV-1), no etiological agent is successfully identified in a proportion of patients.

A 38-year-old male presented to our hospital with a two-month history of progressive dysphagia, odynophagia to solids and liquids, and atypical chest pain. He was previously diagnosed with AIDS with a viral load of 130904 copies/ml and CD4 count of 1 cell/ml, who was not on anti-retroviral therapy. Esophagogastroduodenoscopy (EGD) revealed many large, circumferential, very deep esophageal ulcers without bleeding, 22 to 35 cm from incisors. Biopsies showed ulcerated mucosa with fibrinopurulent exudate, with acute and chronic inflammation, and Immunohistochemical stains were negative for fungal, CMV, HSV-1, and human herpesvirus 8 (HHV-8) viral inclusions. A diagnosis of AIDS-related Idiopathic Esophageal Ulcers (IEU) was made and the patient was started on highly active anti-retroviral therapy (HAART) and oral prednisone 40 mg daily. Follow up visits showed complete clinical improvement after two weeks of treatment with corticosteroid.

The postulated pathogenesis of IEU is mainly based on T-cell activation and subsequent apoptosis of the esophageal mucosa. It is usually diagnosed in patients with CD4 cell counts less than 100/μL. Esophageal ulcer in HIV-positive patient includes a vast differential diagnosis, and IEU can only be diagnosed after ruling out microbial pathogens and other possible causes. IEUs are considered to be associated with HIV infection, therefore differentiation between infectious and noninfectious causes is essential as viral or fungal ulcers are usually treated with potentially toxic antimicrobial drugs and idiopathic ulcers are treated with steroids. Both systemic and intralesional steroids, are reported to be effective in the treatment of idiopathic esophageal ulcers. In our case clinical improvement was noted after the initiation of HAART treatment and a short course of systemic steroids. EGD was not repeated due to complete resolution of symptoms.
Fibrinopurulent exudate and inflamed granulation tissue
The role of probiotics in primary and secondary prevention of pouchitis: A Systematic Review and Meta-Analysis

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1University of Kansas Medical Center, Kansas City, KS, USA
2Washington University School of Medicine, St.Louis, MO, USA
3Northwestern University McGaw School of Medicine

Objectives: Pouchitis is the most common long-term complication after ileal pouch anal anastomosis (IPAA) surgery. Its cumulative incidence is approximately 50% after a 10-year follow up. Several trials have looked at the use of probiotics in prevention of pouchitis, and showed a significant decrease in the development of pouchitis, but other showed no difference. Our data is very limited and the most recent Cochrane review in 2015 showed a possible benefit of probiotics in maintaining the remission, but it’s not widely used in practice, especially in primary prevention. In this systematic review and meta-analysis, we aimed to discern whether probiotics are actually beneficial in primary and secondary prevention of pouchitis.

Methods: A comprehensive search of MEDLINE, EMBASE, Scopus, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews was conducted from each database’s inception to May, 20th, 2017 to search for comparative studies of probiotics use in the prevention of primary (first episode) and secondary (recurrent episodes) pouchitis. The outcome of interest was the development of pouchitis.

Results: Nine studies with a total of 376 patients were included. The use of probiotics in the primary prevention was associated with a decreased incidence of pouchitis (RR: 0.18, 95% CI: 0.08-0.39, p<0.01, heterogeneity I²: 0%) with a NNT of 3.2, and their use in the secondary prevention was associated with a decreased incidence of recurrent pouchitis compared to placebo (RR: 0.20, 95% CI: 0.11-0.36, p-value <0.01, heterogeneity I²: 0%). Overall risk of developing pouchitis was decreased with the use of probiotics use (RR: 0.19, 95% CI: 0.12-0.30, p <0.01, heterogeneity I²: 0%) with a NNT of 2.

Sub-group analysis included only studies that used VSL#3 showed a significant decrease in pouchitis in both primary prevention (RR: 0.23, 95% CI: 0.10-0.50, p<0.01, heterogeneity I²: 0%), secondary prevention (RR: 0.17, 95% CI: 0.09-0.31, p-value <0.01, heterogeneity I²: 0%), and overall risk RR: 0.19, 95% CI: 0.12-0.36, p <0.01, heterogeneity I²: 0%)

Conclusion: The current systematic review and meta-analysis showed that probiotics are superior to placebo in the primary and secondary prevention of pouchitis with a very significant NNT. These findings suggest the use of probiotics in patients after ileal pouch anal anastomosis (IPAA) surgery for primary prevention, or in patients with recurrent pouchitis.
Figure- 1: Forrest plots of meta-analysis comparing probiotics versus placebo in primary and secondary prevention of pouchitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevention = Primary</td>
<td>20</td>
<td>8</td>
<td>20</td>
<td></td>
<td>0.25</td>
<td>[0.06; 1.03]</td>
</tr>
<tr>
<td>Gionchetti, 2003</td>
<td>3</td>
<td>67</td>
<td>27</td>
<td>76</td>
<td>0.13</td>
<td>[0.04; 0.40]</td>
</tr>
<tr>
<td>Gosselink, 2004</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td>8</td>
<td>0.22</td>
<td>[0.03; 1.60]</td>
</tr>
<tr>
<td>Yasdrea, 2016</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Random effects model</td>
<td>96</td>
<td>104</td>
<td></td>
<td></td>
<td>0.17</td>
<td>[0.08; 0.39]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0$, $p = 0.73$
Test for effect in subgroup: $z = -4.22$ ($p < 0.01$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Events</td>
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<td>Events</td>
<td>Total</td>
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<td></td>
</tr>
<tr>
<td>Prevention = Secondary</td>
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</tr>
<tr>
<td>Gionchetti, 2000</td>
<td>3</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>0.05</td>
<td>[0.00; 0.71]</td>
</tr>
<tr>
<td>Kuhbacher, 2006</td>
<td>3</td>
<td>20</td>
<td>15</td>
<td>16</td>
<td>0.16</td>
<td>[0.06; 0.46]</td>
</tr>
<tr>
<td>Mimura, 2004</td>
<td>0</td>
<td>16</td>
<td>1</td>
<td>12</td>
<td>0.25</td>
<td>[0.01; 0.59]</td>
</tr>
<tr>
<td>Pronio, 2008</td>
<td>3</td>
<td>19</td>
<td>8</td>
<td>21</td>
<td>0.41</td>
<td>[0.13; 1.34]</td>
</tr>
<tr>
<td>Tomasz, 2014</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Random effects model</td>
<td>85</td>
<td>74</td>
<td></td>
<td></td>
<td>0.20</td>
<td>[0.11; 0.36]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0$, $p = 0.56$
Test for effect in subgroup: $z = -6.46$ ($p < 0.01$)
Test for overall effect: $z = -6.89$ ($p < 0.01$)
Test for subgroup differences: $\chi^2 = 0.77$, df = 1 ($p = 0.79$)

Figure- 2: Forrest plots of meta-analysis comparing VSL#3 versus placebo in primary and secondary prevention of pouchitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotic = Other</td>
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<td>8</td>
<td>20</td>
<td></td>
<td>0.13</td>
<td>[0.04; 0.40]</td>
</tr>
<tr>
<td>Gosselink, 2004</td>
<td>3</td>
<td>67</td>
<td>27</td>
<td>76</td>
<td>0.41</td>
<td>[0.13; 1.34]</td>
</tr>
<tr>
<td>Tomasz, 2014</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td>8</td>
<td>0.22</td>
<td>[0.03; 1.60]</td>
</tr>
<tr>
<td>Yasdrea, 2016</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Random effects model</td>
<td>95</td>
<td>105</td>
<td></td>
<td></td>
<td>0.23</td>
<td>[0.10; 0.50]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0$, $\tau^2 = 0.0367$, $p = 0.34$
Test for effect in subgroup: $z = -3.69$ ($p < 0.01$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotic = VSL#3</td>
<td>20</td>
<td>8</td>
<td>20</td>
<td></td>
<td>0.17</td>
<td>[0.07; 0.44]</td>
</tr>
<tr>
<td>Gionchetti, 2000</td>
<td>3</td>
<td>20</td>
<td>8</td>
<td>20</td>
<td>0.25</td>
<td>[0.06; 0.53]</td>
</tr>
<tr>
<td>Gionchetti, 2003</td>
<td>0</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>0.05</td>
<td>[0.00; 0.51]</td>
</tr>
<tr>
<td>Kuhbacher, 2006</td>
<td>3</td>
<td>20</td>
<td>15</td>
<td>16</td>
<td>0.16</td>
<td>[0.06; 0.46]</td>
</tr>
<tr>
<td>Mimura, 2004</td>
<td>0</td>
<td>16</td>
<td>1</td>
<td>12</td>
<td>0.25</td>
<td>[0.01; 0.56]</td>
</tr>
<tr>
<td>Pronio, 2008</td>
<td>3</td>
<td>19</td>
<td>8</td>
<td>21</td>
<td>0.41</td>
<td>[0.13; 1.34]</td>
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<tr>
<td>Tomasz, 2014</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Random effects model</td>
<td>85</td>
<td>73</td>
<td></td>
<td></td>
<td>0.17</td>
<td>[0.09; 0.31]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0$, $\tau^2 = 0$, $p = 0.08$
Test for overall effect: $z = -5.74$ ($p < 0.01$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>181</td>
<td>178</td>
<td></td>
<td></td>
<td>0.19</td>
<td>[0.12; 0.30]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0$, $\tau^2 = 0$, $p = 0.02$
Test for overall effect: $z = -6.89$ ($p < 0.01$)
Test for subgroup differences: $\chi^2 = 0.30$, df = 1 ($p = 0.58$)
**Figure-3**: Forrest plots of meta-analysis comparing probiotics versus placebo and risk of pouchitis (overall).

<table>
<thead>
<tr>
<th>Study</th>
<th>Probiotics</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gionchetti, 2000</td>
<td>3</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>0.17 [0.07; 0.44]</td>
<td>24.5%</td>
</tr>
<tr>
<td>Gionchetti, 2003</td>
<td>2</td>
<td>20</td>
<td>8</td>
<td>20</td>
<td>0.25 [0.06; 1.03]</td>
<td>11.1%</td>
</tr>
<tr>
<td>Gosselink, 2004</td>
<td>3</td>
<td>67</td>
<td>27</td>
<td>76</td>
<td>0.13 [0.04; 0.40]</td>
<td>17.0%</td>
</tr>
<tr>
<td>Kuhbacher, 2006</td>
<td>0</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>0.05 [0.00; 0.71]</td>
<td>3.0%</td>
</tr>
<tr>
<td>Mimura, 2004</td>
<td>3</td>
<td>20</td>
<td>15</td>
<td>16</td>
<td>0.16 [0.06; 0.46]</td>
<td>20.2%</td>
</tr>
<tr>
<td>Prono, 2008</td>
<td>0</td>
<td>16</td>
<td>1</td>
<td>12</td>
<td>0.25 [0.01; 5.69]</td>
<td>2.3%</td>
</tr>
<tr>
<td>Tomasz, 2014</td>
<td>3</td>
<td>19</td>
<td>8</td>
<td>21</td>
<td>0.41 [0.13; 1.34]</td>
<td>16.2%</td>
</tr>
<tr>
<td>Yasueda, 2016</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td>8</td>
<td>0.22 [0.03; 1.60]</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

Random effects model: 181 events for probiotics and 178 for placebo, with RR of 0.19 [0.12; 0.30] and 100.0% weight.

Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $p = 0.82$
Test for overall effect: $z = -8.89$ ($p < 0.01$)
Vedolizumab versus anti TNFa agents and the risk of post-operative complications

Shadi Hamdeh1*, Jihan Fathallah1, Osama Altayar2, Dejan Micic3, M.Hassan Murad4, Mojtaba Olyaee1

1University of Kansas Medical Center, Department of Internal Medicine, 2Division of Gastroenterology and Hepatology
2Washington University School of Medicine, Division of Gastroenterology and Hepatology
3University of Chicago Medical Center, Division of Gastroenterology and Hepatology
4Mayo Clinic School of Medicine, Evidence Based Medicine

* These authors contributed equally

Background: Despite medical therapy, up to 25%-35% of ulcerative colitis and 70%-90% of Crohn’s disease patients will require surgical intervention in their lifetime. Since its FDA approval, Vedolizumab (VDZ) has been increasingly used in the treatment of patients with inflammatory bowel disease due to its efficacy in inducing and maintaining remission and its gut-specificity. However, data regarding the safety of its use during the perioperative period remains controversial. Several studies showed conflicting data comparing anti TNFa agent compared to VDZ in the perioperative setting use, therefore we conducted a meta-analysis to compare VDZ to anti-TNF inhibitors and the risk of post surgical complications.

Methods: A comprehensive search of several databases including Ovid MEDLINE Epub Ahead of Print, Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus was performed up to January 2nd/2018. Two independent reviewers systematically identified trials that compared the vedolizumab versus anti TNFa agents use preoperatively and the risk of surgical and nonsurgical complications. A meta-analysis was performed using a fixed effects model to assess the primary outcome (surgical site infections), and secondary outcomes (non-surgical site infections, abdominal abscess formation, and anastomotic leak) with subgroup analysis looking separately at Crohn’s disease and ulcerative colitis. Review Manager 5.3 software program was utilized for statistical analysis.

Results: Five studies met our inclusion criteria, four were ultimately included due to overlapping. 3 studies compared VDZ to anti TNFa in Ulcerative colitis, and 2 in Crohn’s disease. A total of 644 patients were included in the meta-analysis. Our meta-analysis demonstrated no statistically significant difference in surgical site infection (OR: 1.29; 95% CI: 0.42-3.94, p-value: 0.03), non surgical site infection (OR: 1.49; 95% CI: 0.64-3.84, p-value: 0.86), abdominal abscess formation (OR: 0.98; 95% CI:0.01-66.72, p-value: 0.02), and anastomotic leak (OR:1.11; 95% CI: 0.24-5.11, p-value: 0.59) between the 2 groups. Subgroup analysis was performed which showed also no significant difference in all outcomes when looked at CD and UC separately.

Conclusions: Our results indicated no difference in surgical site infections, non-surgical site infections, intra-abdominal abscess formation, and anastomotic leak in both CD and UC patients when VDZ or anti TNFa used preoperatively.
Figure- 1: Forrest plots of meta-analysis comparing VDZ versus anti TNFa agents and the risk of surgical site infections

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lightner 2017</td>
<td>19</td>
<td>88</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrante 2017</td>
<td>1</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamada 2017</td>
<td>1</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lightner 2018</td>
<td>26</td>
<td>100</td>
<td></td>
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</tr>
</tbody>
</table>

Random effects model 286 358 1.29 [0.42; 3.94] 100.0%

Heterogeneity: $I^2 = 66\%$, $\tau^2 = 0.7735$, $p = 0.03$

Experimental = Vedolizumab & Control = anti-TNFa  Outcome = Risk of surgical site infection

Figure- 2: Forrest plots of meta-analysis comparing VDZ versus anti TNFa agents and the risk non-surgical site infections

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lightner 2017</td>
<td>4</td>
<td>88</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrante 2017</td>
<td>3</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yamada 2017</td>
<td>0</td>
<td>64</td>
<td></td>
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</tr>
<tr>
<td>Lightner 2018</td>
<td>6</td>
<td>100</td>
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</tr>
</tbody>
</table>

Random effects model 286 358 1.49 [0.64; 3.48] 100.0%

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$

Experimental = Vedolizumab & Control = anti-TNFa  Outcome = Risk of non-surgical site infections

Figure- 3: Forrest plots of meta-analysis comparing VDZ versus anti TNFa agents and the risk of intra-abdominal abscesss

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
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<td>Lightner 2017</td>
<td>5</td>
<td>16</td>
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</tr>
<tr>
<td>Ferrante 2017</td>
<td>.</td>
<td>34</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Yamada 2017</td>
<td>0</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lightner 2018</td>
<td>.</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Random effects model 214 313 0.98 [0.01; 66.72] 100.0%

Heterogeneity: $I^2 = 81\%$, $\tau^2 = 7.5393$, $p = 0.02$

Experimental = Vedolizumab & Control = anti-TNFa  Outcome = Risk of intra-abdominal abscesss
Figure- 4: Forrest plots of meta-analysis comparing VDZ versus anti TNFa agents and the risk of anastomotic leak

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Experimental Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI</th>
<th>Weight</th>
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</thead>
<tbody>
<tr>
<td>Lightner 2017</td>
<td>0</td>
<td>88</td>
<td>0</td>
<td>62</td>
<td></td>
<td></td>
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<td>Ferrante 2017</td>
<td>1</td>
<td>34</td>
<td>1</td>
<td>60</td>
<td>1.79</td>
<td>[0.11; 29.53]</td>
<td>29.7%</td>
<td></td>
</tr>
<tr>
<td>Yamada 2017</td>
<td>1</td>
<td>64</td>
<td>4</td>
<td>129</td>
<td>0.50</td>
<td>[0.05; 4.53]</td>
<td>47.7%</td>
<td></td>
</tr>
<tr>
<td>Lightner 2018</td>
<td>1</td>
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<td>107</td>
<td>3.24</td>
<td>[0.13; 80.49]</td>
<td>22.6%</td>
<td></td>
</tr>
</tbody>
</table>

**Random effects model**: 286 358

Heterogeneity: $I^2 = 0\%$, $T^2 = 0$, $p = 0.59$

Experimental = Vedolizumab & Control = anti-TNFa  
Outcome = Risk of anastomotic leak
Figure- 5: Forrest plots of subgroup analysis comparing VDZ versus anti TNFa agents and the risk of surgical site infections in both CD and UC patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-Cl</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>ibd = UC</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lightner 2017</td>
<td>19</td>
<td>88</td>
<td>1.62</td>
<td>[0.68; 3.87]</td>
<td>31.3%</td>
<td></td>
</tr>
<tr>
<td>Ferrante 2017</td>
<td>1</td>
<td>34</td>
<td>0.58</td>
<td>[0.06; 5.76]</td>
<td>13.1%</td>
<td></td>
</tr>
<tr>
<td>Yamada 2017 (UC)</td>
<td>0</td>
<td>24</td>
<td>0.13</td>
<td>[0.01; 2.61]</td>
<td>9.0%</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>146</td>
<td>155</td>
<td>0.86</td>
<td>[0.24; 3.17]</td>
<td>53.4%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 34%$, $t^2 = 0.5201$, $p = 0.22$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-Cl</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>ibd = CD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamada 2017 (CD)</td>
<td>1</td>
<td>40</td>
<td>0.38</td>
<td>[0.04; 3.30]</td>
<td>14.3%</td>
<td></td>
</tr>
<tr>
<td>Lightner 2018</td>
<td>26</td>
<td>100</td>
<td>3.83</td>
<td>[1.69; 8.65]</td>
<td>32.2%</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>140</td>
<td>203</td>
<td>1.51</td>
<td>[0.16; 13.98]</td>
<td>46.6%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 74%$, $t^2 = 1.9847$, $p = 0.05$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Random effects model: 286 | 358 | 1.21 | [0.44; 3.33] | 100.0% |

Test for subgroup differences: $\chi^2 = 0.18$, df = 1 ($p = 0.67$), 0.01 0.1 1 10 100

Experimental = Vedolizumab & Control = anti-TNFa  Outcome = Risk of surgical site infection

Figure- 6: Forrest plots of subgroup analysis comparing VDZ versus anti TNFa agents and the risk of non surgical site infections in both CD and UC patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-Cl</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>ibd = UC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lightner 2017</td>
<td>4</td>
<td>88</td>
<td>1.43</td>
<td>[0.25; 8.05]</td>
<td>23.9%</td>
<td></td>
</tr>
<tr>
<td>Ferrante 2017</td>
<td>3</td>
<td>34</td>
<td>2.81</td>
<td>[0.45; 17.70]</td>
<td>21.1%</td>
<td></td>
</tr>
<tr>
<td>Yamada 2017 (UC)</td>
<td>0</td>
<td>24</td>
<td>0.44</td>
<td>[0.02; 11.33]</td>
<td>6.8%</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>146</td>
<td>155</td>
<td>1.61</td>
<td>[0.50; 5.22]</td>
<td>51.9%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0%$, $t^2 = 0$, $p = 0.61$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-Cl</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>ibd = CD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamada 2017 (CD)</td>
<td>0</td>
<td>40</td>
<td>1.30</td>
<td>[0.38; 4.41]</td>
<td>48.1%</td>
<td></td>
</tr>
<tr>
<td>Lightner 2018</td>
<td>6</td>
<td>100</td>
<td>1.30</td>
<td>[0.38; 4.41]</td>
<td>48.1%</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td>140</td>
<td>203</td>
<td>1.45</td>
<td>[0.62; 3.39]</td>
<td>100.0%</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Random effects model: 286 | 358 | 1.45 | [0.62; 3.39] | 100.0% |

Test for subgroup differences: $\chi^2 = 0.06$, df = 1 ($p = 0.80$), 0.1 0.5 1 2 10

Experimental = Vedolizumab & Control = anti-TNFa  Outcome = Risk of non-surgical site infections
Figure- 7: Forrest plots of subgroup analysis comparing VDZ versus anti TNFa agents and the risk of intra-abdominal abscess in both CD and UC patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lightner 2017</td>
<td>5</td>
<td>1</td>
<td>7.27</td>
<td>[0.74; 71.11]</td>
<td>37.9%</td>
</tr>
<tr>
<td>Ferrante 2017</td>
<td>1</td>
<td>60</td>
<td>0.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamada 2017 (UC)</td>
<td>0</td>
<td>24</td>
<td>0.26</td>
<td>[0.01; 5.61]</td>
<td>30.2%</td>
</tr>
<tr>
<td>Random effects model</td>
<td>74</td>
<td>110</td>
<td>1.62</td>
<td>[0.06; 42.47]</td>
<td>68.1%</td>
</tr>
</tbody>
</table>

Heterogeneity: \(I^2 = 66\%, r^2 = 3.7080, p = 0.09\)

Figure- 8: Forrest plots of subgroup analysis comparing VDZ versus anti TNFa agents and the risk of anastomotic leak in both CD and UC patients.

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Odds Ratio</th>
<th>OR</th>
<th>95%-CI Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lightner 2018</td>
<td>100</td>
<td>107</td>
<td>0.17</td>
<td>[0.01; 3.12]</td>
<td>31.9%</td>
</tr>
<tr>
<td>Yamada 2017 (CD)</td>
<td>0</td>
<td>40</td>
<td>0.17</td>
<td>[0.01; 3.12]</td>
<td>31.9%</td>
</tr>
</tbody>
</table>

Random effects model

Heterogeneity: \(I^2 = 61\%, r^2 = 3.0212, p = 0.08\)

Test for subgroup differences: \(\chi^2 = 1.01, df = 1 (p = 0.32)\)

Experimental = Vedolizumab & Control = anti-TNFa  Outcome = Risk of intrabdominal abscesses
Evaluating core competencies of interprofessional collaboration: Thematic analysis of students participating in the Community Health Project

**Authors:** Mark Quinn; Jean Laubinger, MPH; Wendy Hildenbrand, PhD, MPH, OTR/L, FAOTA; Cheryl Gibson, PhD

**Introduction/Background:** Engaging health professional students in team-based care is central to achieving the triple aim of improved patient care and population health, and reduced per capita cost of health care. Many health professions design curricula to prepare students to accomplish this goal by structuring classroom workshops that facilitate student engagement with peers from different health professions. Albeit effective, this approach relies on simulated interprofessional interactions that neglect authentic relational team building strategies developed within the workplace. Immersion into an interprofessional environment independent from the academic setting is an invaluable learning tool.

**Methods:** The tangible effect workplace immersion has on student development was investigated. Journal entries from students participating in a University led Community Health Project (CHP) were analyzed. The CHP is a summer internship program that matches health professional students from different disciplines with non-profit agencies throughout Kansas and Missouri. Student interns work at their agency throughout the summer and record their experience in daily journals submitted online. Using a direct thematic analysis, we analyzed 8 weeks of daily journal entries from 14 health professional interns. Themes were constructed based on core competencies defined by the Interprofessional Collaborative Practice 2016 guidelines.

**Results:** Thematic analysis of journal entries identified the core competencies of Values/Ethics n=80, Roles/Responsibilities n=71, Interprofessional Communication n=342, and teamwork n=116.

**Conclusion:** Students in the immersive CHP experience consistently reported daily events that reflect the core competencies of interprofessional collaboration. This approach instills the values of team-based care and should be a fundamental component to every health professions curricula.

**Funding Sources:**
Introduction: Atypical hemolytic uremic syndrome (aHUS) is an uncommon disease process caused by dysregulation of the alternative complement pathway (ACP) that produces microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure. The most common cause of aHUS is due to genetic abnormalities within the ACP which confer disease predisposition. Genetic alterations in complement factor H (CFH) and membrane cofactor protein (MCP) are the most common predisposing mutations. However, approximately 40% of aHUS cases cannot be explained by our current understanding of the disease model. Novel polymorphisms in less studied complement regulators such as complement factor H related 5 protein (CFHR5) may account for a portion of unexplained cases.

Case: A 20-year-old female presented with a three week history of diarrhea, vomiting, fatigue, and lower extremity swelling. On admission her hemoglobin was 6.4 GM/DL, platelets were 133 K/UL, creatinine 36 MG/DL, and smear revealed 2+ schistocytes. Classic HUS was suspected, however, no causative organism e.g., Shiga toxin-producing Escherichia coli, was identified. Six months following she was re-hospitalized twice for a similar presentation. Kidney biopsy revealed acute on chronic thrombotic microangiopathy and acute interstitial nephritis. In the setting of recurrent disease aHUS was suspected and induction therapy with eculizumab was initiated. Genetic panel specific for aHUS confirmed multiple risk variants which included CFH and MCP along with a novel CFHR5 gene polymorphism. She was discharged in stable condition on maintenance therapy with eculizumab and is anticipating renal transplant.

Discussion: Predisposition to atypical hemolytic uremic syndrome is caused by genetic alterations to CFH and MCP. Increased risk may also occur when multiple genetic “hits” occur concomitantly in regulators of the ACP. Furthermore, polymorphisms in CFHR5 serve as another potential avenue for aHUS disease development. In particular, the homozygous polymorphism (C. 1067G>A, p.Arg3565His) in exon 7 of the CFHR5 gene may predispose to disease. In our patient, the commixture of findings limits our ability to develop a strong etiological conclusion about any one particular variant on its own, but does provide unique evidence of a novel polymorphism for future cases to compare, and ostensibly supports the credibility of the multiple hit hypothesis.

Funding Sources: None
Hypercalcemia in malignancy: An inpatient analysis

Authors: Saqib Abbasi, Divya Asti, Bindu Madhavi Mudduluru, Abhishek D Polavarapu, Avinash Boddapati, Gautam Valecha, Alisa Sokoloff

Background: Hypercalcemia is a common electrolyte abnormality and is known to occur in 20-30% of patients with underlying malignancy. The presence of hypercalcemia in malignancy indicates a poor prognosis with increased mortality. We evaluated NIS data of patients who were admitted to the hospital with a primary diagnosis of hypercalcemia associated with malignancy, to look at inpatient trends to get a better understanding of the condition.

Methods: National Inpatient Sample (NIS) for years 2002-2014 has been utilized to identify patients with a primary admission diagnosis of hypercalcemia (ICD-9-CM :275.42) in conjunction with a diagnosis of malignancy. Total number of patients were sub-categorized based on the type of underlying malignancy. The associated incidence and in-hospital outcomes were determined. Linear regression analysis assessed for annual trends in in-hospital mortality, length of stay (LOS), and total charges. A univariate logistic regression analysis was employed to calculate odds ratios (OR) for the effect on in-hospital mortality of the five most common associated cancers.

Results: The most common malignancies associated with admissions for hypercalcemia of malignancy included breast cancer (16.51%), lung cancer (16.50%), multiple myeloma (12.39%), non-Hodgkin lymphoma (8.15%), renal cell cancer (6.53%). In-hospital mortality was higher in patients admitted with hypercalcemia associated with cancer (6%) compared to patients who did not have an underlying malignancy (2%) (p < 0.001). Among those with cancer, in-hospital mortality has decreased from 6% in 2002 to 3% in 2014. In comparing the five most commonly associated cancers, mortality was the highest among patients with a diagnosis of lung cancer (OR 2.45), and lowest among breast cancer (OR 0.98).

Conclusions: Although, hypercalcemia of malignancy is associated with increased mortality this seems to be even higher in patients with lung cancer. Previous reviews indicate that treating hypercalcemia of malignancy did not improve mortality. However, based on the observed trends, it would be interesting if further studies could shed light if aggressive treatment of hypercalcemia would improve mortality.
In Hospital Burden of Venous Thromboembolism in Cancer: A 13 Year Analysis

Authors: Saqib Abbasi, Manisha Pant, Nishitha Reddy and Terenig Terjanian

Introduction:
Patients with malignancies tend to develop a hypercoagulable state which predisposes them to thromboembolic events such as deep vein thrombosis (DVT) and pulmonary emboli (PE). Cancer increases the risk of venous thrombosis several fold with varying degree of relative risks (range 4-7). Various factors including tumor type, location, stage and time since diagnosis influence such incidence. The hospital burden of venous thromboembolism (VTE) associated with cancer has yet to be determined, as well as it's impact on cost, length of stay and mortality. The purpose of this study was to identify the annual trend in incidence, cost, and length of stay of VTE among patients with a diagnosis of cancer as well as determine the associated in-hospital mortality based on cancer origin.

Methods:
Data on inpatient hospitalizations was collected using the National Inpatient Sample (NIS) for years 2002 to 2014. VTE was identified using the clinical classification software code in conjunction with ICD 9 codes for acute pulmonary embolus. Annual trends for incidence, length of stay, and cost of admission were assessed with a linear regression analysis. Associated cancer type and mortality due to PE was evaluated using univariate logistic regression analysis.

Results:
During the years between 2002 and 2014 a weighted estimate of total admissions for VTE among cancer patients is 903,610. This represents 23% of all admissions for VTE. A trending increase in annual admissions is seen from 61,614 in 2002 to 69,585 in 2014. This increase is primarily driven by a primary diagnosis of acute pulmonary embolus, as these admissions increased from an annual 23,042 to 38,780, while admissions with a primary diagnosis of DVT decreased from 38,571 to 30,805. The total cost of admission increased from $19,380 to $40,105 (p<0.001) while the total length of stay decreased from 6.15 to 4.81 (p<0.001). Mortality among patients with PEs with and without cancer are 2.9% vs 5.6% respectively (p<.0001). Notably, patients with a history of esophageal, gastric, liver, pancreatic and lung cancers all had a more than two-fold increase in the likelihood of mortality.

Conclusion:
Among patients admitted between 2002 and 2014, VTE remains a source of mortality and morbidity, VTE associated with cancer significantly more so. Admissions for VTE are increasing, and this is primarily driven by an increase in acute pulmonary emboli. On the other hand admissions for acute DVT is decreasing which could imply that these are being managed more frequently in the outpatient setting. The mortality from pulmonary emboli doubles with a history of cancer. More specifically mortality in this population is most associated with esophageal, gastric, liver, pancreatic, and lung cancers.
<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Odds Ratio</th>
<th>95% Wald confidence limits</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and Neck</td>
<td>1.241</td>
<td>1.104 - 1.395</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Esophageal</td>
<td>2.477</td>
<td>2.269 - 2.704</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gastric</td>
<td>2.275</td>
<td>2.073 - 2.497</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Colon</td>
<td>1.199</td>
<td>1.138 - 1.263</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rectal</td>
<td>1.053</td>
<td>0.937 - 1.182</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Liver</td>
<td>2.374</td>
<td>2.121 - 2.657</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>2.522</td>
<td>2.381 - 2.672</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lung</td>
<td>2.681</td>
<td>2.614 - 2.75</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Bone</td>
<td>1.381</td>
<td>1.143 - 1.669</td>
<td>0.008</td>
</tr>
<tr>
<td>Skin</td>
<td>0.528</td>
<td>0.829 - 1.037</td>
<td>0.187</td>
</tr>
<tr>
<td>Breast</td>
<td>1.16</td>
<td>1.116 - 1.205</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cervical</td>
<td>1.091</td>
<td>0.96 - 1.239</td>
<td>0.181</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1.704</td>
<td>1.585 - 1.833</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.979</td>
<td>0.932 - 1.029</td>
<td>0.410</td>
</tr>
<tr>
<td>Testis</td>
<td>0.812</td>
<td>0.636 - 1.037</td>
<td>0.096</td>
</tr>
<tr>
<td>Bladder</td>
<td>1.043</td>
<td>0.953 - 1.142</td>
<td>0.357</td>
</tr>
<tr>
<td>Renal</td>
<td>1.232</td>
<td>1.132 - 1.34</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Brain</td>
<td>1.581</td>
<td>1.459 - 1.713</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.856</td>
<td>0.714 - 1.026</td>
<td>0.092</td>
</tr>
<tr>
<td>Non-Hodgkin's</td>
<td>1.595</td>
<td>1.497 - 1.699</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1.688</td>
<td>1.555 - 1.831</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Table 1: Univariate logistic regression analysis for type of cancer and its association with mortality in patients with Pulmonary Emboli.
Metastatic plasmacytoid bladder cancer harboring a \textit{CDH-1} mutation and producing high levels of CA19-9. A case Report

Mohammad Telfah, Rahul Parikh, and Anup Kasi

University of Kansas Cancer Center

\textbf{Background:}

Urothelial carcinoma (UC), is the predominant histological type of bladder cancers. Plasmacytoid urothelial carcinoma (PUC) is a very rare and aggressive variant of UCs. This is a report of a patient with a \textit{CDH-1} mutated PUC who presented with disseminated peritoneal metastasis and had high levels of CA 19-9

\textbf{Case:}

A 65-year-old female presented to the hospital with nausea, vomiting, and fatigue. She denied any urinary symptoms. She was found to have acute renal failure with a creatinine of 9.3 mg/dl. Imaging studies of the abdomen and pelvis showed severe bilateral hydronephrosis and bladder wall thickening without masses. Cystoscopy with ureteroscopy revealed no masses to biopsy, but she had bilateral mid to distal ureteral stenosis, and bilateral stents were placed. Her renal function slowly improved. Repeated cystoscopies were done as of recurrent symptoms which demonstrated a rigid bladder without masses within the bladder, but there was nodularity circumferentially with inflamed mucosa. Random resections for biopsy were done. The patient was eventually admitted with severe vomiting, sepsis, and obstructive jaundice. CT chest, abdomen and pelvis revealed dilation of both common bile duct (CBD) and pancreatic duct without gross masses in the pancreas. Pathology report from the bladder wall biopsy revealed PUC. Carbohydrate antigen (CA) 19-9 was elevated > 17000 U/ml. Endoscopic ultrasound (EUS) and was done and the head of the pancreas was normal without masses. The patient then underwent paracentesis, and ascitic fluid cytology revealed metastatic PUC. Next-generation sequencing (NGS) was done from the bladder wall biopsy which revealed pathogenic mutations in \textit{TP53}, \textit{CDH1}, \textit{RB1}, and \textit{ARIDA1A}. The patient was debilitated, and she decided on best supportive care with hospice service. She passed away after 2 months of her initial presentation

\textbf{Conclusions:}

PUC is a rare and aggressive histological variant of bladder cancer. Advanced stage at diagnosis and high relapse rates after treatment with cytotoxic regimens are common; leading to inferior survival in comparison to UC. At the molecular level, somatic alterations in Cadherin-1 (\textit{CDH-1}) gene seems to be characteristic. Exploring the molecular sphere of this disease is prudent to identify possible new targets which might improve patients’ outcomes.
Vision loss with pembrolizumab treatment: A Report of two cases

Mohammad Telfah, Thomas J. Whittaker, and Gary Doolittle

University of Kansas Cancer Center

Background:
Vision loss, and other ocular toxicities, are rare, but detrimental, side effects of immune checkpoint inhibitors. Herein, we report two patients who developed vision loss while on pembrolizumab treatment.

Cases presentation:
Case-1: A 58-year-old man was started on pembrolizumab for advanced melanoma. He was tolerating the treatment well. After receiving 14 cycles of pembrolizumab, he developed acute bilateral vision loss and occipital headaches. An emergent ophthalmologic evaluation revealed bilateral shallow choroidal effusion with bilateral focal exudative retinal detachment. After excluding other possible etiologies, inflammatory process secondary to pembrolizumab was suspected. Pembrolizumab was stopped, and the patient was started on a course of systemic and topical steroids. His vision improved within days and he recovered completely within two months. Calculated Naranjo Nomogram score was 7 indicating a “probable” correlation.

Case-2: A 57-year-old man with stage IIIC melanoma, was started on adjuvant pembrolizumab. After a few weeks of treatments, he reported minor bilateral vision changes that progressively worsened over a period of six months. An ophthalmologic evaluation revealed bilateral posterior uveitis with right optic disc edema. Pembrolizumab-related inflammatory changes were suspected, and he was started on systemic and topical steroids. His symptoms improved within a few weeks and steroids were tapered. He was re-challenged with pembrolizumab and his symptoms quickly re-occurred. Pembrolizumab was stopped indefinitely and the patient again treated with systemic and topical steroids. His symptoms resolved, and his vision returned to baseline within two months. The Naranjo Nomogram score was 9 indicating a “definite” correlation.

Conclusions:
Vision loss is a serious complication that may occur at any point during treatment with PD-1 inhibitors. Vision loss is very distressing to the patients and their families. It is prudent for practitioners to recognize early vision abnormalities in patients receiving PD-1 antagonists to prevent permanent vision loss.
Progressive Multifocal Leukoencephalopathy
Rinda Mousa, MBBCh; Nida Ashraf, MBBS; Daniel R. Hinthorn, MD

Abstract

Background
Progressive Multifocal Leukoencephalopathy (PML) is a rare, debilitating and frequently fatal demyelinating disease caused by the JC virus in immunocompromised patients. Presently, there is no proven effective treatment regimen, and the most effective intervention to date is restoration of the immune system.

Report of a Case

69-year-old woman, apparently immunocompetent, was transferred to KUH for management of PML. The complaints on presentation at the outside hospital included progressive right upper extremity weakness, and word finding difficulties. Initial radiological imaging was concerning for ischemic stroke versus infection but the initial CSF evaluation was negative for infectious workup. Brain biopsy demonstrated JC virus by immune-histochemical staining on pathology. The serum quantitative PCR (qPCR) for JCV was also positive. After transfer to KUH, the neurological exam revealed aphasia, right upper extremity flaccid paralysis, right LE Babinski, positive Romberg, diffuse hyperreflexia, and inability to use the right leg. Evaluation for immunodeficiency showed a transiently low CD4 count of 119. Initial management included cidofovir and mirtazapine with minimal improvement in symptoms. The serum qPCR for JCV increased during therapy and cidofovir was stopped. Therapy was then begun with maraviroc and mefloquine in combination with mirtazapine. She began to improve clinically as affirmed by the patient and her family, as well as serial examinations. At the same time, qPCR for JCV showed a marked reduction in serum viral loads. The serum qPCR has shown a sustained reduction in JCV for the past 5 months. The qPCR for JCV became undetected in the CSF.

Discussion
PML primarily affects patients that evidence immune system suppression. Characteristically, PML is found in patients who have advanced HIV, hematological malignancies, bone marrow transplantation, connective tissue diseases. More recently, persons treated with certain immunomodulatory monoclonal antibodies have also developed PML. In our case, PML apparently developed in a relatively immunocompetent person. The clinical and virologic response on treatment with a combination of therapeutic agents has been unique as there has been no established regimen demonstrated to be consistently effective for PML. Thus, the use of combination therapy with maraviroc, mefloquine and mirtazapine appears to afford a unique possibility of effective therapy.
Title: Improving the Quality of Care Transitions and Care Access for Adult Survivors of Childhood Cancer

Authors: Becky Lowry MD FACP; Jennifer Klemp PhD; Kyla Alsman BSN RN; Joy Fulbright MD; Wendy Hein MSN RN; Hope Krebill MSW BSN RN; Gary Doolittle MD FACP

Background: Comprehensive care for childhood cancer survivors (CCS) is imperative. With improving survival rates in childhood cancer treatment, this is a growing patient population. Studies evaluating the knowledge and comfort of primary care providers and oncology providers have found limitations in knowledge and expressed discomfort with providing survivorship care for these patients. Most providers prefer to work together with a survivorship clinic. Less information is available on specific patient care transition processes, primary care gaps, patient access to care and patient referral trends and needs. Patient-centered care with navigation support is crucial to providing high quality care for these patients.

Aim: Develop a process map for care delivery for CCS and analyze care trends

Process: Developed regional partners to formulate a referral process map for CCS patients needing to establish care in an adult Survivorship Transition Clinic (STC). Collected patient data for 3 years on care needs and care trends and developed patient-centered care structures based on needs. To understand primary care gaps, primary care physician (PCP) needs were determined upon arrival to STC and patients were enrolled in a care structure personalized to their needs. Retrospective chart review was completed on 117 adult CCS from the Kansas University Cancer Center (KUCC) STC between 2014-2017. Subspecialty and primary care needs were analyzed.

Results / Conclusion: Despite their complex medical history and the importance of maintaining medical care, over half of our CCS arrived to STC without an established PCP. The largest number of clinic referrals were initiated by patients as self-referrals. The need for mental health referral echoed the well described impact cancer history has on overall health. Subspecialty referral trends reflected common late effect manifestations of chemotherapy, therapeutic radiation or both highlighting dermatologic screenings, fertility/reproduction, cardiac health, secondary malignancy and/or post-transplant monitoring. Nurse navigation is essential in supporting the care needs of these complex patients.
EECP Therapy for Patients with Mild Cognitive Impairment

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Background: The development of vascular dementia and Alzheimer’s disease (AD) share an association with hemodynamic risk factors. Prospective studies have demonstrated increased levels of exercise, which improves cerebral blood flow (CBF), are associated with less cognitive decline. Unfortunately, patients with signs of dementia, due to cognitive or physical decline, are not always able to exercise.

External enhanced counter pulsation (EECP) is a non-invasive device used for chronic angina and mild heart failure. EECP contains three pressure cuffs wrapped around the calves, lower and upper thighs which are compressed during diastole and deflated during systole. Coronary perfusion pressure, venous return and cardiac output are all improved after completed treatment (35 one-hour sessions). Additionally, most hemodynamic benefits persist for months following the last treatment.

We aimed to evaluate cerebral perfusion changes in patients with mild cognitive impairment (MCI) after 35 one-hour sessions of ECP.

Method: Four patients with MCI were treated with EECP therapy (35 one-hour treatments over 7 weeks). The Hachinski ischemic index score was used to exclude patients with vascular dementia (mean in this study was 3.5). Arterial spin labeling perfusion magnetic resonance imaging (MRI) was used to measure perfusion in three regions of interest (ROI) the hippocampus, inferior parietal lobe and precuneus. We implemented the Alzheimer’s Disease Assessment Scale (ADAS) aimed at measuring dementia severity.

Cognitive function and CBF were measured 24 hours after the last treatment, and six months post-ECP therapy. CBF of twenty healthy (clinical dementia rating = 0) controls was measured with perfusion MRI for baseline comparison.

Results: At baseline, patients had lower CBF compared to normal age matched controls. After EECP, there was increased perfusion in each ROI, maintained six months following the last treatment. Changes in CBF were correlated ($R^2=0.7794$) with the changes in cognitive function score.

Conclusion: EECP therapy improves cerebral perfusion in certain brain regions and there is evidence that these effects may persist for six months post-treatment. Cognitive function appears to be correlated with perfusion rate in the hippocampus and precuneus. Although this study is small, its results are promising and support a need for a larger randomized controlled trial.
**Pitavastatin Lowers Plasma Levels of CoQ10 less than Equipotent Doses of Rosuvastatin or Atorvastatin**

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**Background:** Reduction of CoQ10 following statin therapy is a mechanism for muscle-related adverse events and may be related to risk of incident diabetes. CoQ10 has been found to be deficient in patients with diabetes and may counteract various metabolic disturbances associated with insulin resistance. Meta-analyses have shown increase in risk of incident diabetes following statin treatments is dose-dependent and statin-dependent. Lipoprotein Insulin Resistance (LPIR) is a new biomarker associated with increased insulin resistance and potentially incident diabetes and may be an early indicator of type 2 diabetes risk. We aimed to examine if pitavastatin will lower CoQ10 less and decrease LPIR more than equipotent doses of rosuvastatin or atorvastatin in impaired glucose tolerant adult patient population with dyslipidemia.

**Method:** Single site double blind study of 134 patients with impaired glucose tolerance randomized to pitavastatin (4 mg/qd), rosuvastatin (5 mg/qd) and atorvastatin (20 mg/qd) for 12 weeks. A secondary analysis of the data measured serum LPIR. Nine patients were unable to complete the study.

**Results:** LDL-C reduction was noted among the 3 groups, (p=0.2626), however, pitavastatin decreased CoQ10 less than atorvastatin and rosuvastatin (p=0.0401). No statistically significant difference was observed in ubiquinone (p=0.6988), however the significant change in ubiquinol allowed CoQ10 (p=0.0697) to be marginally significant. No statistically significant differences were observed in the metabolic or lipid measures. LDL-particle number showed significant difference between treatment groups (p=0.0087); subjects in the rosuvastatin arm exhibited small decrease in LDL-particle number, while those in the atorvastatin arm exhibited the largest decrease, followed by pitavastatin. In LPIR data analysis, mean LPIR did not change significantly from pre- to post-treatment for any treatment arm. Both pitavastatin and atorvastatin showed non-zero decreases in LPIR, with the greatest change being with pitavastatin.

**Conclusion:** Pitavastatin showed the smallest reduction in CoQ10 as well as greatest reduction in LPIR compared to atorvastatin and rosuvastatin. Pitavastatin may be preferred considering a statin therapy for patients needing potent LDL-C and LDL-P reduction but at risk of developing diabetes. Further studies are necessary to determine the relevant changes in CoQ10 and in markers of insulin resistance and incident diabetes with statin therapy.
The Change in HDL Proteomics Following Lipid Apheresis Therapy

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Background/Introduction: Lipid-apheresis (LA) is the ultimate therapy for uncontrolled familial hypercholesterolemia and/or elevated Lp(a). Apo B containing lipids are positively charged, unlike HDL-C. Most LA devices use a negatively charged environment to remove LDL-C and Lp(a). LA reduces HDL-C by 10-20%. We aimed to investigate the effects of lipid-lowering LA on HDL particle composition and function.

Methods: LA was performed using Dextran sulfate LDL adsorption (MAO4 Liposorber, Kaneka, Osaka, Japan) or Heparin-induced extracorporeal LDL precipitation (HELP Futura, B. Braun, Melsungen, Germany) methods on 31 CVD subjects with elevated LDL-C and/or Lp(a). HDL was isolated by sequential density ultracentrifugation from 74 plasma samples collected before and after LA. HDL composition was analyzed by targeted proteomics with 35 HDL-associated proteins. HDL particle concentration (HDL-Pima) was measured by calibrated ion mobility analysis with 6 HDL species quantified. Total and ABCA1-specific cholesterol efflux capacity of serum HDL (HDL CEC) was assessed in J774 and BHK cells expressing ABCA1 transporter under mifepristone control, labeled with 3H-cholesterol. Longitudinal data was analyzed using estimating equation models while accounting for multiple visits for subjects with and without adjustment for HDL-C, and with adjustment for multiple testing using Bonferroni method, or Benjamini-Hochberg adjustment.

Results: LA resulted in more than 50% decrease of total cholesterol, LDL-C, triglycerides and 59% decrease in hsCRP. HDL-C decreased by 14% after LA (p<0.001). In contrast, HDL-Pima was unchanged after LA with 25% decrease of small HDL particle population compensated for by 11% increase in medium sized HDL. Both total and ABCA1-mediated serum HDL CEC were decreased after LA by 10 and 14%. LA had profound effects on HDL protein composition resulting in significant changes of 12 proteins with decrease of APOE (-37%), APOC4(-22%), APOA5 (-30%) and SAA1 (-27%), and increase in LCAT (19%) and PON3 (26%) with APOA1 (5%) and APOA2 (10%) (all p<0.01).

Conclusions: HDL undergoes major remodeling during LA. HDL was depleted in proteins also associated with increased CVD risk and enriched with structural proteins and PON3. Paradoxically, HDL CEC was lowered because of LA possibly due to decrease in small HDL particles, major mediators of ABCA1-specific cholesterol efflux.
HEPATOCYTE PRMT1 PROTECTS FROM ALCOHOL INDUCED LIVER INJURY BY MODULATING ALCOHOL METABOLISM AND OXIDATIVE STRESS RESPONSE

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Protein arginine methylation is a common posttranslational modification that plays a role in multiple pathways, including cell cycle control, immune responses, apoptosis and other processes. PRMT1 is responsible for about 85% of total cellular arginine methylation. It catalyzes arginine mono- and dimethylation using S-adenosyl methionine as a methyl donor. In the liver PRMT1 regulates proliferation by promoting HNF4α expression. We found that in alcohol fed mice PRMT1 function in the liver is altered.

The AIM of this study was to determine the impact of PRMT1 activity changes on the liver’s response to alcohol.

METHODS: Mice were fed with Lieber-DeCarli ethanol or control diet for 3 weeks. Hepatocyte specific PRMT1 knockout mice were generated by AAV mediated Cre recombinase delivery to adult PRMT1 fl/fl mice. PRMT1 posttranslational modifications were analyzed by immunoprecipitation followed by detection using specific antibodies. Modification sites were mutated using site directed mutagenesis.

RESULTS: Under normal conditions PRMT1 in hepatocytes suppresses proliferation. However, we found that in alcohol fed mice PRMT1 prevents oxidative stress and promotes hepatocyte survival. PRMT1 knockout in alcohol fed mice resulted in a dramatic increase in hepatocyte death, inflammation and fibrosis. These changes were associated with changes in gene expression of several oxidative stress response genes and alcohol metabolism genes. We found that several of these genes are direct targets of PRMT1, including Sod1 and Sod2. Thus, PRMT1 protects against alcohol induced oxidative stress in the liver. Interestingly, we observed that alcohol-induced PRMT1 dephosphorylation at S297 is necessary for this function of PRMT1. Dephosphorylation altered PRMT1 target specificity, resulting in a shift toward a less pro-inflammatory, more pro-proliferative and pro-survival form. In vitro, both wild type and S297A ‘alcohol mimic’ PRMT1 protected hepatocytes from oxidative stress induced apoptosis, however S297D phosphorylation mimic PRMT1 promoted cell death in these conditions.

CONCLUSION: Taken together these data suggest that PRMT1 is an essential factor of liver adaptation to alcohol; alcohol-induced dephosphorylation shifts PRMT1 toward a pro-survival form. Low levels of PRMT1 as seen in patients with alcoholic cirrhosis can contribute to liver disease progression in these patients.
Improving Patient Portal Enrollment in an Academic Resident Continuity Clinic: Quality Improvement Made Simple.

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Introduction: A frequent challenge faced in resident continuity clinics is a lack of timely communication of test results to patients. Delays in test result communication lead to patient dissatisfaction and have been identified as a serious quality gap in the management of test results. We hypothesized that increasing enrollment in the patient portal (portal) associated with our electronic health record (EHR) would streamline result communication between resident physicians and patients. We also expected that increased portal enrollment would decrease telephone call volume, lessening the nursing workload.

Methods: A standardized, nurse-initiated portal sign-up process was implemented in the General Internal Medicine resident clinic at the University of Kansas Medical Center over a 12-week period. This included the use of a visual reminder on exam room computer monitors, creation of a script to help nurses speak to patients about sign-up and find the sign-up button in the EHR, placement of patient brochures in exam rooms, and education for all nurses and attending physicians. Two Plan-Do-Study-Act (PDSA) cycles were used to evaluate the intervention. To assess the change between baseline and 3-month follow-up in the proportion of patients who were enrolled into the portal system, chi-square test of independence was performed. Statistical analysis was performed using SPSS (IBM SPSS Statistics v. 21.0; New York, NY), and significance was determined at the 0.05 alpha level. Nurses completed surveys at baseline and after implementation, and participated in semi-structured interviews at the end of the study.

Results: During PDSA cycle 1, portal enrollments increased from 570 to 625; a 9.6% increase. During PDSA cycle 2, portal enrollments increased from 625 to 656 patients; a 15.1% increase from baseline (p<0.01) [see figure]. Nurses noticed positive changes in resident responsiveness to results via increased portal messages and decreased telephone encounters. Nurses perceived improved patient understanding regarding their results. Nurses were pleased that the intervention seemed to decrease time spent making and answering phone calls regarding patient results.

Conclusion: Patient portal enrollment can be increased with a standardized, time efficient, and low-cost intervention to enhance patient care and nursing satisfaction.

Funding Sources: None

Figure 1:

Portal Enrollment across 2 PDSA cycles
Relationship between Insulin Requirements, Energy Supply and Triglyceride Concentrations in Diabetic and Non-diabetic Patients Receiving Parenteral Nutrition

Miles, John M, Dunagan, Kelly, Smailovic, Almira, Isautier, Jennifer, Norby, Barbara, McKusick, Michael Kapoor, Ekta, Simha, Vinaya, Basu, Rita

Background: The relationship between energy supply (ES) and insulin requirements (IR) in patients receiving parenteral nutrition (PN) has not been previously examined. Hypertriglyceridemia is known to reflect insulin resistance in free-living individuals, but a relationship between insulin requirements and triglyceride level during PN has not previously been investigated. The present study was undertaken to determine whether a relationship exists between insulin requirements and both energy supply and triglyceride level in PN patients, both with and without diabetes (DM).

Methods: We conducted a detailed retrospective review of records in 1305 patients (942 non-DM, 363 DM) who received both PN for at least 7 days. Demographic data were recorded, and average daily insulin doses (IV + subcutaneous), average daily PN calories received, and average glucose and triglyceride levels were calculated. Relative energy supply was expressed as a percentage of estimated basal energy requirements (BER, Harris-Benedict equation).

Results: DM patients were older than non-DM (62±1 v 56±1 y) had higher BMIs (30.2±0.5 v 27±0.3 kg/m²), and had higher glucose (165±2 v 133±1 mg/dl) and triglyceride (160±5 v 140±2 mg/dl) concentrations, despite lower relative energy supply (104±1% v 110±1% of estimated BER), all P<0.0001. Insulin requirements were greater in DM compared with non-DM (21±1 v 3±0.3 units/d), P<0.0001. There was a significant correlation between insulin requirement and triglyceride level in DM (R=0.16) and non-DM (R=0.23), both p<0.0001. Insulin requirement was associated with BMI in non-DM (R=0.15, p<0.01) but not in DM (R=0.08, p=NS). In an overweight and obese subset of patients (with and without diabetes analyzed together, n=712), there was a borderline correlation between insulin requirements and relative energy supply (R=0.11, p = 0.07).

Conclusions: PN DM patients have higher glucose and triglyceride levels than do non-DM despite receiving fewer relative calories. Insulin requirements correlate with triglyceride levels in both DM and non-DM, consistent with the previous demonstrations of a relationship between dyslipidemia and insulin resistance. Failure to demonstrate a significant correlation between insulin requirements and energy supply may be due to patient heterogeneity, the use of hypoenergetic feeding in some patients, and the retrospective nature of this study.
Elevated Normetanephrines in a Patient with a Lung Nodule

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**Introduction:** Pulmonary carcinoids are a type of neuroendocrine tumor that are diagnosed with a variety of modalities. We present a case where the diagnosis was achieved using a \(^{68}\)Ga-DOTATATE PET scan.

**Case report:** A 69 year old female with a four month history of persistent cough was found to have a left lower lobe nodule on chest x-ray. A CT chest without contrast showed a lobulated, 1.8 cm left lower lobe nodule. PET scan showed a mildly positive left lower lobe pulmonary nodule (SUV 3.72) compatible with possible primary malignancy. She underwent a CT-guided biopsy. Pathology revealed a neuroendocrine neoplasm that was more compatible with paraganglioma. Laboratory studies were remarkable for elevated plasma normetanephrine (1.1 nmol/L) and elevated 24hr urine normetanephrines (82 mcg). \(^{68}\)Ga-DOTATATE PET showed a stable, somatostatin receptor positive left lower lobe pulmonary nodule and additional small nodule in the organ of Zukerkandl. Prior to resection, she was started on doxazosin 1 mg daily for alpha blockage. She underwent left lower lobectomy with mediastinal lymph node dissection. Pathology returned as a neuroendocrine neoplasm consistent with typical carcinoid. We present a case of a lung nodule with elevated normetanephrines and imaging consistent with a neuroendocrine tumor that was determined to be a pulmonary carcinoid.

**Discussion:** Pulmonary carcinoids (PC) are a type of neuroendocrine tumor that account for approximately 1-5% of all primary lung malignancies. Approximately 10-15% of PCs are functional, the most commonly secreted hormone is ACTH; however, they can also produce a variety of other hormones. Most PCs are diagnosed incidentally on CT. Almost 80% of PCs expressed somatostatin type receptor-2 (SSTR-2). Therefore, \(^{68}\)Ga-DOTATATE PET can be used to detect receptor positive PCs as \(^{68}\)Ga-DOTATATE shows higher affinity for SSTR-2. A recent study compared \(^{68}\)Ga-DOTATATE PET to Octreotide Scan in patients with neuroendocrine tumors, found that \(^{68}\)Ga-DOTATATE PET identified 168 lesions vs. 27 with Octreotide Scan. Depending on the study, the sensitivity and specificity of \(^{68}\)Ga-DOTATATE PET ranges 80-100%. In our patient CT and PET scan only revealed a left lower lobe nodule; whereas, the \(^{68}\)Ga-DOTATATE PET showed and additional small nodule in the organ of Zukerkandl.
Miliary TB in a Patient with end-stage liver disease

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Introduction: Miliary tuberculosis (TB) is a rare form of TB that results from massive lymphohematogenous dissemination. We present a case of fatal miliary TB in a patient with end stage liver disease (ESLD).

Case Report: A 52 year-old male with a history of ESLD presented to the emergency department due to multiple falls and confusion. He was recently discharged after admission for pneumonia and culture-negative spontaneous bacterial peritonitis. On admission, a CT chest showed tiny nodular opacities in all lobes and an irregular lytic lesion in the T9 vertebral body. He was also noted to have severe thrombocytopenia and altered mental status. An interferon gamma release assay was obtained and later returned positive. Due to concern for miliary TB, empiric treatment with a liver sparring regimen was initiated - ethambutol, rifampin, levofloxacin and three times weekly amikacin. A bone marrow biopsy showed multiple granulomas, but special stains were negative for acid fast and fungal organisms. The diagnosis was confirmed when his peritoneal culture from previous hospitalization returned positive for mycobacterium tuberculosis (MTB) complex and one sputum sample grew MTB complex. Unfortunately, he went on to develop acute hypoxic respiratory failure, worsening mental status and acute renal failure, which ultimately lead to a fatal arrhythmia.

Discussion: In 2016 approximately 10.4 million people fell ill with TB. Miliary TB is a rare form of disseminated TB that affects up to 2% of those with TB and carries a 33% mortality rate. Miliary TB diagnosis is often delayed as presenting symptoms are non-specific and vary depending on the sites involved. The most common symptoms include fever, cough, weight loss and anorexia. The diagnosis of miliary TB involves obtaining tissue/fluid of the sites involved and sending for AFB smear and culture. Treatment of miliary TB has yet to be standardized. Currently the IDSA recommends 6 months duration for drug suscpetibly miliary TB, however this must be extended if there is bone, joint or meningeal involvement. We suspected both bone and meningeal involvement in this patient. Therapy choice was further complicated by his liver disease, thrombocytopenia, and eventual renal failure.
Detection and Intervention of Prediabetes in A Large Urban Health System: Systematic Failure or Looming Opportunity?

Emily A Newbold, Susan E Carlson, Debra K Sullivan, David C Robbins, Alvin Beltramio, Maren Lowrance, Lemuel R Waitman

Introduction:
Efficient early detection of prediabetes is critical in order to intervene and reduce conversion to T2DM since lifestyle interventions and/or metformin are proven to reduce progression. Retrospective data from a nationally-ranked tertiary academic medical center were analyzed to determine diagnosis rates, frequency of lifestyle and prescription interventions, and to assess characteristics of patients who were most likely to be clinically identified or treated.

Methods:
Data from the EpicCare EMR were analyzed using the University of Kansas Medical Center i2b2-based clinical data repository (HERON). Data were collected for 69,781 patients established in academically affiliated primary care clinics between 2015 and 2017. After excluding for previous diabetes/prediabetes diagnoses or use of glucose lowering agents, 46,855 patients remained to assess for incident prediabetes (ADA criteria). Clinical recognition of the prediabetes diagnosis, nutrition or weight management referral, and metformin prescription were assessed.

Results:
Incident prediabetes occurred in 2,581 patients (5%). Thirty eight percent of those received a charted prediabetes diagnosis, 9% received either a referral to nutrition or weight management, and 4% received a metformin prescription. Females (OR 1.57) or those who had higher BMI (OR 1.02) or A1c values (OR 5.67) had higher odds of receiving clinical recognition (p<0.0001).

Conclusion:
We conclude that relatively few people with prediabetes are clinically noted and even fewer receive interventions that may reduce the conversion to T2DM. There are gender and weight biases; patients with higher BMI, higher A1c values, and females were more likely to have documentation for diagnosis and treatment for prediabetes. These low rates of recognition and treatment are likely to be similar among health care systems across the country. The low rates of recognizing, documenting, and intervening are opportunities to better utilize the EMR and reduce conversion to T2DM.
Miltefosine and Acanthamoeba Keratitis

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Background

Acanthamoeba is a robust, free-living protozoan, ubiquitously found in water and soil, that can cause vision loss in contact lens users. Early diagnosis of acanthamoeba keratitis is of paramount importance, as eradication of the parasite in dormant/cystic stage becomes progressively cumbersome requiring long-term anti-amoebic therapy (of about a year) which may eventually fail causing blindness.

Report of a Case

A 59-year-old woman, contact lens wearer, presented to the KU Ophthalmology clinic with c/o worsening left eye pain, photosensitivity, and redness after having failed treatment with Vigamox and steroid drops for two weeks. Vision was 20/20 in R eye, 20/800 in L eye. Confocal microscopy revealed double walled cysts and lacunae in the epithelium concerning for Acanthamoeba. She was empirically started on oral Voriconazole. Routine culture grew bacillus not anthracis (thought to be a contaminant), AFB and fungal cultures were negative. Acanthamoeba was confirmed by PCR on corneal scraping. Management included oral doxycycline and voriconazole (which was later discontinued and switched to drops); atropine, Vigamox, chlorhexidine, Brolene (propamidine isethionate) and polyhexamethylene biguanide (PHMB) eye drops. The patient was reluctant to pursue penetrating keratoplasty (PKP), and wanted the infection to resolve to decrease chances of repeat graft. She was started on oral miltefosine based on case reports and referred to Infectious Diseases for monitoring of toxicities. She tolerated the medication well, and subsequently underwent deep anterior lamellar keratoplasty (DALK) a month later. Pathology revealed no definitive acanthamoeba organisms. When re-evaluated at four months post-surgery, there was clinical improvement with vision 20/125 in L eye and 20/30 in the R eye.

Discussion

Topical chlorhexidine and PHMB are effective against both trophozoites and cysts and have become the mainstay of therapy for AK. It has been postulated that miltefosine interferes with the mitochondrial function and membrane integrity of Acanthamoeba by disrupting lipid activity, and has excellent activity against the trophozoite and is partially active against the cystic stage. Its use in our patient, in conjunction with topical PHMB and chlorhexidine eradicated the parasite within a month. Potential toxicities to monitor include elevated liver function tests, renal dysfunction, thrombocytopenia, and Stevens-Johnson syndrome.
Electronic medical record alert improves HCV testing for baby boomers in primary care setting: adults born during 1945 -1965

Eyad Al-hihi, Caylin Shankweiler, David Stricklen, Cheryl Gibson, Winston Dunn

Background. Approximately 3.5 million people (1.3%) in the USA are infected with hepatitis C virus (HCV). Although the current generation of direct-acting antiviral agents (DAA) are highly effective, screening, referral and treatment are the rate-limiting factors in HCV eradication. To improve screening rates, the Centers for Disease Control and Prevention (CDC) has expanded risk-based screening to include a one-time 1945–1965 birth cohort “Baby Boomer” screening. Despite these efforts, approximately 50% of persons infected with HCV are unaware of their infections and significant barriers that impede the implementation of testing in primary care settings have been reported. Continuous quality improvement activities are crucial to increasing the rates of HCV screening, making necessary adjustments to address unanticipated barriers and successfully implementing strategies to perform birth cohort testing. In response, this project aims to implement the HCV birth cohort screening guidelines over a 9-month period in the primary care setting at the University of Kansas Health System General Internal Medicine Division.

Methods. To understand the extent of the HCV screening issue, the project team examined baseline data and identified that only 30% of the eligible population had been screened for HCV. An electronic medical record (EMR) intervention was implemented to identify baby boomers who did not have an HCV screening or diagnosis. Additionally, education was provided to all primary care providers in the clinic to increase awareness of the HCV birth cohort screening.

Results. The quality improvement methods increased the percentage of baby boomers who obtained a one-time screening test for HCV from a baseline of 30% to a 55% screening rate during the nine-month project period.

Conclusion. Identifying the HCV screening needs and creating a visual reminder in the EMR can be used to facilitate sustainable awareness and improvement of screening rates. The project team recognizes that continued work is required to close the HCV screening care gaps in the primary care setting.
Osteoporosis management in patients who had a fracture: Women aged 67 and older

Eyad Al-hihi, Caylin Shankweiler

Fragility fractures in older adults are common yet because the fracture is the initial clinical presentation, osteoporosis is often missed. In this study, we retrospectively addressed if patients were receiving proper treatment for osteoporosis after diagnosis of fracture. Our study found that there are many missed opportunities for osteoporosis treatment and are acting to develop a system approach at the inpatient, skilled nursing and rehab, and outpatient levels to appropriately treat and manage osteoporosis. This study aims to develop a system process to address gaps in care for patients with fragility fracture.

The University of Kansas Hospital published results from February 1, 2013-July 31, 2014. During that time 1,219 patients >67 years old sustained a non-traumatic fracture. Evaluation of treatment showed 48 (12%) of the 399 males received a bone mineral density (BMD) or treatment. Additionally, 208 (25.4%) of the 820 females received BMD evaluation or treatment.

Action being taken to treat osteoporosis in women who’ve had fracture include: data collection to identify current care gaps, increase in provider awareness about post-fracture treatment guidelines, implementation of best practice alerts in the electronic health records, and post-hospitalization surveillance reports to identify patients at risk for osteoporosis after fracture.

To conclude, efforts are ongoing to develop effective and efficient post-fracture treatment practices for osteoporosis. Based off our previous data results, oftentimes following the fracture medical treatment and management for osteoporosis is not started. Further action needs to be developed at a system level to identify and address missed treatment opportunities from inpatient to outpatient care. Our project team plans to implement the above action items in three separate PDSA cycles, measure and analyze the results for further improvement efforts.
Treating Lipoprotein(a)-Hyperproteinemia and Progressive Cardiovascular Disease with Lipid-Apheresis in North America

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Background: Lipoprotein(a) [Lp(a)] is an independent cardiovascular risk factor, found in more than 20% of the world’s population, but presently no appropriate pharmacotherapy exists for lowering Lp(a). In Germany, lipid-apheresis (LA) therapy, acutely lowers Lp(a) >60%, is approved for Lp(a)- hyperproteinemia and progressive cardiovascular disease (CVD) irrespective of LDL-C levels. In North America, LA treatment for Lp(a) is approved for patients if their LDL-C level is >160mg/dL.

Methods: Examine a single site’s experience using biweekly LA therapy for the reduction of cardiovascular events in CVD patients who received LA therapy for more than 6 months with an Lp(a) >50mg/dL and LDL-C <160mg/dL.

Results: A total of 15 CVD patients (9 male), ages 56±16 (range 13-82), qualified with a mean Lp(a) level of 123.28 mg/dL and LDL-C level of 100.14 mg/dL. The mean period of LA treatment was 3.54 years (range 8 months-7.5 years). Mean pre-apheresis cardiovascular events and interventions occurred 4.28 years (range 1-11.5 years) before initiation of LA therapy. Since beginning LA therapy only 2 patients experienced a cardiovascular event consisting of stent placement (6 months and 3 years post-LA) for angina symptoms.

Conclusion: Lp(a) is an independent CVD risk factor and LA is currently the only therapy available to successfully treat Lp(a). Until future treatments become available LA therapy should be considered for Lp(a)-hyperproteinemia patients with progressive CVD, on maximum lipid modifying pharmacotherapy, irrespective of their LDL-C levels.

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<td><strong>Lipid Lowering Therapies</strong></td>
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<tr>
<th><strong>Cardiovascular event</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
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<tr>
<td>Myocardial infarction</td>
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<tr>
<td>CABG</td>
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<tr>
<td>Stent</td>
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</tbody>
</table>

*Pre-LA is defined as the time period before LA therapy was initiated, post-LA is defined at the time period that patients received LA therapy.*
Regulation of Dietary Fat Storage and Lipolysis in Visceral Fat of Dyslipidemic Subjects.

**Authors:** Miles, John M, Dunagan, Kelly, Smailovic, Almira, Isautier, Jennifer, Norby, Barbara McKusick, Michael, Kapoor, Ekta, Simha, Vinaya, Basu, Rita

**Background:** The regulation of fat storage and lipolysis in the splanchnic bed is not well understood.

**Methods:** Visceral fat was determined by single-slice CT in overweight and obese subjects (n=12, age 51±3 y, BMI 31±1 kg/m^2) with dyslipidemia (triglycerides 265±40 mg/dl, HDL cholesterol 37±2 mg/dl) but not diabetes (fasting glucose 92±2 mg/dl). After an overnight fast, blood sampling catheters were placed in the femoral artery and in the hepatic and femoral veins. Continuous oral feeding with a liquid meal (50% carbohydrate, 35% fat, 5% protein) was initiated and continued for 8.5h to establish steady-state meal absorption and insulin-mediated suppression of lipolysis in visceral fat. Systemic and splanchnic oleate rate of appearance (Ra) and fractional spillover of lipoprotein lipase-generated fatty acids from circulating triglycerides (a reflection of the efficiency of dietary fat storage) were determined during meal absorption with infusions of [U-^{13}C] oleate and [^{3}H] triolein.

**Results:** Insulin concentrations were 36±4 µU/ml. Systemic and splanchnic oleate Ra were 80±7 and 49±6 µmol/min, respectively; The splanchnic bed was responsible for 64±6% of systemic oleate Ra. Splanchnic spillover was greater than systemic spillover (83±6/ v 32±3%, p<0.0001). Visceral fat was 230±30 cm^3. There was no correlation between visceral fat and systemic oleate Ra (R = 0.38, p=NS). However, there was a strong positive association between the size of the visceral depot and splanchnic oleate Ra (R = 0.72, p = 0.013). Splanchnic oleate Ra also correlated positively with splanchnic spillover (R = 0.75, p = 0.007).

**Conclusions:** In summary, in overweight and obese people with dyslipidemia, the majority of circulating free fatty acids during meal absorption derive from splanchnic lipolysis, which occurs primarily in visceral fat. Rates of splanchnic lipolysis are increased in relation to the size of the visceral fat depot. Further, spillover in visceral fat appears to be coupled to intracellular lipolysis, such that there is increasing inefficiency in dietary fat storage as lipolysis increases. Resistance to the antilipolytic effects of insulin in visceral fat may play an important role in the pathogenesis of dyslipidemia.

Isautier, Jennifer, Hurley, Daniel, McMahon, Molly, Miles, John

**Purpose:** Current ASPEN-SCCM guidelines for energy provision in hospitalized patients recommend that for non-obese individuals, in the absence of indirect calorimetry, a predictive equation (PE) or a simplistic weight-based equation (WBE, 25 or 30 kcal/kg/d) should be used. The present study was undertaken to assess the equivalency of PEs and WBEs.

**Methods:** We calculated energy needs for 1531 normal weight (NW) and overweight (OW) parenteral nutrition patients by comparing estimated basal energy requirements (BER) from the Harris-Benedict (HB) and Mifflin-St Jeor (MSJ) PEs with two WBEs: 25 kcal/kg and 30 kcal/kg. Eight groups were analyzed: young NW (body mass index [BMI] 18.5-24.9 kg/m$^2$), young OW (BMI 25.0-29.9 kg/m$^2$), older NW, and older OW.

**Results:** The mean BMI for the 4 NW groups ranged from 21.4 to 22.5 kg/m$^2$, whereas the mean BMI for the 4 OW groups ranged from 26.9 to 27.3 kg/m$^2$. The relationship between the WBEs and the PEs was highly variable. In the table, weight-based calculation of BER is expressed as a percent of the estimate derived from the two PEs, mean±SD. Estimated BER using WBEs were higher in relation to PEs in older compared to younger patients, and were higher in OW compared to NW patients. In relation to estimates of BER from both HB and MSJ, calculated energy needs using WBEs were systematically greater for women than for men and for older versus young (both P<0.0001); the gender-based discrepancy was greater with MSJ than with HB. There was a strong correlation between weight-based estimates of BER in relation to the two PEs and relative weight (BMI) within all groups, $r^2 = 0.76-0.98$ (P<0.0001).

**Conclusions:** These results suggest that WBEs may underfeed some young, NW individuals (especially men) and may overfeed older, OW patients (especially women). At the very least, the results demonstrate that PEs and WBEs should not be considered equivalent techniques for estimating BER. When calculating BER, practitioners should be aware that WBEs will generate estimates that increasingly diverge from PEs as a function of age and relative weight. These findings suggest that equations that take age, sex, height and weight into consideration are preferable.

<table>
<thead>
<tr>
<th></th>
<th>Young (18-25 y)</th>
<th>Older (63-67 y)</th>
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<tbody>
<tr>
<td></td>
<td>NW</td>
<td>OW</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>women</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>169</td>
<td>115</td>
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<tr>
<td><strong>HB, 25 kcal/kg</strong></td>
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<tr>
<td>Men</td>
<td>97±5</td>
<td>102±8</td>
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<tr>
<td><strong>MSJ, 25 kcal/kg</strong></td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>101±7</td>
<td>108±6</td>
</tr>
<tr>
<td><strong>HB, 30 kcal/kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>116±6</td>
<td>123±9</td>
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<tr>
<td><strong>MSJ, 30 kcal/kg</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>120±8</td>
<td>129±7</td>
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</table>
Spontaneous regression of metastatic adenoid cystic carcinoma – a case report.

Authors: Sajjad Bhatti, Prakash Neupane.

Introduction:
Adenoid cystic carcinoma is an uncommon malignant cancer arising from the salivary glands. For patients with metastatic disease requiring treatment, therapeutic options are limited to multiagent chemotherapy with modest benefit. Here, we describe a rare case of a gentleman with spontaneous regression of biopsy-proven metastatic adenoid cystic carcinoma.

Case Description:
64-year-old male presented to the ENT clinic with the chief complaint of left facial paresthesia and parotid mass for two months. On exam, patient had vague fullness in the left parotid gland with no discrete mass. CT scan showed a lobular mass in left parotid gland measuring 2.7x2.4x1.9 cm. FNA was consistent with cylindromatous neoplasm.

Patient underwent left total parotidectomy with suprathyoid neck dissection. Intraoperatively, a large parotid gland mass was seen displacing the intact facial nerve inferiorly. Pathology revealed high grade adenoid cystic carcinoma measuring 2.6x1.6x1.3 cm. Lymph nodes were negative for metastatic involvement.

Due to pathology findings, metastatic work up was pursued. CT chest showed bilateral pulmonary nodules with a representative RLL nodule measuring 1.6x1.1 cm. FNA from RLL nodule showed metastatic adenoid cystic carcinoma.

He was referred to Oncology to discuss systemic treatment. Due to paucity of effective systemic treatments and absence of symptoms, we recommended active surveillance. Patient completed palliative radiation to primary site to decrease risk of local recurrence and symptoms.

Imaging obtained 6 months later showed interval progression of lung metastasis with representative RLL nodule increasing to 1.9x1.9 cm. He was still asymptomatic. Repeat scan 6 months later showed spontaneous regression in pulmonary metastasis with RLL nodule now measuring 0.9x0.5 cm. Successive scans over the next two years continue to show shrinking size of the lung nodules with the representative RLL nodule most recently measuring 0.8x0.4 cm.

Discussion:
The abscopal effect is a phenomenon in which local radiotherapy is associated with the regression of cancer at a distant metastatic site. This is mediated by priming of immune cells from tumor antigens released from dying irradiated cancer cells. Per our review of the literature, this is the only known case of a patient with metastatic adenoid cystic carcinoma with spontaneous regression.

Peter S. N. Rowe¹, Aditi Gupta¹, Travis Hagedorn² Jason Stubbs¹ and Ellen T. McCarthy¹.

1: Kidney Institute & Department of Medicine University of Kansas Medical Center, KS, United, and 2: LAR, University of Kansas Medical Center, KS

Chronic Kidney Disease – Mineral Bone Disorder (CKD-MBD) is a systemic disorder of mineral and bone metabolism due to progressive renal failure. As the kidneys fail abnormalities in calcium, phosphorus, PTH, vitamin D metabolism, bone (renal osteodystrophy) and vascular/soft tissue calcification occur. Cognitive function also declines as the disease progresses. Morbidity and mortality correlate closely with arterial and coronary calcification and hyperphosphatemia. There are no quality interventions to address these clinical issues. Bone derived ASARM peptides are strong inhibitors of mineralization and induce hypophosphatemia by inhibiting phosphate uptake from the gut. We hypothesize treatment of CKD-MBD rats with ASARM peptides will reverse hyperphosphatemia, reduce soft tissue calcification and improve mortality.

To test our hypothesis, we used a rat 5/6 Nephrectomy CKD model (NEPHREX). Sham operated rats were used as controls (SHAM). Male rats (16 wk, 250 gm) were fed a high phosphate diet to worsen mineral metabolism defects (2% P, 2000 IU Vit D and 0.8% Ca; TEKLAD 170496). ASARM peptide was infused continuously for 4 weeks using subcutaneous implantation of Alzet osmotic pumps. As controls, co-implanted osmotic pumps were used to co-infuse SPR4 peptide - a peptide that neutralizes ASARM peptide. Sera collections were taken at the beginning middle and end of the study. NEPHREX rats treated with ASARM-peptide showed major reductions in hyperphosphatemia with strikingly reduced cardiovascular and brain calcification compared to controls treated with vehicle (Figure 1).

In summary our study shows ASARM peptides infused into a rat model with CKD corrects hyperphosphatemia and suppresses cardiovascular and brain calcification. These findings also confirm our hypothesis and supports the utility of ASARM peptide treatment in patients with CKD-MBD.
Nephrogenic Systemic Fibrosis (NSF) is caused by ASARM peptide induced release of Gadolinium from Gd$^{3+}$-Binding Contrast Agents.

Peter S. N. Rowe$^1$, Travis Hagedorn$^2$ and Ellen T. McCarthy$^1$.

1: Kidney Institute & Department of Medicine University of Kansas Medical Center, KS, United, and 2: LAR, University of Kansas Medical Center, KS

High contrast Magnetic Resonance Imaging (MRI) requires the use of Gadolinium Binding Contrast Agents (GBCAs). Subsets of chronic kidney disease (CKD) patients exposed to GBCAs develop Nephrogenic Systemic Fibrosis (NSF), a progressive disease that leads to acute morbidity and death. Toxic gadolinium (Gd$^{3+}$) release from GBCAs likely plays a role but the etiology of release is unknown. Our previous work showed circulating ASARM-peptides bind to GBCAs and induce release of Gd$^{3+}$. Bone-derived ASARM peptides induce renal-handling defects and bone-mineralization abnormalities. We hypothesize increased levels of acidic ASARM-peptides induce release of free Gd$^{3+}$ resulting in NSF pathology.

To test our hypothesis, we used a rat 5/6 Nephrectomy CKD disease model (NEPHREX). Sham operated rats were used as controls (SHAMX). Male rats (16 wk, 250 gm) were fed a high phosphate diet (2% P, 200IU Vit D and 0.8% Ca; TEKLAD 170496). ASARM peptide was infused continuously for 4 weeks using subcutaneous implantation of Alzet osmotic pumps. As controls, co-implanted osmotic pumps were used to co-infuse SPR4 peptide - a peptide that neutralizes ASARM peptide. Sera collections were taken at the beginning middle and end of the study. Three consecutive, daily bolus injections of Gd$^{3+}$-containing contrast agent (Omniscan$^TM$, gadodiamide) were given 3 days after pump implantation through surgically implanted jugular-vascular-catheters. NEPHREX rats treated with Omniscan$^TM$ and ASARM-peptide developed severe skin pathology, behavioral abnormalities, and joint abnormalities that were consistent with NSF. Also, computed tomography (µCT) showed renal/dermal metastatic calcifications and bone defects in GBCA treated Rats. SPR4-peptide inhibited the ASARM-induced changes.

In summary our study shows ASARM peptides infused into a rat model with CKD induces severe NSF like pathology. Also, these findings agree with our published studies that show: 1. ASARM peptide induces release of toxic Gd$^{3+}$; 2. SPR4 binds to ASARM and inhibits Gd$^{3+}$ release. In conclusion, ASARM peptides likely cause NSF in a subset of CKD patients with high ASARM peptide levels and SPR4-peptide is an ideal candidate adjuvant. These findings have clinical importance for GBCA use in inherited or acquired renal bone-mineral loss disorders with increased circulating ASARM-peptides.
Introduction: Pediatric donor kidneys are important pool of donor kidneys which despite the early surgical complications have good long-term graft survival. We hypothesize that this could be due to decreased Acute Rejection (AR) in pediatric donor kidneys. With increasing age of donor organ there is accelerated immune response especially during the early period of transplantation and compromised repair mechanism of the allograft.

Methods: We used Scientific Registry of Transplant Recipients database to investigate the difference in AR following 1 year of kidney transplant for the years 2000-2015. Deceased pediatric donors were defined as between 0-3 years old. Results. Pediatric donor kidneys had significantly less rejection at both 6 months and 1 year follow up post-transplant (Table 1). At one-year post-transplant, the adjusted odds of AR was 0.50 (CI 0.43-0.59) when adjusted for significant donor and recipient characteristics on univariate analysis. In addition, AR for donors aged less than 1 year had the lowest odd of rejection as compared to other specific ages although the N was small in this group. Long term graft survival was better in the cohort that received pediatric kidneys.

Discussion: We observed statistically significant difference in AR between pediatric (<3 years) using retrospective cohort. There is data suggesting that with increasing age there are more proinflammatory cytokines detected after ischemic reperfusion injury, higher expression of MHC molecules, compromised phagocytic function of dendritic cells, enhanced endothelial cell activation, all contributing to an augmented immune response. This may explain the decreased AR and better graft survival in pediatric donor kidneys.
Table 1. Primary and Secondary Outcomes stratified by donor group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pediatric Donors (&lt;=3ys) (n=2415)</th>
<th>Donors (&gt;3yrs) (n=109300)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Rejection within 1 year (%)</td>
<td>Y</td>
<td>177 (7.3)</td>
<td>12060 (11.0) &lt;0.01</td>
</tr>
<tr>
<td>Acute Rejection within 6 months (%)</td>
<td>Y</td>
<td>130 (5.8)</td>
<td>9033 (8.8) &lt;0.01</td>
</tr>
<tr>
<td>Hospital Length of stay post transplant (median [IQR])</td>
<td></td>
<td>5.00 [4.00, 7.00]</td>
<td>6.00 [4.00, 8.00] &lt;0.01</td>
</tr>
<tr>
<td>Graft Status, as of last follow up (%)</td>
<td>Failed</td>
<td>543 (22.5)</td>
<td>36517 (33.4) &lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Functioning</td>
<td>1872 (77.5)</td>
<td>72783 (66.6)</td>
</tr>
<tr>
<td>Patient status, as of last follow up (%)</td>
<td>Alive</td>
<td>2025 (83.9)</td>
<td>81135 (74.2) &lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Dead</td>
<td>390 (16.1)</td>
<td>28165 (25.8)</td>
</tr>
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</table>
NPM1-TYK2 Fusion Is an Oncogene and a Novel HSP90-Client Protein

Sudhakiranmayi Kuravi, M.S.1, Siddhartha Ganguly, M.D.1, Sunil Abhyankar, M.D.1, Yogen Saunthararajah, M.D.2, Kojo S.J. Elenitoba-Johnson, M.D.3, Jensen Roy, M.D.4, Carolyn Vivian, M.S5, Danny Welch, Ph.D.5, Joseph McGurk, D.O.1, and Ramesh Balusu, PH.D.

1Department of Internal Medicine, Division of Hematologic Malignancies and Cellular Therapeutics, University of Kansas Medical Center, Kansas City, KS; 2Leukemia Program, Department of Hematologic Oncology and Blood Disorders, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; 3Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; 4Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, KS; 5Department of Cancer Biology, University of Kansas Medical Center, Kansas City, KS

Cutaneous CD30-positive lymphoproliferative disorders (LPDs), the second most common type of cutaneous T-cell lymphoma include a clinicopathologic spectrum of benign lymphomatoid papulosis (LYP) and primary cutaneous anaplastic large-cell lymphoma (ALCL). NPM1-TYK2 is the newly identified tyrosine kinase chromosomal translocation in CD30-positive LPDs. Understanding the deregulated functions resulting from new chromosomal translocations in these neoplasms is essential to discover novel therapeutic approaches. Nucleophosmin 1 (NPM1) is a nucleolar phosphoprotein, which functions as a molecular chaperone for proteins and nucleic acids. Tyrosine kinase 2 (TYK2) is a non-receptor tyrosine kinase that belongs to the family of Janus Kinases (JAKs). NPM1-TYK2 is an 81 kDa fusion protein comprising of NPM1 (1-257 amino acids) and the kinase domain of TYK2 (726-1187 amino acids). Since NPM1-TYK2 is a recently discovered fusion gene, we conducted experiments to determine its oncogenic potential. Transduction of lentiviral particles bearing NPM1-TYK2 gene transformed the interleukin-3 (IL-3) dependent Ba/F3 cell line to IL-3 independent growth through constitutive activation of TYK2 kinase and downstream STAT signaling. We used Ba/F3-NPM1-TYK2 xenograft model for understanding the oncogenic potential of the fusion gene in vivo. NPM1-TYK2 induced tumorigenicity in xenograft model was driven by constitutive phosphorylation of TYK2 and activation of downstream effector signaling molecules as observed in transformed Ba/F3 cells in vitro. We also studied the role of N-terminal NPM1 fusion partner in NPM1-TYK2 mediated oncogenicity. Our gene deletion results clearly indicate that NPM1 fusion partner is essential for fusion gene oncogenic potential. Here we report that the treatment of cells with small molecule HSP90 inhibitor, 17-AAG promotes degradation of NPM1-TYK2 fusion protein resulting in downregulation of its oncogenically induced downstream STAT signaling pathways. Mechanistically, dephosphorylation of STAT1, 3, and 5 following 17-AAG treatment resulted in apoptotic cell death of the lymphoma cells. The results obtained using 17-AAG were further corroborated using other HSP90 small molecule inhibitors AUY922 and PU-H71. Immunoprecipitation studies clearly demonstrate that 17-AAG treatment disrupts the interaction between HSP90 and NPM1-TYK2 chimeric protein. Finally, our studies using Ba/F3-NPM1-TYK2 xenograft model tumor growth inhibition was evident in mice treated with HSP90 inhibitor 17-AAG. Collectively, these in vitro and in vivo findings provide evidence for NPM1-TYK2 oncogenicity and therapeutic potential of HSP90 inhibitors for the treatment of a subset of cutaneous CD30-positive lymphoproliferative disorder patients expressing the NPM1-TYK2 chimeric gene.
Forkhead Box F1 (FOXF1) can not only induce a Barrett’s esophagus like metaplastic change but also induce malignant behavior in normal esophageal cells.

Authors: Alok De, Jianping Zhou, Mukut Sharma, Sumedha Gunewardena, Lane Christenson, Ajay Bansal

Background: Multiple GWAS studies have found Foxf1 to be significantly associated not only with risk of Barrett’s metaplasia (BM) but also with its major complication i.e. esophageal adenocarcinoma (EAC). However, data about the role of Foxf1 in Barrett’s pathogenesis are limited.

Aim: To determine whether Foxf1 can induce metaplasia and/or malignant phenotype in an in-vitro model

Methods: Two normal esophageal squamous cell lines (Epc2 and Het-1A) were grown in keratinocyte-SFM medium with supplements (Gibco). Cells were transfected with plasmid construct for Foxf1 with the vector pCMV6-AC-IRE-GFP or empty vector by using Lipofectamine 2000. We performed dose-dependent Foxf1 transfection with serial dilution by a factor of 10 from $4 \times 10^{-1}$ mg to $4 \times 10^{-5}$ mg. Two primary endpoints were: 1) conversion of squamous cells to a Barrett’s like metaplasia defined by increased columnar cytokeratins CK7/CK18 and reduced squamous cytokeratins CK10/CK13 by immunostaining and 2) acquisition of malignant behavior by squamous cells based on epithelial-mesenchymal transition [immunostaining for epithelial (E-cadherin) and mesenchymal (vimentin and SNAIL) markers] and scratch assays. Deep sequencing included control cells, lipofectamine-treated cells and Foxf1-transfected cells to discover Foxf1 regulated transcripts and pathways.

Results: Foxf1 transfection in EPC2 cells increased columnar cytokeratins 7 and 18 and decreased squamous cytokeratins 10 and 13. This metaplastic effect was seen across a 10,000-fold variation in the dose of the transfected plasmid suggesting high potency. Scratch assays showed that Foxf1 promoted wound healing at both 8 and 24 hours in scratch assays. Foxf1 transfection found reduced E-cadherin expression and increased vimentin and SNAIL expression suggesting EMT. All of the above results were confirmed using Het-1A cells. Pathway analysis after deep sequencing found 89 genes to change (up- or down-) that mapped to pathways such as MAPK and p38 signaling. The most differentially expressed gene in Foxf1 transfected cells was $PPM1H$, protein phosphatase, Mg2+/Mn2+ dependent 1H, down-regulated by 89-fold. This gatekeeper gene regulates excessive BMP signaling and its down-stream targets, SMAD proteins.

Conclusion
Foxf1 is a potent inducer of Barrett’s metaplasia like change as well malignant behavior in normal esophageal squamous cell lines. A novel gene regulator of BMP pathway, $PPM1H$, may mediate this effect.
Title: MICRORNA NANOTHERAPEUTICS FOR ESOPHAGEAL ADENOCARCINOMA

Authors: Ajay Bansal, Achim Aigner, Xiamon Hong, Lane Christenson

Background: Esophageal adenocarcinoma (EAC) has a dismal 5-year survival rate of 20%. RNAi using microRNAs (miRNAs) has huge potential in cancer therapeutics. We have devised a novel system of miRNA delivery by complexing them with polyethylenimines (PEIs, inert, positively charged, linear or branched polymers) to form nanoscale complexes to promote cellular delivery.

Aim: To test the feasibility of complexed miRNA nanoparticles as novel therapy for EAC

Methods: Male mice 6-8 weeks of age were administered PEI complexed miRNA both intraperitoneally (i.p.) and orally on days 0, 2, 4, 6, 8. Given that specific microRNAs can be tumor-suppressive or oncogenic and therefore require replacement or inhibition, we tested replacement (miR-192 mimic) and inhibition (locked nucleic acid against miR-205 i.e. antimiR-205) at 10 µg/150µL per injection or gavage. These miRNAs were previously shown to be important in EAC. PEI-complexed scrambled miRNA was used for controls. Mice (n=10 per group) were sacrificed on day 10. A trained animal pathologist reviewed liver and kidney H&E stained sections for toxicity.

Results: During replacement of miRNA-192 that is minimally expressed in the native esophagus: i.p. administration increased miRNA-192 in the esophagus by 150±20 fold, in the proximal stomach by 100±15 fold and in the distal stomach by 120±13 fold and oral administration increased miRNA-192 in the esophagus by 4±3 fold and in the distal stomach by 10±3 fold. During inhibition of miRNA-205 that is highly expressed in the native esophagus: i.p. administration reduced miRNA-205 in the esophagus by 4±1.5 fold, in the proximal stomach by 5±1.6 fold and in the distal stomach by 4±1.7 fold and oral administration did not reduce miRNA-192 in the esophagus (fold change 1.1±0.4) but reduced it in the proximal stomach by 2.1±1.2 fold and in the distal stomach by 2.5±1.2 fold. There were no deaths. H&E sections did not demonstrate necrosis of hepatocytes or glomeruli.

Conclusion: Our novel method of delivery was more effective at miRNA replacement than miRNA inhibition and should be further tested in animal models of EAC.
Yield of Screening for Lynch Syndrome – A Comparison between Pre-Surgical Biopsies and Surgical Specimens

Jack Harrigan; Christian Davis; Rashna Madan, MBBS; Dan Buckles, MD; Kevin Kennedy, MS; Amit Rastogi, MD; Mojtaba Olyaee, MD; Anwaar Saeed, MD; Ajay Bansal, MD

Introduction: Lynch syndrome is a genetic disorder characterized by a high risk of developing colorectal cancer. Accurate pre-surgical information about the presence of Lynch syndrome can allow the surgeon to determine the extent of surgical resection to reduce risk of metachronous cancers. Whether the yield of screening for Lynch syndrome by pre-surgical biopsies and surgical specimens is comparable remains uncertain.

Aim: To compare the yield of screening for Lynch syndrome between pre-surgical biopsies and surgical specimens by immunohistochemistry (IHC) and microsatellite instability (MSI) testing.

Methods: A structured electronic RedCap database of patients diagnosed with colon cancer was constructed for this retrospective, single-center study. SNOMED codes were used to identify patients diagnosed with colon cancer between January 1, 2016 and June 30, 2018. Colon cancer biopsy or surgical specimens were screened either via IHC for loss of expression of 4 mismatch repair (MMR) proteins: MLH1, MSH2, MSH6, and PMS2 or via PCR for low versus high MSI, based on the recommendations of the referring oncologist. All patients for whom the specimen showed loss of expression of any of the MMR proteins or high MSI underwent confirmatory genetic testing using commercial assays. Statistical analysis was performed by Student’s T-test with Bonferroni correction for multiple testing. A P value of < .05 was considered significant.

Results: Of the 258 patients with colon cancer, 69.0% (178/258) underwent screening using colon biopsies and 30.6% (79/258) using surgical specimens. The two groups were well-matched for age, gender, ethnicity, cancer location and PREMM risk score (Table 1). A higher proportion of patients in the surgical group had early stage cancers (Table 1). The proportion of patients with absent MMR proteins was similar between the biopsy group and the surgical group (MLH1: 15.3% vs. 12.0%, P=0.63; MSH2: 4.0% vs. 1.3%, P=.35; MSH6: 6.3% vs. 2.7%, P=.33; 13.1% vs. 14.9%, P=.50) (Table 2). The proportion of patients with high MSI was similar between the biopsy group and the surgical group (19.5% vs. 19.1%, P=.95) (Table 2). The proportion of patients with the final diagnosis of Lynch syndrome was similar between the biopsy group and the surgical group (5.1% vs. 3.8%, P=0.65).

Conclusions: IHC and MSI testing had a similar proportion of abnormal results between the pre-surgical biopsies and the surgical specimens. This led to similar rates of final diagnosis of Lynch syndrome between the two groups. Pre-surgical testing for Lynch syndrome in biopsy specimens of colon cancer is accurate in a real-world setting.
Table 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Colon Biopsy</th>
<th>Surgical Specimen</th>
<th>P-Value</th>
</tr>
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<tr>
<td>Mean ± SD</td>
<td>61.4 ± 15.5</td>
<td>64.2 ± 13.0</td>
<td>0.169</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>60.9 (50.4, 72.8)</td>
<td>64.5 (53.3, 73.6)</td>
<td>0.169</td>
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<td>Missing</td>
<td>5</td>
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<th>Gender</th>
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<tr>
<td>Male</td>
<td>74 (41.6%)</td>
<td>31 (39.2%)</td>
<td>0.725</td>
</tr>
<tr>
<td>Female</td>
<td>104 (58.4%)</td>
<td>48 (60.8%)</td>
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<th>Ethnicity</th>
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<tr>
<td>Asian</td>
<td>8 (4.5%)</td>
<td>0 (0.0%)</td>
<td>0.236</td>
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<tr>
<td>Black or African American</td>
<td>12 (6.8%)</td>
<td>7 (8.9%)</td>
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<td>White/Non-Hispanic</td>
<td>149 (84.2%)</td>
<td>67 (84.8%)</td>
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<tr>
<td>Hispanic</td>
<td>4 (2.3%)</td>
<td>4 (5.1%)</td>
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<tr>
<td>Other</td>
<td>4 (2.3%)</td>
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<th>Colon Cancer Location</th>
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<td>Cecum</td>
<td>23 (12.9%)</td>
<td>14 (17.7%)</td>
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<tr>
<td>Ascending</td>
<td>28 (15.7%)</td>
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<td>3 (1.7%)</td>
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<td>Transverse</td>
<td>14 (7.9%)</td>
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<td>Splenic</td>
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<td>6 (3.4%)</td>
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<td>28 (15.7%)</td>
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<td>1 (1.5%)</td>
<td></td>
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<tr>
<td>I</td>
<td>20 (12.3%)</td>
<td>16 (23.5%)</td>
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<td>IA</td>
<td>15 (9.3%)</td>
<td>0 (0.0%)</td>
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<tr>
<td>IB</td>
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<tr>
<td>IIA</td>
<td>24 (14.8%)</td>
<td>14 (20.6%)</td>
<td></td>
</tr>
<tr>
<td>IIB</td>
<td>2 (1.2%)</td>
<td>1 (1.5%)</td>
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<td>IIC</td>
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<td>11 (6.8%)</td>
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<td>26 (16.0%)</td>
<td>7 (10.3%)</td>
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<td>16 (9.9%)</td>
<td>6 (8.8%)</td>
<td></td>
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<tr>
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<td>29 (17.9%)</td>
<td>12 (17.6%)</td>
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<tr>
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<td>Mean ± SD</td>
<td>4.5 ± 7.7</td>
<td>3.2 ± 5.9</td>
<td>0.178</td>
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<td>Median (IQR)</td>
<td>2.3 (1.5, 4.3)</td>
<td>1.8 (1.3, 3.2)</td>
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<tr>
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<td>5</td>
<td>1</td>
<td></td>
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<td>MMR Protein</td>
<td>Colon Biopsy</td>
<td>Surgical Specimen</td>
<td>P-Value</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
<td>------------------</td>
<td>---------</td>
</tr>
<tr>
<td>MLH1 loss</td>
<td>15.3%</td>
<td>12.0%</td>
<td>0.628</td>
</tr>
<tr>
<td>MSH2 loss</td>
<td>4.0%</td>
<td>1.3%</td>
<td>0.352</td>
</tr>
<tr>
<td>MSH6 loss</td>
<td>6.3%</td>
<td>2.7%</td>
<td>0.329</td>
</tr>
<tr>
<td>PMS2 loss</td>
<td>13.1%</td>
<td>14.9%</td>
<td>0.500</td>
</tr>
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</table>
Is low health literacy associated with more medication discrepancies?

Ammar Haikal, Brittany Melton, Crystal Burkhardt, Deon Cox Hayley

University of Kansas Medical Center, KC, KS

Supported By: Kansas City Area Life Sciences Institute

**Background:** Many studies have linked poor health outcomes and higher mortality to low health literacy in the elderly. This study evaluated the relationship between low health literacy and increased medication discrepancy events in a vulnerable geriatric population.

**Methods:** Baseline data from a prospective study assessing an Interprofessional Chronic Care Management model for Geriatrics included illness severity, self-reported functionality, health literacy, and potentially inappropriate medications (PIM). Additionally, medication discrepancies were identified on initial reconciliation. Medication discrepancies were grouped as 1) documented medications that are not currently being taken (omission by patient); 2) documented medications that are being taken differently (such as different dose, frequency); and 3) additional medications that were not previously documented.

**Results:** Preliminary data showed that out of 58 patients enrolled in this study, the median age was 72 years, 52% male, and 43% had some cognitive impairment (CI). Average Charlson Comorbidity Index (CCI) was 5.7. On the Short Form 12v2, 24% reported their health as excellent to very good and 42% reported limitations in completing moderate activities. 50% were not completely confident in filling out forms and 40% received help at least occasionally to read hospital materials. 76% had low health literacy for reading and 62% had low health literacy for filling out forms. Medication reconciliation was completed on 49 patients. All of the 49 patients had at least one identified PIM. There were 337 total medication discrepancies noted. Among patients with medication discrepancies, ANOVA analysis showed a significant difference between those with a high and low CCI score (p=0.002) and approaching significance for reading between high and low literacy (p=0.068) and not significant for filling out forms between high and low literacy (0.127).

**Conclusions:** Low health literacy in older adults maybe associated with higher medication discrepancies. Higher occurrence was identified in males. Patients with a high CCI had higher medication discrepancies than in those with low CCI. This suggests that improving disease comorbidities may decrease occurrence of medication discrepancies. More studies are needed to identify the influence of low health literacy on medication discrepancies.
Feasibility and Implementation of a Post-Hospital Follow-up CF Clinic in a Rural Catchment Area

Joel Mermis MD, Tisha Bromstedt RRT, Natalie Holland RN, Mike Crosser MD, Jamie Klamm ARNP, Cynthia Orscheln RN, Joyce Funk RN, Dena Kemble RN

Background:
The adult CF center at UKHS cares for more than 230 adults with from five area states, with 49% of patients residing outside of the KC greater metro. As pulmonary exacerbation is a high-risk time for lung function loss, we established a post-hospitalization follow-up clinic for patients discharged on home IV antibiotics. He we report the feasibility of this clinic with such a large patient catchment area.

Methods:
Patients hospitalized at UKHS for CF exacerbation who were discharged home on IV antibiotics with an FEV1 that was not yet at baseline were offered a follow-up clinic appointment. The appointment was scheduled at day 14 of IV antibiotic treatment. If FEV1 was not yet at baseline, IV antibiotic extension for at least 1 week was recommended. Distance traveled, antibiotic duration, and patient satisfaction were assessed.

Results:
Forty-four patients between Aug. 2017 and April 2018 qualified for the follow-up clinic. Three patients (7%) met criteria but were not offered a follow-up and were excluded from analysis. Twenty-eight patients (64%) maintained their follow up appointment and traveled an average round trip distance of 117.4 miles (range 1-774 miles). Ten pts (23%) with average distance to travel of 150.9 miles declined the follow-up. Three pts (7%) with average travel distance of 125.7 miles did not show or canceled their appointment. Mean antibiotic duration of those who attended the follow-up clinic was longer than those who did not attend clinic at 17.1 vs. 16.4 days, respectively. Patients who declined or did not show for follow-up appointment had lower FEV1 than patients that maintained the appointment at 47% vs 55.6%, respectively (p-value 0.3). Of patients who completed the survey, when asked if the follow-up clinic was beneficial, the average score was a 4.5, with 4.0 being ‘agree’ and 5.0 being ‘strongly agree.’

Conclusions:
Many adult patients prefer to complete antibiotics at home instead of the hospital. Despite a large catchment area, our results suggest pulmonary exacerbation follow-up clinic was valued by patients and has a positive effect on post-hospitalization outcomes. Future work will evaluate the impact post-hospitalization follow-up clinic has on probability of FEV1 recovery.
NARCOTICS USAGE PATTERNS IN THE INPATIENT SETTING - IDENTIFYING WAYS TO IMPROVE PATIENT SAFETY

Khaldoun Haj Mahmoud, Ahmad G Tarakji, Chris Groutas, Eyad Reda, Rafia Rasu, Jaehoon Lee, Cheryl Gibson

Background

Inpatients frequently require opioid analgesics, with more than half of patients receiving opioids. With the rise of opioid therapy and mortality from these medications, the need to identify prescription patterns has become urgent. This study aims to determine the prevalence of type of opioid used on internal medicine admissions, and to discern patterns of opioid use.

Methods

Data for patients who received any opioid analgesic therapy during their inpatient stay between 2015-2017 were included in the analyses. Opioid dosages administered were obtained and standardized by converting to the oral morphine equivalent. Mean cumulative daily dose of opioids was calculated for each admission. Bivariate analysis was conducted to identify variables that have a significant association with opioid analgesic therapy for inclusion in a subsequent multivariable analysis. Stepwise regression using Bayesian Information Criterion and forward-backward selection method was used.

Results

The sample included 716 admissions. Patient age was 56 ± 18 years with 57% female. Mean stay was 3.5 days. The most frequently administered opioids were oxycodone and fentanyl. 13% of inpatients received 2 doses of IV opioid medications in the last 24 hours of the inpatient stay. The mean opioid dose for each patient remained consistent regardless of length of admission; however, frequency of opioid administrations decreased throughout the patient stay. Variables associated with opioid therapy were history of diabetes (DM), diabetes complications (DMcx), drug abuse, psychoses, and length of stay. DM and DMcx have a significant effect on opioid daily use. Drugs, history of psychoses, and LOS have a positive effect on opioid daily use. These predictor variables explained 14% of the variance of opioid daily use.

Conclusions

This study provides insight into opioid prescribing patterns for inpatients and the need to set appropriate protocols for pain relief practices. 13% of patients received IV opioid medications within 24 hours of discharge. This study suggests high utilizers of opioid therapy can be characterized as those who have longer periods of inpatient stays and a history of diabetes, psychoses, or drug abuse. However, a substantial degree of unexplained variance in the best fit model suggests that other factors are in play.
Bi-Valvular Fungal Endocarditis: Challenging to diagnose and harder to manage

Ethan Hacker MD, Jesse Richards DO, Michael Pieropoline DO, Fernando Merino MD.

University of Kansas Medical Center, Kansas City, KS

Introduction:
Fungal Endocarditis (FE) is a rare, serious disorder with mortality approaching 50%. Diagnosis can be difficult, is usually made post-mortem, and presents resembling bacterial endocarditis.

Case description:
A 33-year-old man with a medical history of osteosarcoma, IV drug abuse, infected femur hardware, amputation and subsequent bacterial endocarditis requiring valve replacement presented with complaint of arm weakness, fevers, and facial droop. Physical exam revealed hypotension, tachycardia, and weakness in his left arm. He had an active precordium, loud mechanical mitral valve murmur, left above knee amputation, but otherwise normal exam. CT confirmed MCA ischemic stroke, and echocardiography showed aortic insufficiency, mitral stenosis from obstructing vegetations, pulmonary hypertension, and an akinetic, dilated right ventricle. Repeated cultures grew Candida albicans, confirming a diagnosis of FE. Antifungal therapy was initiated, and surgery was consulted for valve replacement. Informed of his high risk, the patient declined surgery. His cardiac function declined, though repeat echocardiography showed decrease in size of the vegetation. Shortly thereafter, he developed left arm paralysis, and MRI demonstrated new cerebral infarction. The patient then developed pain, loss of pulses, and purple macules on his right leg. CTA showed complete occlusion of the popliteal artery, and a fungal embolus was removed. Despite these events, the patient survived on a course of amphotericin B, flucytosine, and fluconazole. Even still, FE is a formidable diagnosis, and his long-term prognosis remains guarded.

Discussion:
FE is a serious infection, posing a >50% mortality to the patient, and prompt diagnosis can be challenging. Here, diagnosis was made via positive blood cultures despite adequate antifungal therapy, however it is not always so straightforward. To further complicate diagnosis, invasive infection can be present without fungemia, making negative blood cultures unreliable. It is important to maintain high suspicion for the disease in high risk patients, particularly when no improvement is observed on antibacterial coverage.

This case demonstrates the propensity for embolic phenomena in FE, further complicating its management. It was clear in our patient that surgery was indicated, but repeated embolic events despite heparinization complicated his treatment. Fortunately, this patient improved with medical treatment and embolectomy.

References
BARRETT’S ESOPHAGUS INTERNATIONAL CONSORTIUM STUDY: DETECTION OF POST-ENDOSCOPY NEOPLASTIC PROGRESSION IN PATIENTS UNDERGOING SURVEILLANCE


Introduction: Post-colonoscopy colorectal cancer (PC-CRC) is used as a key quality indicator of colonoscopy. A comparable tool for surveillance of patients with Barrett's esophagus (BE): the number of post-endoscopy high-grade dysplasia or esophageal adenocarcinoma (PE-HGD/EAC). In this study, we aimed to assess the PE-HGD/EAC, which reflects the expected number of cancers missed.

Methods: In this multicenter prospective cohort study inclusion criteria were: confirmed intestinal metaplasia (IM) and a BE length 2 cm at baseline, and surveillance 6 months, without development of HGD/EAC during this interval. Data was collected at every surveillance endoscopy and histopathological results obtained. The study endpoint was HGD or EAC development. We assumed BE to progress stepwise from no IM to NDBE to LGD to HGD, EAC. we determined the number of successive endoscopies in which steps were passed over in the expected stepwise progression, and the deviation of surveillance intervals from guidelines both in patients who eventually developed HGD or EAC (cases), compared to patients without HGD or EAC (controls).

Results: We included 1780 patients (83% male, median age 59.7 years) with a median BE length of 4 cm (IQR 2-6). In 102/8199 (1.2%) endoscopies at least 1 step was missed. HGD was diagnosed in 97 patients; the last endoscopy prior to diagnosis of HGD showed NDBE in 42 (43%) and LGD in 44 (45%). Similar proportions were detected for the 32 patients who developed EAC (47% NDBE, 41% LGD) (Table 1). If the histology was no IM/NDBE, the surveillance interval was as recommended for cases in 9.0% of endoscopies, for controls in 14% (p=0.05). For endoscopies with LGD the surveillance interval was more often lengthened in controls (17%), than in cases (5.4%, p<.01) (Table 2).

Conclusion: The prevalence of missed steps of uncomplicated BE to neoplastic progression was the highest in the endoscopy prior to diagnosis of HGD or EAC. This could not be explained by a difference between cases and controls in the mean deviation of surveillance intervals. It may be a sign for either missed abnormalities, misdiagnosis due to sampling error, or because the expected stepwise progression is not required in pathogenesis.
Table 1. Transition matrix of lag endoscopy to current histopathology diagnosis, reported per surveillance endoscopy. Results of baseline and FU endoscopies were reported. *Boxes with $1$ missed step.

<table>
<thead>
<tr>
<th>FROM</th>
<th>TO</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>missing</td>
<td>missing</td>
<td>999 (12%)</td>
</tr>
<tr>
<td>no IM</td>
<td>no IM</td>
<td>406 (5.0%)</td>
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<tr>
<td>NDBE</td>
<td>NDBE</td>
<td>5623 (56%)</td>
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<tr>
<td>LGD</td>
<td>LGD</td>
<td>1171 (14%)</td>
</tr>
<tr>
<td>1320 (16%)</td>
<td>544 (8.6%)</td>
<td>5228 (64%)</td>
</tr>
<tr>
<td>977 (12%)</td>
<td>97 (1.2%)</td>
<td>32 (0.4%)</td>
</tr>
<tr>
<td>8199 (100%)</td>
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Table 2. Difference in deviation from surveillance interval as recommended by the guideline between cases and controls in absolute (shortened, as recommended, lengthened) and mean deviation (in years), subdivided for endoscopies with prior histology no IM/NDBE or LGD.

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<th>Deviation in absolute numbers</th>
<th>Total number of endoscopies</th>
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<td>controls</td>
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<table>
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<th>Deviation in mean deviation (time in years with 95% CI)</th>
<th>Total number of endoscopies</th>
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</thead>
<tbody>
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<td></td>
<td>controls</td>
</tr>
<tr>
<td>no IM / NDBE</td>
<td>-1.9 (-2.4;1.0)</td>
</tr>
<tr>
<td>LGD</td>
<td>-0.6 (-0.8;0.4)</td>
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</table>
Regurgitation is an Independent Risk Factor for Nocturnal Symptoms in Patients with GERD: Results from a Single Center Prospective Observational Study

Jesica Brown, Vijay Kanakadandi, Sreekar Vennelaganti, Prashanth Vennalaganti, Sravanthi Parasa, Benjamin Alsop, Mohammad A. Titi, Ajay Bansal, Kevin Kennedy, Abhiram Duvvuri, Kapil Kohli, Babak Gachpaz, Anusha Vittal, Neil Gupta, Prateek Sharma

**Background:** Gastroesophageal reflux disease (GERD) affects a large percentage of adults and is the most common reason for performing upper endoscopies. The symptoms of GERD, including heartburn and regurgitation, can significantly affect the patient's quality of life. However, regurgitation and its manifestations are often not addressed, or are under-elicited by clinicians. Objectives: To assess the frequency and factors that predicts heartburn and regurgitation in GERD patients.

**Methods:** Consecutive patients presenting to a tertiary Veteran's Affairs referral center for index upper endoscopy were enrolled in this prospective cohort study. In all included subjects, the indication for endoscopy was upper GI symptoms. Patients were asked to complete a validated questionnaire to document the onset, duration, frequency and severity of GERD symptoms (heartburn and acid regurgitation). Demographic information, body mass index (BMI), and use of aspirin/nonsteroidal anti-inflammatory drugs were recorded. A univariate analysis of symptom patterns (need to tell us which symptom patterns) was performed with chi squared and t-tests. A multivariate logistic regression model was used to evaluate independent predictors of each symptom profile. Variables chosen included: Age, Gender, Hiatal Hernia, Erosive Esophagitis, BMI, Nocturnal Symptoms, and Proton-Pump Inhibitor Use. Results: A total of 1,180 patients were included in the study. 1,087 (92%) reported having symptoms of regurgitation, heartburn or both. 229 (19%) reported heartburn without regurgitation. 858 (73%) reported regurgitation, with (94%) or without (6%) heartburn (93% male, 83% Caucasian, mean age 56.5 years SD ± 12.9). Nocturnal symptoms were significantly more common among patients who had regurgitation versus heartburn alone (79.7% vs. 49.8%, p<0.001). After adjusting for age, gender, race, hiatal hernia and erosive esophagitis, regurgitation was an independent predictor of nocturnal symptoms on a multivariate analysis (OR 4.51 (3.25, 6.26)) (Table).
**Conclusion:** Clinicians tend to focus on heartburn more than regurgitation in symptomatic GERD patients. Our study showed that regurgitation is an independent risk factor for nocturnal symptoms. When evaluating patients with GERD, clinicians should specifically address the issue of regurgitation given its association with potentially distressing nocturnal symptoms and is less likely to respond to pharmacologic acid suppression but may potentially need antireflux surgery.

<table>
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<tr>
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<th>Any Regurgitation (n=858)</th>
<th>No regurgitation (n=229)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
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<td>Age</td>
<td>56.5±12.9</td>
<td>58.5±12.3</td>
<td>0.99 (0.97,1.00)</td>
<td>0.63</td>
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<tr>
<td>Female Gender</td>
<td>7.4%</td>
<td>5.7%</td>
<td>1.13 (0.59,2.18)</td>
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<td>Caucasian</td>
<td>83.0%</td>
<td>85.2%</td>
<td>0.93 (0.60,1.44)</td>
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<td>Hiatal Hernia</td>
<td>49.8%</td>
<td>49.3%</td>
<td>0.87 (0.63,1.21)</td>
<td>0.95</td>
</tr>
<tr>
<td>Erosive Esophagitis</td>
<td>32.8%</td>
<td>29.3%</td>
<td>1.01 (0.71,1.45)</td>
<td>0.95</td>
</tr>
<tr>
<td>Nocturnal Symptoms</td>
<td>79.7%</td>
<td>49.8%</td>
<td>4.51 (3.25,6.26)</td>
<td>&lt;0.001</td>
</tr>
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Table 1: Regurgitation in GERD Patients
Computed Tomography Dependent Diagnosis of Crowned Dens Syndrome; a Cervical Manifestation of Patients with Calcium Pyrophosphate Dihydrate Crystal Deposition Disease

Ammar Haikal1, Brian M Everist2, Pim Jetanalin3, Mehrdad Maz2, 1Department of Internal Medicine; 2Department of Radiology (MSK); and 3Division of Allergy, Clinical Immunology and Rheumatology, Department of Medicine; The University of Kansas Medical Center,

Background: Crowned Dens Syndrome (CDS), a variation of Calcium Pyrophosphate Deposition Disease (CPPD), is a radiologic-clinical entity defined by the association of radiological calcifications around the odontoid process and periodic cervico-occipital pain. We report a retrospective review of 34 cases in a tertiary medical center.

Methods: This is a retrospective chart and imaging study review from a tertiary medical center from 11/1/2005-10/31/2015. A total of 191 Patients with a diagnosis of CPPD and/or CDS were included. Terms used in the search included pseudogout, CPPD and CDS. The terms chondrocalcinosis and calcification were used in the radiology registry. 57 patients had CT imaging of the cervical spine performed. The CTs were analyzed by a musculoskeletal radiologist for the presence of periodontoid calcifications.

Results: Of the 191 patients with CPPD, 57 had c-spine CTs obtained for different indications; 34 of whom (34/57, 59.64%) had periodontoid calcifications. Only 12/34 patients were formally diagnosed with CDS by rheumatologists. The others, 64.7% (22/34) were either not seen by a rheumatologist or not diagnosed with CDS if seen by other specialties. The median age was 78.5 years, with 73.52% over 70 years-old, and 24/34 (70.58%) were female. 50% (17/34) were symptomatic, defined as presence of acute to sub-acute neck pain within 6 weeks of performing the c-spine CT. The majority (82.35%, 28/34) had additional sites of chondrocalcinosis on joint radiographs: 8 patients (28.57%) had three or more sites of chondrocalcinosis in locations typical of CPPD (wrist ligaments, menisci, symphysis pubis, hips, or shoulders). Six patients did not have joint radiographs for review. 47.5% (16/34) of patients who had CDS and chondrocalcinosis elsewhere, also carried metabolic diseases, including: hyperparathyroidism (2), hypothyroidism (10), hypomagnesemia (2) and hypophosphatemia (2). None of the patients had a documented history of hemochromatosis or evidence of iron overload based on laboratory tests.

Conclusion: Crowned Dens Syndrome is an under-recognized entity, which should be considered when evaluating elderly patients with neck pain in the setting of CPPD. Our data concludes that (59.64%) of patients with CPPD who had c-spine CTs demonstrated findings consistent with CDS. However, the true incidence and prevalence of CDS in general population or in those with CPPD remains unknown. C-spine CT should be considered in the workup of patients with neck pain and associated diagnosis of CPPD or chondrocalcinosis in other joints, as radiographs and MRI may not be diagnostic.
Typical findings of periodontoid calcifications on noncontrast cervical spine CT with curvilinear calcification of the transverse ligament seen in both sagittal (A) and axial (B) planes.
A Single Center Experience of Temporal Artery Biopsies Performed in 30 African American Patients

Ammar Haikal¹, Garth Fraga², Jason Springer¹, Mehrdad Maz¹. ¹Division of Allergy, Clinical Immunology, and Rheumatology, Department of Internal Medicine; ²Department of Pathology; The University of Kansas Medical Center

Background/Purpose: Giant cell arteritis (GCA) is a systemic vasculitis of large and medium-sized arteries mostly reported in Caucasians (CCs) over 50 y.o. There is limited data in the literature on the incidence of GCA in patients of African descent. Here, we review the incidence of GCA based on temporal artery (TA) biopsies in a comparatively large cohort of African-American (AA) patients.

Methods: This is a retrospective chart review of patients (pts) who underwent TA biopsies (TABs) for suspicion of GCA between 1/1/1997 and 1/31/2018 at a tertiary medical center in USA. Cases were identified by searching the pathology database at our institution. Terms used in the search included temporal artery, temporal arteritis, giant cell arteritis, and borderline arteritis. Self-reported demographics were obtained from the charts. Glass slides from 2 AA pts with a positive pathology report for GCA were reviewed by a pathologist to confirm positivity based on histopathologic features for GCA. Comparisons were made with Fisher Exact Test, using two-tailed test with < 0.05 considered significant.

Results: 200 patients with TABs were identified (Table 1). Of these 30/200 (15%) were AA with a total of 33 TABs (3 bilateral). The median age of diagnosis was 66.5 (range 45-90), and 23/30 (75.66%) were female. Although 2/30 (6.7%) were originally reported as positive for GCA, upon review by the pathologist, one was consistent with small vessel vasculitis with fibrinoid necrosis, and the other did not have histopathologic features of GCA. In contrast, 25/155 (16%) CC patients had positive TABs with a median age of 76 (range 56 - 87) and 98/155 (63.22%) were female. The remaining 15/200 pts were of other ethnicities of whom 2 had positive TABs. GCA was less frequent in AAs than CCs based on TAB ($P=0.0163$). Only 3 AAs were seen by a rheumatologist before biopsy as most of the biopsies of AA pts were requested by ophthalmologists, neurologists and primary care physicians. Reasons for biopsy referral among AAs were headache; 24/26 (92%), Scalp tenderness; 9/17 (53%), jaw claudication; 3/13 (23%), and vision loss; 6/21 (28.6%). 14/25 (56%) AA pts had ESR > 50 mm/hr, and 19/22 (86.4%) met 3/5 ACR classification criteria for GCA.

Conclusion: This is one of the largest reported case series in the literature of TA biopsies (TABs) performed in patients of African descent in a single institution in North America. Pathological features of GCA were not present in any TABs in this cohort of 30 African-American (AA) pts. Our data correlates with the clinical observation that GCA usually presents in Caucasians and is rare in AAs. The suspicion and diagnosis of GCA should be made with caution in AA pts. Awareness of this among other specialists and primary care physicians may reduce the need for performing unnecessary TABs.
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<th>Median Age at biopsy (range)</th>
<th>Female Gender (F)/total (%)</th>
<th>Biopsy consistent with GCA N/ (%)</th>
<th>P-Value by Fisher Test (compared to Caucasians)</th>
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Infections Among Patients With Left Ventricular Assist Devices
Aniket S. Rali, Rachel Foster, Tarun Dalia, Daniel Kandah, Zubair Shah, Travis Abicht, Andrew Sauer, Nicholas Haglund.

Background
Post LVAD infections remain a major cause of morbidity and mortality among LVAD patients. INTERMACS reports rates of early (first 3 months) and late infections to be 16.33 and 4.11 per hundred patient months, respectively. Efforts to reduce infectious complications is especially relevant considering the surge in LVAD implantations in recent years.

Methods
Retrospective chart review of LVAD patients at the University of Kansas Medical Center from October 2015 to October 2017. The incidence, infection type, risk factors for infection, site of acquisition and treatment used within the first six months of LVAD implantation were analyzed.

Results
A total of 33 LVADs were implanted in the study period of which 30 patients were included in the study analysis. Two patients died during their index hospitalization and one patient’s LVAD implantation was an LVAD revision. The mean age of our patients was 52 years and it included 23 males. Our patients had a total of 49 infections with rates of infections per 100 patient months being 28. Most common infections were driveline infections at 22% of total infections.

Conclusions
Incidence of infections in our cohort is higher than national rates and those reported by INTERMACS for KUMC. Higher incidence is attributed to younger patients, higher percentage of DT LVADs, and low threshold for treating suspected infections. Pump related complications including exchange, urgent listing for transplantation and thrombosis are lower or at par with national averages. Post implant LOS, 30-day readmissions and annual mortality are lower than national averages.
Does non-invasive cardiac output monitoring (NICOM) correlate with standard invasive hemodynamic monitoring in patients with acute decompensated heart failure?

Authors


Keywords

NICOM, Cardiogenic Shock, Hemodynamic Monitoring

Background

Cardiac output (CO) and cardiac index (CI) measured by pulmonary artery catheter (PAC) are used to diagnose cardiogenic shock (CS) and monitor response to therapies. Indirect Fick and Thermodilution are generally considered the “gold standard” for measurements of CO and CI. Non-invasive Cardiac Output Monitoring NICOM system is a non-invasive bioreactance technology that is approved by the FDA for stroke volume measurements. However, NICOM has never been assessed in patients with acute decompensated heart failure (ADHF) and cardiogenic shock.

Methods

Thirty-seven patients admitted for ADHF to the cardiac intensive care unit who had PAC’s placed were included. All patients underwent three measurements of CO and CI six hours apart for a total of 111 distinct measurements. At each time point, CO and CI were measured using indirect Fick, Thermodilution and NICOM methods. Also, at each time point NICOM measurements were repeated thrice to evaluate precision. Statistical analyses were performed to evaluate correlation between CO and CI measurements obtained by all three different methods at different time points within the same patient. All statistical analyses were performed using SAS software (SAS institute Inc., Cary, N.C.).

Results

Baseline characteristics were 65% male, with mean age 61 years and mean BMI of 29 kg/m². Correlation coefficient (r) between Fick and NICOM and Thermodilution and NICOM measurements showed no linear relationship. Fick and Thermodilution measurements at any time point were noted to have moderate positive correlation (0.37-0.63). The r (0.87-0.96) between three NICOM measurements obtained at any given time point was strongly correlated.

Conclusion

Cardiac output and cardiac index measurements obtained by NICOM do not correlate with invasive Fick or Thermodilution measurements in patients with ADHF. NICOM is an unreliable method to assess CO and CI in this patient population.
A Rare Case of Prekallikrein Deficiency

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Prekallikrein (PK) deficiency is an extremely rare autosomal recessive disease. First described in 1965, PK deficiency was originally discovered in 4 siblings with an asymptomatic and prolonged aPTT. It has since only been reported around 80 times in the literature. We hereby report a patient with confirmed PK deficiency.

A 41-year-old African-American female without a significant past medical history was referred to our Hematology and Oncology clinic due to a prolonged aPTT (100.7 seconds) on her pre-operative workup prior to a hepatic hemangioma resection. She denied any personal or family history of abnormal bruising, bleeding or thrombotic phenomena. The patient has had two C-sections and a hernia surgery without hemorrhagic complications. Physical exam was unremarkable.

Hematological workup confirmed a prolonged aPTT with full correction on mixing study, normal PT/INR, normal thrombin time, normal von Willebrand Factor profile, and normal platelet function assay. The patient had normal clotting factor levels including XII, XI, IX, VIII, X, V, II, and a normal HMW kininogen. Additional testing confirmed a severe PK deficiency (<5%). A confirmatory assay at a reference lab confirmed the results. She underwent the planned resection of hepatic hemangioma without special precautions and had no abnormal bleeding. The PK deficiency and prolonged aPTT persisted after resection of the hemangioma.

PK is a single-chain protein that is converted to its active form, kallikrein, by activated factor XII. Activated kallikrein may further activate factor XII, promote the activation of the fibrinolytic system, and cleave kininogen to release bradykinin. PK deficiency can either be inherited or acquired in patients with hepatic disease or disseminated intravascular coagulation. The deficiency has been localized to mutations in the KLKB1 gene on chromosome 4. PK deficiency has been reported in nearly all races, however it is seen more frequently in African-American patients. The true prevalence of PK deficiency is unknown as most affected people are usually asymptomatic. PK deficiency can be identified by an isolated prolonged aPTT and normal PT, in which the aPTT corrects to normal in mixing studies. It is then finally confirmed with a specific PK assay.

Identification of such a rare deficiency is clinically significant in that a prolonged aPTT will repeatedly prompt an extensive workup that may unnecessarily delay treatments or procedures. Despite a prolonged aPTT, there is no increased risk of bleeding due to compensation by the extrinsic pathway. PK deficiency may however be associated with thrombotic phenomena due to defective activation of the fibrinolytic system, as well as hypertension secondary to decreased bradykinin levels; demonstrating the far-reaching and complicated effects of prekallikrein.
GSK3β inhibits Tubular Regeneration in Acute Kidney Injury by a FoxM1 Dependent Mechanism

Abeda Jamadar, Dhairya Raval, Sonali Sinha, Nidhi Dwivedi and Reena Rao

The Jared Grantham Kidney Institute, University of Kansas Medical Center, Kansas City, KS

**Background:** Acute kidney injury (AKI) is characterized by injury to the tubular epithelium that leads to apoptotic or necrotic cell death. Although renal tubules are capable of regeneration, severe or repeated injury can lead to inadequate repair and fibrosis. Glycogen synthase kinase 3β (GSK3β) is known to inhibit renal tubular regeneration, but the mechanism is unknown. FoxM1 is a forkhead box family member transcription factor which regulates cell division, cell survival and oxidative stress, whose role in renal tubular repair is unknown. In this study, we tested the hypothesis that GSK3β suppresses tubular epithelial cell repair by inhibiting FoxM1.

**Methods:** To determine the role of FoxM1 in tubular repair, the effect of systemic pharmacological FoxM1 inhibition was examined in renal ischemia/reperfusion (I/R) induced AKI in wildtype C57BL/6J mice and in HK2 proximal tubular cells *in vitro*.

**Results:** FoxM1 expression was increased in cells subjected to hypoxia/re-oxygenation and kidneys of I/R induced AKI in mice and was accompanied by increased cell proliferation. Treatment with Thiostrepton, a FoxM1 inhibitor reduced renal tubular cell proliferation and kidney tubular repair. To test if GSK3β is an upstream regulator of FoxM1, the effect of FoxM1 inhibitor on tubule-specific GSK3β knockout mouse was also determined. In GSK3β knockout mice, FoxM1 expression, cell proliferation and tubular repair was significantly high, leading to improved renal function. FoxM1 promotes expression of S-phase kinase associated protein 2 (Skp2), an E3 Ubiquitin Protein Ligase which suppresses p21, a cell cycle inhibitor. Significant increase in p21 levels and reduction in pro-proliferative factors was found in cells and kidneys where GSK3β was inhibited. However, when treated with Thiostrepton, the improved tubular repair in GSK3β knockout mice was abolished. These studies demonstrate that FoxM1 is an important factor for renal tubular regeneration following AKI, and that GSK3β suppresses tubular repair by inhibiting FoxM1.
Moving from episodic/static to rapid/living systematic reviews: case studies demonstrating benefits and applications of a collaborative approach

Authors: Robert G Badgett, Steven G Simpson

Background:
We propose enhancing systematic reviews by combining methods of living systematic reviews, rapid systematic reviews and scoping reviews in a collaborative setting.

Methods:
We present four case studies of this approach (available online at http://openmetaanalysis.github.io/). We use meta-narrative to identify applications, barriers and solutions to collaborative reviews.

Results:
The four case studies and their implications are: 1) a review of bronchiolitis treatment with hypertonic saline illustrates how a living review can add new studies that are published after acceptance of the review and prior to publication, 2) separate reviews of the treatment of septic shock with steroids and sciatica with gabapentinoids were able to support commentaries for ACP Journal Club, 3) a review of chronic back pain treatment with tramadol with new studies added in time to support a substantive reassessment of a practice guideline by the American College of Physicians (ACP).

Meta-narrative categorizes barriers into costs, technical, and social. A technical barrier is the difficulty in building on a research thread when multiple, sometimes conflicting systematic reviews exist but do not reliably cite prior reviews and prior trials. Focusing on social barriers, these include scholarly credit for contributors and project governance. Regarding scholarly credit, proposed solutions are: labeling authors of focused contributions with the NLM ‘contributor’ designation or creation of ‘limited authorship’ as a new designation. Examples of new designations have been created by Contributor Roles Taxonomy (CRediT). Additional approaches are nanopublications and microattribution. Governance can be addressed by linking living reviews to practice guidelines and thus using the governance of the guideline.

Conclusion:
Traditional systematic reviews may benefit from conversion to reviews that are living, rapid, and collaborative. Cases studies suggest applications include 1) providing current data synthesis for use by editorialists and other commenters on new studies, and 2) improving the updating of practice guidelines. We propose that when previous, relevant systematic reviews exist authors of new reviews should provide tables that reconcile conclusions, as well as studies included, of the current and prior reviews.

Aniket S. Rali, Nilay Patel, Venkat Vuddanda, Travis Abicht, Nicholas Haglund, Andrew Sauer and Zubair Shah

Background

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) provides cardiopulmonary support in cardiogenic shock (CS) as a bridge to recovery, durable left ventricular assist device (LVAD) or orthotopic heart transplant (OHT). Over the past decade, there has been an increase in the use of VA-ECMO in treatment of CS. However, there is a paucity of data on the outcomes of patients in CS treated with VA-ECMO as it pertains to concomitant left ventricular (LV) support.

Methods

We queried National Inpatient Sample common etiologies for CS such as acute myocardial infarction, cardiac arrest, myocarditis, valvular heart disease, ventricular arrhythmias and OHT related complications using ICD 9 codes for years 2007 through 2014. Intra-aortic balloon pump (IABP) placement and percutaneous ventricular assist device (pVAD) following initiation of VA-ECMO were identified using appropriate procedural codes. Primary outcome was in hospital mortality & secondary outcomes were length of stay (LOS) & bridge to LVAD or OHT.

Results

Out of 6679 patients on VA ECMO for CS, 1583 (24%) patients also had concomitant LV support with IABP (1336, 20%), pVAD (168, 3%) or IABP followed by pVAD (79, 1%). Mean age was 59 years. 30% were female and 70% were Caucasian. In hospital mortality remained high regardless of LV support (57% among IABP, 59% among pVAD, and 59% among both vs 57% among no LV support, p value), while median LOS was significantly reduced with concomitant LV support (18.25 days among IABP, 24.15 days among pVAD, and 17.22 days among both vs 25.28 days among no LV support, p value). More patients without LV support were successfully bridged to LVAD or OHT during index hospitalization as compared to patients with concomitant LV support (1121 vs 218, p value).

Conclusion

In hospital mortality among patients in CS treated with VA-ECMO remains high regardless of LV support. While the median LOS was shorter among patients with concomitant LV support, there was no difference rates of in hospital mortality. Greater number of patients receiving durable LVAD or OHT originated from the non LV support group.
**Babesiosis in an immunocompromised patient**

Sonya Parashar MD, Rachel Weihe MD, Karsten Evans MD, Jessica Newman DO  
Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS  
Department of Pathology, University of Kansas Medical Center, Kansas City, KS

**Introduction/Background:**  
In the United States, *Babesia microti*’s reservoirs include white-footed mice, vole and deer. The vector is the *Ixodes scapularis* nymph, which is commonly seen in the Northeast and upper Midwest. Risk factors for severe disease include age > 50, asplenia, HIV, malignancy, and immunosuppressive therapy exposure, namely with TNF-α inhibitors and rituximab.

**Case presentation:**  
A 62-year-old man with a history of chronic lymphocytic leukemia presented with a 3-week history of daily episodes of 103°F fever and abdominal pain. He previously completed 5 cycles of chemotherapy with bendamustine and rituximab. During his last cycle of chemotherapy, he developed increasing left upper quadrant pain, fatigue, anorexia and progressive splenomegaly. He underwent laparoscopic splenectomy and pathology showed extramedullary hematopoiesis with no malignancy. Following splenectomy, he developed fever with progressive leukopenia (WBC 2.4 with ANC 1800) and was treated with cefepime and vancomycin without improvement. Antibiotics were broadened to meropenem, tobramycin, and amphotericin B without defervescence. He developed septic shock and was transferred to our institution. A thorough exposure history was taken, noting he lived on a wooded property outside Lawrence, Kansas where he often trapped raccoons and had a lake home in Wisconsin (last visited 9 months prior). Laboratory revealed hemolytic anemia, total bilirubin of 9.7 and AST of 296. A peripheral blood smear revealed 50% parasitemia and Babesia microti PCR was later positive. The patient was treated with two exchange transfusions reducing parasitemia to less than 5% resulting in rapid improvement and he was started on azithromycin and atovaquone for a total of 6 weeks with repeat negative smears. Three months after therapy, he had recurrent fever with low levels of parasitemia. This resolved after a 6-month course of atovaquone-proguanil and azithromycin.

This patient’s advanced age, asplenia, malignancy, and immunosuppression all contributed to his severe Babesiosis. Studies in relapsed cases show that resistance can occur to atovaquone and azithromycin but clinical cure can be achieved with atovaquone-proguanil and azithromycin over a 6-month period. Though raccoons may carry babesia, the PCR for babesia microti suggested he was more likely exposed in Wisconsin with disease resting in a dormant stage until his splenectomy.

**References**


Acute Myelomonocytic Leukemia Presenting as Pulmonary Infiltrates Secondary to Leukemic Infiltration

Introduction
Malignant infiltration of pulmonary parenchyma is a rare complication of acute leukemia and more commonly found on autopsy of patients without prior clinical pulmonary symptoms. We present a case of a 75-year-old female with acute myeloid leukemia presenting as rapidly progressive respiratory failure with pulmonary leukemic infiltration.

Case Presentation
The patient presented to her local hospital after 2 weeks of fevers, chest pain, dyspnea, and cough. CT angiogram revealed bilateral diffuse pulmonary infiltrates, loculated pleural effusions, and no evidence of pulmonary embolism. She underwent a left thoracentesis that yielded 13ml of an exudative effusion with following counts (RBCs 16 k/uL, WBCs 5.8 k/uL with 41% neutrophils, 8% lymphocytes, 6% monocytes, 43% macrophages & 2% mesothelial cells), as well as negative cultures and cytology.

Initial blood counts at our institution revealed abnormal peripheral monocytosis (AMC 1.8 k/uL, 32%) with a normal WBC count at 5.6 k/uL. Peripheral smear revealed premature monocytes. She underwent exploratory thoracoscopy, lung wedge resection and intraoperative bronchoalveolar lavage. Lavage was significant for a WBC count of 400 per uL, 66% of which were monocytes. Lavage and pleural fluid cytologies were negative for malignant cells. Follow up blood counts showed progression of her monocytosis with appearance of promonocytes and peripheral blasts. Peripheral blood flow cytometry revealed 6% atypical myeloblasts and 45% atypical monocytic cells. Pleural and lung biopsies revealed an atypical interstitial mononuclear cell infiltrate with monocytic differentiation consistent with involvement by myeloid leukemia. Faced with a grave prognosis, her family elected to transition to comfort measures. She was palliatively extubated and passed away 4 days after her transfer. Autopsy was performed and confirmed acute myelomonocytic leukemia with leukemic infiltration of lungs, pleura, pericardium and spleen.

Discussion
We presented a case were progressive respiratory failure secondary to pulmonary and pleural involvement was an early presentation of acute myelomonocytic leukemia with a fatal outcome.

Conclusions
Although uncommon, leukemic lung infiltration remains in the differential of acute pulmonary infiltrates in setting of blood dyscrasias suggestive of acute myeloid leukemia and can cause profound respiratory failure before a leukemia diagnosis is established.
Histologic sections of the lungs (H&E, 10 and 20x magnification). A) Interstitial infiltration by atypical cells (solid arrows) and adjacent fibrin deposition (open arrow); B) Higher power image showing intra-alveolar accumulation of atypical mononuclear cells, which have moderate cytoplasm and irregular nuclear contours.
Evaluation of different treatments for Specific Antibody Deficiency with Normal Immunoglobulins
AAAAI Abstract Submission SADNI Project

Authors: Aarti Pandya, MD¹; Emily Buren, MPH²; G. John Chen, MD, PhD, MPH²; Arman Pirzad, MD²; Mary Nguyen, MD³; Jessica Zibert, MD¹; Sadia Hayat, MD¹

1: University of Kansas Medical Center, Department of Allergy, Immunology, and Rheumatology
2: University of Kansas Medical Center, Department of Internal Medicine
3: University of Kansas Medical Center, Department of Pediatrics

Rationale: Specific Antibody Deficiency (SAD) is a primary immunodeficiency characterized by normal immunoglobulins with deficient response to polysaccharide antigen vaccination. Sinopulmonary infections are a frequent complication of this disease and management strategies are largely based on expert opinion. Currently there is a lack of consensus regarding the management of this disease. The aim of this study was to determine whether there was a statistically significant difference in rate of infections in patients diagnosed with SAD who were managed with IVIG, prophylactic antibiotics, and clinical observation.

Methods: We conducted a retrospective review of 26 patients recruited from the University of Kansas Medical Center with the diagnosis of specific antibody deficiency who were above the age 18. We determined the rate of antibiotic prescriptions per year for patients with SAD treated with immunoglobulin supplementation, prophylactic antibiotic, or clinical observation.

Results: There was a significant rate of decreased antibiotic prescriptions in patients treated with IVIG (n = 11, p = 0.002) or prophylactic antibiotics (n = 5, p = 0.001) versus those clinically observed (n = 11) using a paired t test. The mean difference in antibiotic prescriptions in those patients treated with IVIG versus prophylactic antibiotics was not statistically significant (p = 0.254) using an analysis of covariance. The mean IgG level was 914 among all the patients. The mean number of years followed post intervention was 1.25.

Conclusions: In patients diagnosed with SAD, there was a notable difference in infection rate between treatment with either IVIG or prophylactic antibiotics versus clinical observation. However, there was no notable difference in infection rate between IVIG and prophylactic antibiotics. Prophylactic antibiotic therapy for patients with SAD may serve to be more cost effective and practical approach to management.
Anaplastic large cell lymphoma (ALCL) represents a rare and aggressive subtype of CD30-positive peripheral T-Cell lymphoma which accounts for 5-10% of non-Hodgkin lymphomas in adults and 10-30% in children. More than 80% of ALK-positive ALCLs hallmarked by fusion gene NPM1-ALK generated by t(2;5) chromosomal translocation. The fusion kinase NPM1-ALK mediates constitutive activation of the chimeric tyrosine kinase activity leading to downstream signaling pathways responsible for oncogenicity. The current therapeutic approaches used for the treatment of ALK-positive ALCLs has limited effectiveness with poor outcomes. Celastrol, a triterpene molecule extracted from the Chinese herbal plant Tripterygium wilfordii Hook F, blocks the interaction between HSP90 and CDC37 and triggers the degradation of its dependent client protein kinases. In this study, we tested the fusion oncogene NPM1-ALK dependency on co-chaperone CDC37 using celastrol in ALCL cells. Celastrol treatment resulted in degradation of NPM1-ALK fusion kinase which inhibited downstream survival signaling pathways including AKT, ERK1/2, STAT3, and induced apoptosis. Celastrol also decreased ALCL cell proliferation and downregulated CD30 expression. In summary, our results demonstrate targeting CDC37 using celastrol is a novel therapeutic approach to induce apoptosis in ALCL cells expressing NPM1-ALK and warrants developing future therapeutic intervention strategies.
Expression of Activated BRAF Induces Cyst Formation and Accelerates Disease Progression in ADPKD mice

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Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation and progressive enlargement of fluid-filled cysts, leading to massively enlarged kidneys, interstitial fibrosis and a decline in renal function. Intracellular cAMP promotes cyst growth by stimulating the MEK/ERK pathway and proliferation of the cystic cells. By contrast, cAMP is anti-mitogenic in normal kidney cells. This phenotypic difference in the proliferative response to cAMP appears to involve BRAF, a kinase upstream of the MEK/ERK pathway. In normal cells, BRAF is repressed by a Ca\textsuperscript{2+}-dependent mechanism, thereby preventing cAMP activation of ERK and cell proliferation. In ADPKD, mutations in the PKD genes disrupt intracellular Ca\textsuperscript{2+} homeostasis, relieving BRAF inhibition and allowing cAMP stimulation of the BRAF/MEK/ERK pathway. We hypothesize that expression of activated BRAF in collecting duct (CD) cells induces cyst formation and accelerates progression of ADPKD.

We generated a novel transgenic mouse that conditionally expresses BRAF\textsuperscript{V600E}, a common activating mutation in cancer. BRAF\textsuperscript{V600E} mice were bred to Pkhd1-Cre mice to selectively overexpress active BRAF in CD cells. BRAF\textsuperscript{V600E} mice were then bred to Pkd1\textsuperscript{RC/RC} mice, an orthologous model of ADPKD, to determine if BRAF activation accelerates disease progression. At 10 weeks, mice were sacrificed for measurement of kidney weight as percent body weight (KW\%BW), cystic area, interstitial fibrosis, cell proliferation and blood urea nitrogen (BUN), a marker of renal function.

Expression of active BRAF in CD cells increased KW\%BW compared in wild-type (WT) mice. There was an 8-fold increase in the percentage of cells that stained positive for Ki-67, a marker for cell proliferation, and formation of numerous cysts within the BRAF\textsuperscript{V600E} kidneys. Expression of active BRAF in Pkd1\textsuperscript{RC/RC} mice caused a 2.3-fold increase in KW\%BW, 2.3-fold increase in the number of cysts and a 3.6-fold increase in cystic area. These changes were accompanied by an increase in the number of proliferating cells in the cysts and interstitium. Pkd1\textsuperscript{RC/RC}: BRAF\textsuperscript{V600E} mice also had a significant increase in interstitial fibrosis and a higher BUN, indicating a more rapid decline in renal function. We conclude that BRAF activation is sufficient to induce cyst formation and accelerates disease progression in ADPKD mice.
Exposure to Antiretrovirals and Risk of Chronic Kidney Disease in HIV positive Patients with Normal Renal Function: A Single Center Cohort Study

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Background. Some antiretrovirals, including tenofovir disoproxil fumarate (TDF), have been associated with increased risk of chronic kidney disease (CKD).

Methods. We performed a retrospective cohort study of adult HIV-positive patients, with initial estimated glomerular filtration rate (eGFR) > 90 ml/minute/1.73 m². Patients were followed from initial eGFR measurement until one of the following: CKD, last eGFR measurement plus 3 months or Nov 29, 2016. CKD was defined as sustained eGFR < 60 ml/minute/1.73 m² for at least 3 months. Poisson regression was used to estimate the incidence rate of CKD associated with exposure to TDF, ritonavir-boosted atazanavir (ATV/r), ritonavir boosted lopinavir (LPV/r), or nucleoside reverse transcriptase inhibitors (NRTIs) excluding TDF.

Results. Between January 1, 2004 and November 29, 2016, 518 eligible patients were included. Participants had a median age 37.5 years, a median CD4 count of 488 cells/uL and a median baseline eGFR of 111 ml/minute/1.73m². During 1963.5 person-years of follow-up (at a median of 3.1 years; IQR 1.94-8.24), 10 (1.9%) patients developed CKD (incidence 5.09 per 1,000 person-years of follow-up; 95% CI 1.94-8.24). On univariate analysis age, (BMI) < 26 kg/m², anemia, and nadir CD4 < 200 were associated with increased CKD. On multivariate analysis, variables associated with increased risk of CKD were time on TDF (adjusted Incidence Rate Ratio (aIRR) 1.236 per year of exposure; 95% CI 1.028–1.409; P = 0.002), current NRTI excluding TDF use (aIRR 10.692; 95% CI 2.184–52.352; P = 0.003), and prior NRTI use excluding TDF (aIRR 10.686; 95% CI 1.730–65.983; P = 0.011). BMI > 26 kg/m² was associated with decreased risk of CKD (aIRR 0.053; 95% CI 0.004–0.629; P = 0.020). Time on NRTIs excluding TDF was not associated with increased CKD risk.

Conclusion. The incidence of CKD in this cohort of HIV-positive patients with normal renal function is higher than reported in the literature. Time on TDF was associated with increased risk of CKD as previously reported. The increased risk of CKD with exposure to NRTIs excluding TDF could be due to residual confounding.
A Catastrophic Collision between Critical Illness and Immune Dysregulation: A case of relapsing Hemophagocytic Lymphohistiocytosis in a previously healthy adult male.

Author: Benjamin Mulloy, MD

Introduction:
Acquired Hemophagocytic Lymphohistiocytosis (HLH) is a rare and often fatal hyperinflammatory syndrome that chiefly occurs as a complication of immune dysfunction. Immunologic triggers range from hematologic malignancies, connective tissue diseases, severe infections; each culminating in impaired lymphocyte cytotoxicity and unregulated cascade of inflammatory (1). Here we report an interesting case of HLH secondary to extra-nodal NK-T-Cell lymphoma (ENTKL) with relapsing HLH as a consequence of treatment.

Case Presentation
A previously healthy 46-year-old male presented with 3 months of fatigue, malaise, and weight loss. He was found to be hypotensive, jaundiced and confused. Labs revealed pancytopenia, mild renal insufficiency, and acute liver injury. In the absence of fevers or identifiable causes, he developed refractory shock, coagulopathy, progressive renal and liver injury (INR 2.7, aPTT 62, sCr 6.9, TBili 18.7, AST 1,880). Further evaluation established the potential for acquired HLH syndrome (ferritin >7500, fibrinogen 55, TGS 716, LDH 7,803, IL-2 receptor 19,600) secondary to reactive EBV (>5 M copies). Bone marrow biopsy demonstrated ENTKL with (+) EBV. Etoposide/Vincristine were initiated with resolution of multiorgan dysfunction, followed by further significant clinical response to ENTKL directed chemo. Pt returned 3 weeks after discharge home with neutropenic fevers, septic shock, and relapsing HLH (Ferritin >18,000) due to Candida fungemia (C. Kefyr) with retinal and lung involvement. Pt initially improved with aggressive antifungal therapy with a parallel normalization of serum Ferritin levels. Subsequently his infection widely disseminated with relapsing HLH, ultimately leading to death.

Discussion
Early identification of acquired HLH remains a challenge to clinicians due to variable, non-specific clinical findings, including fevers, bi-cytopenia, coagulopathies, acute hepatic dysfunction, and notable hyperferritinemia. Overactivation of macrophages and impaired lymphocyte cytotoxicity lead to a profound cytokine-mediated inflammatory response, often lending to catastrophic injury (1,2). As a result of chemo-induced neutropenia, our patient developed a systemic fungal infection, found to be a second trigger precipitating relapse of HLH.

Conclusions:
Acquired HLH from a range of diseases precipitates a common immunopathologic state of impaired lymphocyte cytotoxicity and profound cytokine-mediated inflammation. Early identification of the immunologic trigger is essential to effect appropriate treatment, as delayed diagnosis is associated with high mortality.

Reference #1:

Reference #2:
Markedly Improved ABIM Certifying Examination Pass Rate Utilizing a Mentored Educational Prescription Targeting At-Risk Residents

Jane Broxterman, Becky Lowry, John Bonino and Leigh M Eck  Department of Internal Medicine, University of Kansas School of Medicine, Kansas City, KS.

Background
With a 2011-2013 American Board of Internal Medicine certifying examination (ABIM-CE) pass rate of 80%, below the national average as well as at the cusp of the ACGME minimum standard, our program sought to improve our ABIM-CE pass rate by implementing an educational prescription for at risk residents. Utilizing published data correlating Internal Medicine-In Training Examination (IM-ITE) performance with ABIM-CE performance, we defined at risk residents as those scoring ≤30%ile rank on the IM-ITE.

Description of Innovation
Our educational prescription was required for residents with ≤30%ile rank ITE. We initially focused on PGY2 and PGY3 residents, but with realized success expanded to at-risk PGY1 residents. The educational prescription entails the following:

1. A learning style assessment with a learning specialist.
2. Review of an evidenced based approach to medical knowledge remediation.
3. Weekly IM-ITE educational objectives and board style questions completion.
4. Minimally, monthly mentor compliance tracking.

Initially, residents “graduated” from the educational prescription with IM-ITE scores >30%ile rank; however, based on outcomes data, this metric was moved to >70%tile rank score.

Results to Date
Our 2011-2013 3-year ABIM pass rate was 80%. We initiated the educational prescription in the spring of 2014. Subsequent pass rate data as follows:

2012-2014: 88%
2013-2015: 89%
2014-2016: 96%
2015-2017: 96%

To date, 10 high risk residents have completed the educational prescription and taken the ABIM-CE. Eight of 10 have passed boards; the two residents that did not pass on first attempt had “graduated” from the educational prescription with IM-ITE scores >30%ile rank. Based on this, we now retain residents in the educational prescription cohort unless their IM-ITE performance improves to >70%ile rank.

Discussion
Our program has yielded an improvement in our ABIM pass rate by implementing an educational prescription for at-risk residents. Our targeted approach has allowed our leadership team to focus energies on the cohort of residents that are most vulnerable for ABIM-CE failure. This intervention has proven to be effective, sustainable, and well received; now accepted as our culture. Based on our experience with two residents’ ABIM-CE failure whom had graduated from their educational prescription with an IM-ITE score of >30%ile rank, we now set that “graduation” bar much higher.
Mast Cell Mediated Inhibition of Systemic IL-6 in *Candida albicans* Water-Soluble Fraction (CAWS) Induced Model of Large Vessel Vasculitis

Zhang M, Maz M, Smith DD, Miura NN, Ohno N, Dileepan K, Springer J

**Background:** In forms of large vessel vasculitis (LVV) systemic IL-6 has been shown to follow disease activity. Furthermore, IL-6 inhibition is an effective treatment for giant cell arteritis, a form of LVV. Our group has demonstrated that systemic mast cell degranulation results in inhibition of LPS-induced systemic IL-6 production. Further studies demonstrated that this effect may be mediated through stimulation of histamine-1 receptor (H1R). The purpose of this study was to determine if mast cell degranulation could inhibit systemic production of IL-6 in a mouse model of vasculitis (*Candida albicans* water-soluble fraction induced model or CAWS).

**Methods:** Two month old male C57BI6/J mice were randomized to 4 groups (n=4/group). Mice were given intraperitoneal injections of either: a) normal saline (controls), b) CAWS extract, c) compound 48/80 (C48/80, systemic mast cell degranulation agent), or d) CAWS + C48/80. Injections were given on five consecutive days. Animals were sacrificed at 30 days for measurements of systemic TNF-α, INF-γ and IL-6 by ELISA as well as aortic expression of messenger RNAs coding for IL-6, suppressor of cytokine signaling-1 (SOCS1), INF-γ, IL-10 and TNF-α. Two tailed student’s T-test were used for comparisons with p<0.05 considered significant.

**Results:** CAWS mice had significantly higher systemic IL-6 levels compared to controls (345.2 pg/ml±132.9 vs 56.4pg/ml±19.3, p<0.001). Mice injected with C48/80 + CAWS had significantly lower IL-6 compared to CAWS alone (177.3pg/ml±113.6 vs 345.2pg/ml±132.9, p=0.02). There was significantly higher systemic INF-γ in both the CAWS and CAWS+C48/80 compared to controls. No difference in TNFα was observed between the groups. No significant differences were observed in aortic IL-6 expression between groups. Comparing CAWS+C48/80 to CAWS alone, there was significantly higher aortic expression of both SOCS1 (p<0.001) and TNF-α (p=0.03).

**Conclusions:** The results demonstrate that systemic mast cell degranulation inhibits systemic IL-6 levels in a mouse model of LVV. This was not accompanied by reduced aortic expression of IL-6 suggesting that this effect is occurring in other tissues, possibly the liver. Mast cell degranulation was also associated with increased aortic expression of SOCS-1, a negative inhibitor of IL-6 signaling, suggesting that mast cells may play a direct role in IL-6 signaling as well. Since our prior studies suggest mast cells mediate IL-6 production through H1R stimulation, future research will be devoted to determining if H1R inhibition can inhibit the formation of LVV in a mouse model.

**Acknowledgements:** Endowment from Division of Allergy, Clinical Immunology and Rheumatology and Basic Science Research Development Award from Department of Medicine, University of Kansas Medical Center
Greater Plains Collaborative Reusable Observable Unified Study Environment (GROUSE)
2018 Status

Russ Waitman¹, Dan Connolly¹, Lav Patel¹, Mary Schroeder²

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²Division of Health Services Research, Department of Pharmacy Practice and Science, University of Iowa, Iowa City, IA

Background:

PCORI funded PCORNet the goal for Clinical Data Research Network’s to include claims with their electronic health record (EHR) data. Our network, the Greater Plains Collaborative (GPC), covers nine states with varied insurance coverage. Our strategy was to incorporate federal/state claims from the Centers for Medicare and Medicaid Services (CMS).

Objectives:

While GROUSE can be reused for other hypotheses, the GPC is using this integrated environment for 3 cohorts: breast cancer (BC), amyotrophic lateral sclerosis (ALS), and the consequences of healthy and unhealthy (obesity) weight.

GROUSE provides a de-identified resource that merges CMS claims and GPC site data to: 1) characterize the increase in data completeness and comprehensiveness provided through claims integration to provide in a more “complete” picture of our patients’ health. 2) Evaluating the distributions of health and care processes for the patients with our three conditions and their treatment patterns within the GPC versus the larger Medicare and Medicaid populations in our region to understand how studies of the GPC population generalize to the broader populations in our states. 3) Using CMS claims data to enhance quality control processes for aggregating health system-derived clinical data and establishing correlations with CMS claims data for health system-derived data to support trial recruitment and observational studies, i.e. validating the use of EMR data for recruitment.

Current Statistics:

Over 24 million patients with claims data creating over 73 billion facts. Currently, seven health systems data are integrated with over 6 million patients. Original crosswalk: 2011-2015 claims 1.65 million patients. New crosswalk pending but original to 2012 Medicaid, 2016 Medicare -> 2.4 million.

Reuse and future plans:

Investigators seeking to use GROUSE should contact Dr. Russ Waitman to evaluate their project’s alignment with current cohort activity or the need to develop a protocol and data management plan for reuse with CMS. Reuse will require budgeting for review by CMS and a Medical Informatics co-investigator and team support.

The team will be adding 2017 Medicare and 2013 Medicaid data in 2019. We are cultivating funded collaborations to use and support environment and additional data; evaluating an NIH NIA opportunity for aging resources.
Dual role of FOXO3 in regulating the evolution of the macrophage inflammatory phenotype in response to alcohol

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We have previously shown that alcohol causes phosphorylation of FOXO3 at S574 (pFOXO3) which enhances its apoptotic function. Furthermore, FOXO3 KO mice have an exaggerated inflammatory response to alcohol and monocytes from AH patients are defective in the formation of pFOXO3.

The **AIM** of this study was to determine whether pFOXO3 is anti-inflammatory and whether myeloid cell apoptosis contributes to its ability to reduce alcohol-induced inflammation.

**Methods**: Mice were fed alcohol via Lieber-DiCarli diet; apoptosis was measured by TUNEL assay; inflammatory cytokines and M1 and M2 markers were measured by RT-PCR.

**Results**: Alcohol feeding resulted in apoptosis of 8.8±0.9% of intrahepatic macrophages in WT mice. This was absent in whole body KO and mFoxo3−/− mice. At day 3, there was a similar increase in Ly6C+ cells in both genotypes but at day 11, WT mice had less Ly6C+ cells in spite of no change in IM numbers. In contrast, Ly6C+ cells persisted and further increased in KO mice and mFoxo3+/− mice at day 11. Restoring a pulse of MF cell death in KO mice by GdCl3 1d after alcohol exposure prevented the pro-inflammatory phenotype at day 11. Finally, we found that in response to alcohol, hepatocyte produce IL4 in FOXO3-dependent mechanisms which also promote M2 differentiation of hepatic macrophage. Conclusions: Alcohol induces pFOXO3 which reduces subsequent inflammation by 2 mechanisms. First, pFOXO3 causes intrahepatic macrophage apoptosis. The apoptotic cells then convert IMs from a pro-inflammatory to anti-inflammatory phenotype. Second, FOXO3 in hepatocyte also produces IL4 which further promotes M2 differentiation.
Description of How Problem was Identified and Explored

The Accreditation Council for Graduate Medical Education (ACGME) and Clinical Learning Environment (CLER) outline the importance of training residents in quality and safety. Programs must “provide formal educational activities” for patient safety and ensure residents “know how to report patient safety events” (ACGME V1.A.1a). Despite these expectations, it is not always clear the best route to deliver training around this comprehensive topic.

Description of the Innovations

This initiative included developing an experiential curriculum analyzing an actual patient safety event identified from resident clinic through the patient safety reporting system. The event was investigated in resident small group teams utilizing a root cause analysis. Residents reviewed the system process for event reporting and nomenclature around patient safety events and then applied this knowledge to the chart details, event timeline, and interviews of stakeholders for the actual patient safety case. Residents then collaborated on the development of an Ishikawa (fishbone) with the support of a faculty mentors to identify contributing factors to the safety event. Lastly, results were shared leading to health system process optimization.

Results to Date

Significant gains were seen in resident pre and post intervention surveys around comfort and ability to utilize the hospital event reporting system as well as navigation of a root cause analysis. Residents further rated the experience as highly valuable and relevant to their training and practice.

Discussions/Reflection/Lessons Learned

Small group experiential models for education improve resident confidence to tackle patient safety event reporting, and serve as a spring board for root cause analysis of real life patient safety issues. These serve an important role in responding to hospital, health system and training program expectations as set forth by CLER and ACGME. This initiative will continue on an annual basis and serve as the push for additional department patient safety conferences and root cause analysis throughout the academic year.
BOURBON VIRUS- A NOVEL VIRUS

Theresa L. King, M.D.

A 68 year-old male transferred from an outside hospital to this tertiary care academic medical center. He presented at the outside hospital with syncope, nausea, diarrhea, rash, profound weakness and fever. Because he was a rancher and frequently had tick bites, with one recently found to be deeply embedded and engorged with blood, he was started on IV doxycycline. He transferred due to persistent fevers, leukopenia, thrombocytopenia and mild transaminitis. Differential diagnosis included Heartland virus versus Severe Fever with Thrombocytopenia Syndrome (SFTS). Multiple serologies were obtained and were negative, including Rocky Mountain spotted fever, tularemia, brucella, babesiosis, and Q fever; molecular testing for Ehrlichia spp. and Anaplasma phagocytophilum; and blood thin smears for Babesia were negative. Results of evaluations for fungal pathogens (Aspergillus spp. galactomannan, antibodies against Histoplasma and Histoplasma antigen in serum and urine) were negative. Evaluations for cytomegalovirus, Epstein-Barr virus, and parvovirus showed past infection. Test results for hepatitis B and C viruses, West Nile virus, and HIV were also negative. Blood, sputum, and urine bacterial cultures were negative. Some tests resulted after the time of death. On the 9th day of illness he developed rapidly progressing respiratory failure and was transferred to the ICU, quickly developing ARDS requiring intubation, multiple pressor shock and worsening lactic acidosis. An echocardiogram revealed a reduced EF and global hypokinesis consistent with myocarditis. He developed renal failure and CRRT was initiated. Despite broadening of antibiotic treatment the patient's condition rapidly deteriorated. He ultimately developed PEA cardiac arrest resulting in his demise. Virology results revealed a novel virus not previously known, given the name of Bourbon Virus.

The purpose of this case study is to increase awareness of this novel, likely tick-borne, virus, its signs, symptoms and possible clinical course of infection and to alert providers that other novel viruses may emerge.
Qualitative Assessment of VA-Based Oncologists’ Attitudes and Behaviors Regarding Genomic-Based Targeted Therapy for the Management of Advanced Lung Cancer

Arney J, Chen GJ, Helm A and Hayes TG

Background: Genomic-based targeted therapy (GBTT) has emerged as a treatment option for patients with advanced lung cancer. Clinical practice guidelines of the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend testing all metastatic adenocarcinomas for EGFR mutation, and use of EGFR-TKIs (erlotinib) as first-line therapy for advanced adenocarcinoma lung cancer patients with EGFR mutation positive. Little is known about how oncologists utilize genomic testing and GBTT in a clinical setting. Drawing from the Cabana, et al. theoretical framework on providers’ adherence to guidelines, this study aims to elicit provider- and facility-level barriers and facilitators to using GBTT in VA healthcare delivery system.

Methods: We conducted 25 in-depth, qualitative interviews from a sample of VA-based oncologists during a period of March, 2015 and January 2016. Consistent with the Cabana, et al. theoretical framework, interviews sought to elicit oncologists’ knowledge, attitudes, and intent to use GBTT, and barriers and facilitators for practicing GBTT in a VA-setting. Analysis was dictated by thematic saturation.

Results: We identified varying degrees of guideline-consistent utilization of genomic testing and GBTT. Oncologists estimated that roughly 20-90% of metastatic adenocarcinomas are tested for a mutation. Many participants had never found a positive mutation and had never used GBTT in a first-line setting. Almost all participants had used GBTT in a second-line setting or as maintenance. Consistent with the Cabana et al. framework, nonadherence to guidelines seems to result from oncologists’ lack of familiarity with guidelines and some barriers, including patient factors, facility resources, and organizational constraints.

Conclusions: This is the first study to examine oncologists’ knowledge, attitudes, and experiences with using GBTT in a clinical setting. Findings reveal a need for provider education on genomic testing and treatment guidelines. Further research is needed to fully understand how facility resources—specifically, budgetary issues in the pathology department—shape oncologists’ ability to adhere to testing guidelines.
EVALUATION OF TRABECULAR BONE SCORE IN CYSTIC FIBROSIS PATIENTS

Anabtawi, A; Holyoak, M; Cristiano, E; Grdinovac, K; Graves, L.

**Background:** Patients with cystic fibrosis (CF) have an estimated fracture rate of 15-25% yet bone mineral density (BMD) is not always abnormal in such patients. Multiple studies have evaluated TBS (Trabecular Bone Score) in other high-risk fracture groups as a bone quality measure. However, no study evaluated TBS in CF patients. This study evaluated TBS in CF patients and correlated with factors potentially influencing fracture risk.

**Methods:** A retrospective study where adult patients with CF who underwent DXA (Dual X-ray absorptiometry) scan between 2009 and 2017 were included, TBS was applied to lumbar spine images. Higher TBS score indicates better microarchitecture. Clinical data were collected through chart review and surveys. Data are presented as mean ± SD.

**Results:** One hundred and thirty-six patients were included. Mean age was 28.1 ± 9.9 years, BMI was 21.8 ± 3.4 kg/m2, and 25-hydroxyvitamin D was 28.7 ±11.1 ng/ml. There were 58.5% males, F508del mutation was present in 93% of patients. Diabetes was present in 36.6% (mean A1c 7.2% ± 1.98). Mean FEV1 was 64.4 ± 25.5 % predicted. Mean TBS was 1.41± 0.10, Lumbar Spine BMD was 1.09 ± 0.15 g/cm2. Lumbar spine Z-score was ≤-1 and <-2 in 45.7% and 28.7% of patients, respectively.

Multiple regression analysis and Pearson’s correlation calculations showed that TBS significantly negatively correlated with age (decrease of 0.002 per year, r = - 0.21, P 0.04), and positively correlated with FEV1 (increase by 0.001 per 1% increase in predicted FEV1, r = 0.4, P 0.007). There was a significant positive correlation between TBS and lumbar spine BMD (r = 0.62, p 0.00). Negative correlation between mean A1c, presence of F508del and TBS was observed, however did not reach statistical significance.

**Conclusion:** Our study shows positive correlation between TBS and FEV1 as well as Lumbar spine BMD. However, observed mean TBS score in CF patients was higher than reported in other disease groups such as type 1 diabetes. While this could be explained by younger age groups in CF, further studies are needed to evaluate TBS cutoff point for fracture prediction and utility of TBS use in CF.
The role of LKB1-AMPK signaling on renal mTOR and cyst progression in PKD

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Background: In polycystic kidney disease (PKD), downstream components of the mTOR pathway, i.e. ribosomal protein S6, are aberrantly phosphorylated in cyst-lining cells, suggesting that mTOR activation contributes importantly to cell proliferation and cyst growth. Fluid accumulation within the cyst cavity is driven by Cl-dependent fluid secretion via an apical CFTR Cl channel. Liver Kinase B1 (LKB1) is a well-known tumor suppressor that directly phosphorylates and activates AMP kinase (AMPK), an important negative regulator of both mTOR and CFTR Cl channels. Our hypothesis is that the LKB1-AMPK pathway modulates cyst growth and the progression of PKD.

Methods: We crossed \textit{LKB1}^{flox/flox} and \textit{Pkhd1-Cre} mice to knock out LKB1 selectively in collecting ducts (CDs). In addition, we isolated cells of \textit{LKB1}^{flox/flox}:ROSA26-Cre \textit{ERT2} mouse kidneys to generate an inducible LKB1 knockout cell line. To directly activate LKB1, we used a novel small molecule LKB1 activator called BIT-11. BIT-11 was delivered by daily gavage from 5 to 20 weeks of age in \textit{PKD1}^{RC/RC}:PKD2$^{+/+}$ mice, an ADPKD model that develops a prominent cystic phenotype by 5 weeks of age that progresses slowly thereafter.

Results: Epithelial cells cultured from \textit{LKB1}^{flox/flox}:ROSA26-Cre \textit{ERT2} kidneys were treated with tamoxifen to delete LKB1 expression. The loss of LKB1 significantly decreased P-AMPK, but had no effect on mTOR signaling. CD-specific knockout LKB1 in otherwise normal mice resulted in hydronephrosis; however, renal cyst formation was not observed, indicating that the loss of LKB1 was not sufficient to induce cyst formation in mice. On the other hand, direct LKB1 activation with BIT-11 increased P-AMPK and decreased P-S6 in human ADPKD cells. BIT-11 decreased Cl secretion across ADPKD cell monolayers and blocked cyst-like tubule dilations in \textit{Pkd1}^{+/+} mouse kidneys in metanephric organ culture. Treatment with BIT-11 caused a significant decrease in kidney weight (percent body weight), blood urea nitrogen and interstitial fibrosis in \textit{PKD1}^{RC/RC}:PKD2$^{+/+}$ mice.

Conclusion: The LKB1/AMPK pathway does not appear to regulate basal mTOR levels in the kidney; however, direct activation of the pathway using a novel LKB1 activator decreased mTOR, cell proliferation, Cl secretion and cyst growth, suggesting that this may be a potential therapeutic target for the treatment of PKD.
OBJECTIVE: Current first-generation mutant cystic fibrosis transmembrane conductance regulator (CFTR) class II correctors provide limited clinical improvement in most cystic fibrosis (CF) patients, possibly due to chronic inflammation. Therefore, we sought to test adjuvant anti-inflammatory therapy to improve class II corrector efficacy. Losartan is an inexpensive, well-tolerated anti-hypertensive drug with documented anti-inflammatory properties. In this study, we explored whether losartan could enhance the effectiveness of the CFTR corrector VX-809 (lumacaftor) during TGF-β1-induced inflammation in patient-derived CF bronchial epithelial (CFBE) cells. The expression of miR-145 and miR-494 is upregulated in CF vs. non-CF bronchial epithelium both in vivo and in vitro and both suppress CFTR mRNA expression. We thus evaluated whether losartan exerts its anti-inflammatory effects through these microRNAs.

METHODS: Fully-differentiated F508del CFBE cells were used to examine the effects of TGF-β1 (10 ng/ml), losartan (10 μM), and VX-809 (5 μM) on parameters of mucociliary clearance (MCC). CFBE cultures were mounted in Ussing chambers and CFTR short circuit currents (I_sc) were recorded upon CFTRinh-172 addition after forskolin stimulation in the presence of amiloride. ASL volumes were measured by meniscus scanning. Relative mucus viscosity was assessed by measuring the lateral diffusion of dextran-labeled FITC in the mucus layer using fluorescence recovery after photobleaching (FRAP). microRNAs were quantified using RT-PCR and U6 as reference.

RESULTS: VX-809 improved F508del CFTR function and TGF-β1 significantly reduced this effect (p ≤ 0.05). Losartan rescued CFTR function impaired by TGF-β1 in the presence of VX-809 (p ≤ 0.05). VX-809 significantly enhanced ASL volume of the cultures, but TGF-β1 diminished this improved ASL volume (p ≤ 0.05). Losartan restored ASL volume (p ≤ 0.05), suggesting improved airway hydration by losartan. The addition of TGF-β1 increased mucus viscosity alone and when co-treated with VX-809. Consistent with the previous measures, losartan protected against this outcome (n ≥ 5). Losartan treatment induced a trend towards decreased miR-145 and miR-494 expression in the presence of TGF-β1 and VX-809 (n ≥ 5).

CONCLUSIONS: These data suggest that losartan reverses the loss of VX-809 efficacy caused by TGF-β1 and significantly improves parameters of MCC, possibly through the regulation of miR-145 and miR-494.
Exploring Readmission After Discharge to Home Hospice

Authors: Amy Johnson BA, Thuy Cao BS, Justin Coogle BS, Kristen Funk BS, Adam Zuzelski BS, Sharon Fitzgerald MPH, Vishal Kapadia DO, Ky Stoltzfus MD

Background: Home hospice is designed to provide comfort to patients at the end of their life. A primary goal is to keep the patient at home and avoid inpatient hospital care or undue interventions. Readmission to the hospital is incongruent with this goal. The purpose of this study was to investigate the prevalence and characteristics associated with hospital readmissions at a quaternary care teaching hospital over a two-year period.

Methods: This was a retrospective cohort study where 814 possible patients who discharged home with hospice were identified through automated coding within the electronic medical record. During our chart review, 705 of these patients met the inclusion criteria. The primary outcome was readmission after discharge to home with hospice. Secondary measures included characteristics of patients who were readmitted, including age, sex, race/ethnicity, primary language, marital status, insurance status, and presence or absence of a palliative care consult. In addition, reasons for readmission was abstracted by chart review. Multivariate analysis using odds ratio and chi-square test with a step-wise forward selection compared the proportions of other secondary factors between the readmission and non-readmission groups.

Results: Readmission rate was found to be 10.50% (74/705) and median days from discharge to readmission was 32.5 days. The mean age of the readmitted and non-readmitted groups was 65.73 ± 15.03 years and 66.80 ± 13.76 years, respectively. The following were associated with readmission: female OR 2.04 (CI 1.21-3.46, p-value = 0.0051), non-white OR 2.39 (CI 1.41-4.06, p-value < 0.0001), and hospice diagnosis with cardiac disease OR 4.73 (CI 2.20-10.14, p-value< 0.0001). Reasons for readmission included new unanticipated medical issues with 44.60% (33/74), uncontrolled symptoms with 33.78% (25/74), misunderstanding of hospice status with 16.21% (12/74), and caregiver distress with 5.41% (4/74).

Conclusions: Compared to prior studies, our findings in this single institution revealed a lower readmission rate from home hospice. Our findings showed female sex, non-white race or ethnicity, and individuals with a hospice diagnosis belonging to the category of cardiac disease were more likely to be readmitted.
A Case of Serum Sickness as a Delayed Reaction Infusion of Infliximab

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Introduction: Infliximab is a commonly used biologic approved in the treatment of fistulizing Crohn’s disease. A delayed systemic reaction or serum sickness-like reaction is a known complication in patients receiving treatment with Infliximab who have had prior exposure. We present a case of a patient who developed severe serum sickness as a result of a reinitiation infusion.

Case Presentation: A 26-year old male with Crohn’s disease presented with acute onset of severe, symmetrical polyarthralgia and myalgias with associated immobility secondary to pain. He also reported dysphagia to solids and liquids. Physical exam was remarkable for bilateral synovitis of his MCPs, PIPs, wrists, elbows, shoulders, knees and ankles as well as a macular, erythematous rash over his bilateral wrists and forearms and a malar-appearing rash on his face. He developed fever the night of admission with leukocytosis. He had received an Infliximab infusion nine days prior to admission, his second exposure after a ten-year interval. His initial exposure to Infliximab caused an allergic reaction with hives. He denied any recent travel, insect bites or sick contacts. His procalcitonin was elevated, but infectious workup was negative. Rheumatologic workup was negative, as well. The patient showed marked clinical improvement on IV steroids and was discharged on a steroid taper.

Discussion: A delayed serum sickness-like reaction is a known complication in patients with prior exposure to Infliximab, and according to the literature, is most commonly associated with a distant second infusion (≥ 20 weeks from the first infusion). The clinical manifestations include: polyarthralgia, myalgias, rash, fever, pruritis, edema, sore throat, and dysphagia and generally appear 3-12 days after infusion. It is important for physicians to be aware of such a complication as the presentation can be striking and can mimic several infectious and rheumatologic diseases. Several treatment strategies, including concomitant treatment with steroids or immunomodulators and the development of structured induction and maintenance regimens that avoid lengthy periods between treatments, have been outlined to reduce the incidence of a severe reaction.
Poly-chemotherapy in effective salvage of malignant glioma; a case report

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Malignant gliomas (grade III/IV) remain a challenging entity to treat due to the limited numbers of patients and paucity of available effective treatments. Involved field radiation and oral temozolomide offer modest survival benefit to some, but at recurrence, patients with either grade III or grade IV tumors have no standard options and survival is limited to months on average. The use of repurposed drugs offers several advantages, first these are already FDA approved, so obtaining them off-protocol is more straight-forward, second they have known toxicity profiles and third, they are often off-patent and relatively less expensive to use. Presented here is a patient who continues to receive effective salvage therapy utilizing a repurposed drug cocktail for malignant glioma.

This is a 30-year-old male who presented with seizures in 2011. Debulking surgery demonstrated astrocytoma (II), 1p/19q intact, IDH-wildtype and was followed by 1-year of 5-day temozolomide. In 2015 he had recurrent enhancing disease and underwent second craniotomy which demonstrated anaplastic astrocytoma (III). He was treated with radiation and concurrent/adjuvant temozolomide chemotherapy; after several cycles he had further progression of enhancing tumor. He was started on low-dose (BID) temozolomide salvage along with Celecoxib and Naloxone. From 2015 through 2017 he continued this therapy, at that time with further progressive enhancement Depakote was added. Since 2017 he has had resolution of the enhancing tumor and thinning of the residual FLAIR signal. He continues to tolerate this treatment well, works full time and has no toxicity.

Case reports are meant to be hypothesis generating. Striking here is the effective treatment of biopsy proven recurrent high-grade disease in this patient with poor molecular profile tumor. Second is the very unusual circumstance of resolution of previous enhancing tumor along with thinning of the residual FLAIR signal. Finally, the extremely favorable side effect profile, now going on 4 years of salvage therapy. Patient and family are well aware of the unknowns in this situation in regards both long-term efficacy and long-term toxicity. They are further aware of the survival “averages” in malignant glioma and are very much in favor of continuing salvage therapy at this time.
Not your usual suspect: a case of pill-induced esophagitis caused by demeclocycline

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Introduction:
Pill-induced esophagitis is a well-recognized phenomenon. Most commonly reported cases are linked to tetracycline and its variant doxycycline. This case is unique in that demeclocycline, a semi-synthetic tetracycline derivative, is the causative agent. In a search of FDA adverse event reporting system and WHO adverse drug reactions database, only one similar case of esophagitis attributable to demeclocycline was found.

Case Presentation:
A 59 year-old Caucasian woman presented to outpatient endoscopy lab for evaluation of odynophagia. She had a medical history of small cell lung cancer (SCLC) complicated by syndrome of inappropriate anti-diuretic hormone secretion (SIADH). This was being managed with demeclocycline. Her physical exam was without notable abnormalities. On endoscopic evaluation, the patient was found to have a circumferential, ulcerated, necrotic, and fungating mass approximately 17 centimeters from the incisors. This appearance was suspicious for malignancy, and biopsies were obtained. Microscopic examination of the specimen demonstrated fibrinopurulent exudate and abundant foreign material, but no malignant cells. The patient was admitted to the oncology service for further evaluation, and underwent PEG placement for nutritional support. Given the high suspicion for underlying malignant etiology of the esophageal lesion, two subsequent EGDs were performed. Both sets of subsequent biopsies were also negative for malignancy. Upon review of the patient’s medications, it was felt that patient was likely suffering from pill-induced esophagitis related to demeclocycline. Her demeclocycline was stopped, and the patient was started on a proton-pump inhibitor. Due to severe hyponatremia, a decision was made to restart the demeclocycline but to administer via her PEG tube. On subsequent follow up in clinic, she reported complete resolution of her odynophagia. Due to her overall prognosis, in the setting of advanced lung cancer and other comorbidities, a repeat elective EGD was not scheduled.

Discussion:
This patient presented with a common complaint of odynophagia. Earlier recognition of demeclocycline’s association with pill induced esophagitis may have negated the need for multiple repeat endoscopies in the presence of non-diagnostic biopsy results. This case highlights the need to consider pill induced esophagitis in the differential of individuals using demeclocycline who present with esophageal symptoms.
Steroid-Dependent Episodic Angioedema with Eosinophilia (Gleich Syndrome) in a Patient with Rheumatoid Arthritis

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INTRODUCTION/BACKGROUND: Episodic angioedema with eosinophilia, or Gleich syndrome, is a rare disorder characterized by periodic episodes of angioedema and leukocytosis with marked eosinophilia. Symptoms resolve spontaneously or are treated with corticosteroids as first-line therapy. Treatment of patients unresponsive to or dependent on corticosteroids is poorly defined. Several rheumatologic diseases, including rheumatoid arthritis (RA), can also present with elevated eosinophilia in blood or tissue. Here we present a case of steroid-dependent Gleich syndrome complicated by concurrent rheumatoid arthritis.

METHODS: A retrospective chart review of a patient with Gleich syndrome at a university hospital-based Allergy/Immunology outpatient clinic in Kansas City, KS.

RESULTS: This patient with seropositive RA had multiple episodes of angioedema with eosinophilia and associated dyspnea. Labs showed absolute eosinophil count of 12.9 K/UL and WBC 25.51 K/UL. Tryptase was elevated at 26.1 ug/L. CT neck showed subglottic swelling. Further workup included normal ACE and C1 esterase inhibitor levels and negative ANCA serologies. Bone marrow biopsy showed hypercellular marrow and normal cytogenetics. A diagnosis of Gleich syndrome was suspected. She was initially treated with glucocorticoids but with attempts at weaning experienced recurrent pharyngeal swelling and increase in serum eosinophilia. She was then started on rituximab for RA and hypereosinophilia with decrease in eosinophil count and ability to tolerate further steroid tapers.

CONCLUSIONS: To our knowledge, this is the first reported case of Gleich syndrome in a patient with RA. Rituximab therapy has been described in hypereosinophilic syndromes but not reported specifically for Gleich syndrome, demonstrating the importance of recognizing alternative therapies for complex, steroid-dependent disease.

FUNDING SOURCE: Not applicable
Gastrointestinal Histoplasmosis After Orthotopic Heart Transplant with Atypical Gastric and Duodenal Involvement

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Introduction/Abstract:
Systemic dissemination of *Histoplasma capsulatum*, a dimorphic fungus, carries significant mortality if left unrecognized and untreated. Disseminated histoplasmosis (DH) may present in a variety of ways. Gastrointestinal histoplasmosis (GIH) has been well described. GIH most commonly affects the terminal ileum and colon. We present a case of an immunocompromised male, six months post orthotropic heart transplant (OHT), diagnosed with GIH of the stomach and duodenal involvement.

Case Description:
A 69 year-old male farmer with a history of OHT six months prior to admission, presented with progressive anorexia, early satiety, and post-prandial bloating for 3 months. His immunosuppressive regimen included tacrolimus, mycophenolate, and prednisone.

His physical exam was notable for tachycardia. Laboratory studies showed a stable microcytic anemia, normal white blood cell count. Na was 125mmol/L, creatinine 1.36mg/dL, and mildly elevated AST and ALT of 42u/L and 83u/L, respectively. Fungal studies galactomannan and fungitell were elevated, 8.011 and 355, respectively. Histoplasma serum antigen was positive, histoplasma urine antigen was also positive at 18.29 ng/ml. An esophagogastroduodenoscopy (EGD) was performed. Endoscopic findings were notable for mucosal changes of congestion and nodularity in the duodenum. A Grocott silver stain of the gastric fundus, duodenum and a mesenteric lymph node were all positive for fungal organisms. An endomyocardial biopsy was negative for acute rejection. The patient was initiated on liposomal amphotericin B and quickly transitioned to voriconazole with improvement of fatigue and appetite. Upon discharge his immunosuppressive regimen was modified, including withholding mycophenolate. He was scheduled for at least 12 months of outpatient antifungal therapy.

Discussion
Greater than 99% of humans exposed to *H. capsulatum* are asymptomatic or develop mild, self-limiting respiratory symptoms due to the antigenic control by an intact T cell immunity [1, 2]. The incidence of gastrointestinal (GI) involvement, causing significant symptomatic disease, has been reported to be as low as 3-12% [3, 4]. Those with weakened or compromised immunity are at risk for clinically significant disseminated Histoplasmosis (DH). Dissemination carries a high rate of morbidity, and the mortality rate may surpass 50% [5]. Extremes of age, concomitant chronic infection (e.g. tuberculosis), and immunosuppressive states are established risk factors for DH [1, 6]. Living in an area endemic to Histoplasmosis also raises this risk [2].

The nonspecific nature of the symptoms associated with GIH can delay its diagnosis [8]. Though terminal ileum and colonic involvement of the GI tract are most common, gastric or
duodenal involvement should be considered in any immunosuppressed patient with upper GI complaints.

GIH most commonly involves the terminal ileum (TI), thought to be due to ample lymphoid tissue. [1, 7] Gastric involvement, seen in our patient, is rare and occurred in only 4% of cases in an autopsy series. [7]

Biopsies with evidence of histoplasma establishes the diagnosis (figure 1). Characteristically there will be a mixed lymphohistiocytic and neutrophil infiltrate. Associated granulomas are only occasionally seen. GMS stain helps highlight the fungal organisms (Figure 2). In this case, numerous organisms were present in the stomach and duodenum, while colon biopsies were negative. In addition, biopsy of a mesenteric lymph node showed necrosis with abundant Histoplasmosis organisms. Endoscopic findings are nonspecific and may include patchy or continuous areas of superficial mucosal erythema, edema, or ulceration. Advanced disease may be seen in the form of obstructive masses, strictures, or perforation.[11]

Additional modalities can aid the in the diagnosis of GIH. Cross sectional imaging can reveal abdominal lymphadenopathy in nearly two-thirds of patients with GIH.[12] This finding also raises concern for Post-Transplant Lymphoproliferative Disorder, as seen in our case, and should be explored in all SOT patients. Urinary Histoplasma antigen test is not only a rapid and sensitive diagnostic tool, but can also be utilized as a method of monitoring treatment response with decreased antigen concentrations correlating with waning disease activity.[9] Higher Urine Histo antigen titers, along with older age and fungemia, has been correlated to increased rates of mortality.[8]

GIH is treated initially with IV amphotericin with treatment courses of several months.[9]

Awareness for the potential of GIH in SOT patients is pivotal for early diagnosis, treatment, and appropriate management. This diagnosis is often based upon clinical acumen given patient’s presentations with nonspecific symptoms. Our case highlights the importance of considering GIH in immunosuppressed individuals with persistent upper GI symptoms.

Photos:
Figure 1: H&E 400X: Acute and chronic inflammation is present throughout the duodenal mucosal tissue with numerous intracellular organisms seen (arrows)
Figure 2: GMS 400X: Grocott methenamine silver stain highlights numerous ovoid fungal microorganisms, consistent with Histoplasmosis

Evaluation for Primary Immunodeficiency in a Patient with a Historical Diagnosis of Primary Ciliary Dyskinesia

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Primary Ciliary Dyskinesia (PCD) and Primary Immunodeficiency (PID) are rare, congenital disorders that share common features of recurrent oto-sino-pulmonary infections beginning in childhood. Common Variable Immunodeficiency (CVID) is a primary immunodeficiency characterized by low IgG, plus low IgA or IgM, and abnormal response to vaccination. PCD is an autosomal recessive disorder of abnormal ciliary function resulting in impaired mucociliary clearance. Situs inversus totalis (SIT) and male infertility are additional characteristics of some patients with PCD. Normal ciliary structure is a circle of 9 peripheral microtubule doublets, each with an inner and outer dynein arm, plus a central pair of microtubules joined by radial spokes.

We present a 30 year old man with PCD and CVID diagnosed in childhood, who presented to our institution for continued care, and subsequently unexpectedly fathered a child. Initial sinus biopsy in childhood, obtained during an acute sinus infection, showed a defect of the inner dynein arm of ciliary ultrastructure and led to a diagnosis of PCD. Because of the rarity of these disorders and confirmatory paternity test results, evaluations for both PCD and PID were repeated. A repeat sinus biopsy following a course of antibiotics was completed and showed normal cilia ultrastructure. An evaluation for PID, 6 months following his last IVIg infusion, was normal except for low IgG and an abnormal antibody response to pneumococcal vaccination, leading to a diagnosis of unspecified hypogammaglobulinemia and abnormal antibody response to polysaccharide antigens. As a small subset of PCD-causing genes may have normal ciliary ultrastructure, genetic testing to further evaluate for PCD was completed and was negative.

Diagnosis of PCD is made by characteristic structural ciliary defects, evidence of abnormal ciliary function, or identification of causative genetic mutations, and the presence of a characteristic clinical phenotype. Transient inner dynein arm defects have been documented on sinus biopsies of individuals with acute infectious sinusitis, and can resolve following infection. This case highlights the importance of a complete immunodeficiency evaluation in any patient with a history of recurrent infections, and the importance of cautious diagnosis of PCD if there is evidence of infection during biopsy sampling.
Introduction/Background:
- Subacute bacterial endocarditis can have many different presentations; in rare instances, it can present as leukocytoclastic vasculitis owing to the effect of circulating immune complexes and micro-emboli on the vascular endothelium. A high index of suspicion needs to be maintained to differentiate between infectious vs noninfectious autoimmune vasculitides, keeping in mind that missing a diagnosis can have fatal results. In this case, we introduce a forty-two year old female patient who initially presented with a picture of idiopathic autoimmune cutaneous vasculitis delaying the diagnosis of an underlying infective bacterial endocarditis with aortic valve involvement due to initially negative blood cultures and no correlating cardiac findings on physical exam.

Methods:
- To diagnose the patient with subacute bacterial endocarditis in the setting of cutaneous leukocytoclastic vasculitis a general and vasculitis specific lab work up, blood cultures, a skin biopsy, and a trans-esophageal echocardiogram were performed.

Results:
- Labs showed anemia, elevated ESR, CRP, normal white count with 82% neutrophils, bacteruria, positive cryoglobins and anti-proteinase antibody’s which later normalized. A skin biopsy revealed leukocytoclastic vasculitis. Blood cultures were positive for Enterococcus faecalis late in the hospital course. A Trans-esophageal echocardiogram (TEE) revealed a large 1.6 cm vegetation on the aortic valve with severe aortic insufficiency.

Conclusion:
- In conclusion, it becomes clear that cutaneous vasculitis is a rare though potential presentation of bacterial endocarditis. The initial presentation of the latter can be misleading and a high index of suspicion needs to be maintained to avoid adverse and sometimes fatal outcomes derived from providing the wrong treatment. It is also crucial not to be fooled by the initial response to treatment in confirming the diagnosis in such patients.

Funding Sources: none
Clostridium difficile Infection as a Predictor of Acute Graft versus Host Disease among Allogenic Stem Cell Transplant Recipients

Subject category: B5. Studies at the interface of host-microbe interaction.

Key words: Clostridium difficile, Graft versus Host Disease, Allogenic Stem Cell transplant

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Abstract Text:

Background: Clostridium difficile infection (CDI) is a major cause of infectious diarrhea especially among allogenic stem cell transplant (SCT) recipients. The relationship between CDI and acute Graft versus Host Disease (aGvHD) has been a topic of great interest, as either of the two conditions may affect the other. We studied the temporal relation of CDI on aGvHD in the first 100 days posttransplant in a large cohort of allogeneic SCT recipients.

Methods: We conducted an analysis of retrospective data extracted from the medical records of adult patients (more than 18 years of age) who underwent their first allogenic SCT between January 1, 2010 and December 30, 2016 at the University of Kansas Health System. Patients were followed for CDI events between day -10 to day +100 of allogenic transplant. Diagnosis and staging of aGvHD were determined based on standardized aGvHD grading scale utilizing clinical and pathological information between day 0 and day +100. Analysis included descriptive statistics, multivariable logistic regression, and survival analysis with CDI as a time-dependent variable.

Results: A total of 656 allogenic SCT recipients were included in the analysis. Of the total sample, 419 (64%) developed aGvHD within the first 100 days. CDI was observed in 111 (17%) of all allogenic SCT recipients, 72 (64%) of CDI cases developed prior to the onset of aGvHD. Fidaxomicin was used in the treatment of 57 (50%), whereas, vancomycin was used in 53 (47%) of CDI cases. On unadjusted analysis, CDI was associated with aGvHD (p = 0.0036), high grade aGvHD (p = 0.0132), and GI aGvHD (p = 0.0003). On multivariate survival analysis, the following predictors were associated with aGvHD: CDI (adjusted Hazard Ratio (aHR) = 1.44, p = 0.0047), matched unrelated donor versus matched related donor transplant type (aHR = 1.40, p = 0.0023), myeloablative versus reduced intensity conditioning (aHR = 1.87, p < 0.0001). This was consistent with the stepwise logistic regression model. Treatment with fidaxomicin was associated with lower risk of gastrointestinal (GI) aGvHD compared to treatment with vancomycin (odds ratio=0.236, confidence interval (0.059 – 0.940), p 0.0312).

Conclusion: Allogenic SCT recipients with CDI have a higher risk of aGvHD compared with those without CDI.
HISTOPLASMOSIS INDUCED HEMOPHAGOCYTIC LYMPHOHISTOCYTOSIS IN HUMAN IMMUNODEFICIENCY VIRUS AND HEPATITIS B COINFECTED PATIENT

Raed Jabr, MBBS and Kassem Hammoud, MD

Introduction:

Hemophagocytic lymphohistiocytosis (HLH) is a rare disease characterized by excessive immune activation caused by impaired function of natural killer and cytotoxic T-lymphocytes. If not treated promptly, mortality of patients with HLH is high especially in the first month after the diagnosis. [1] Data are limited regarding optimal treatment and clinical outcomes in adults. [2] We reported a fatal case of histoplasmosis induced HLH in HIV/HBV co-infected patient.

Case report:

A 41-year-old previously healthy male presented to a community hospital with chronic cough and fever. Initial work up showed pancytopenia, elevated liver enzymes, and bilateral lungs infiltrates seen in CXR. He was admitted for the management of presumed community acquired pneumonia. Given the history of multiple female sexual partners in the past and transaminitis, hepatitis serology and HIV scree were obtained. HIV antibody/antigen (fourth generation) and hepatitis B surface antigen were reactive, consistent with newly diagnosed HIV infection and reactivation of hepatitis B (IgM for hepatitis B core antigen was non-reactive arguing against acute infection). He was transferred to our institution for the management of pneumonia in the setting of possible HIV/AIDS and hepatitis B coinfection. CD4 count was 10 and HIV viral load 727082 copies. Trimethoprim/sulfamethoxazole was started for possible PJP pneumonia. Given pancytopenia, fever, ferritin level above level of quantification, HLH was suspected with histoplasma as a trigger given pulmonary infiltrates. Histoplasma urine antigen was above level of quantification, liposomal amphotericin was started in hospital day number 4. He met 5 of 8 criteria of HLH (fever, pancytopenia, splenomegaly, high ferritin, elevated soluble IL-2 activity 14,240 [normal <1033]). Hematology was consulted with plan was to treat the underlying triggering infection. Pancytopenia persisted after the completion of 2 weeks of liposomal amphotericin, so dexamethasone was started according to HLH-94 protocol. The patient developed septic shock due to Serratia marcescens pneumonia and bacteremia on hospital day 23. He developed DIC and died on hospital day 43.

Discussion and teaching point:

Histoplasmosis induced HLH diagnosis is challenging. Fever, splenomegaly, and high ferritin usually explained by histoplasmosis. This leads to underdiagnosis of associated HLH. In a previous case series and review of literature, 43 from 51 patients (84%) with histoplasmosis associated HLH had immunosuppression conditions with HIV/AIDS being the most common condition. [3]. The delay in diagnosis of HLH is often the most common barrier to treatment. Clinical and lab findings that should prompt evaluation for HLH are splenomegaly, an extremely elevated ferritin, and pancytopenia especially in immunocompromised or HIV infected patients.

References:

Accurate CMS Documentation of ADL Self-performance and Support.
Guy Fogg MD, Courtney Huhn MD

BACKGROUND:
Medicare uses a Prospective Payment System [PPS] to pay Skilled Nursing Facility services a case-mix adjusted per diem payment rate to compensate staff and facility costs. The present iteration, the Resource Utilization Groups – Version IV [RUG-IV], has 8 reimbursement groups tiered by level of skilled service, clinical complexity, and resident cognitive function. These are further subdivided by depression and functional independence through Minimal Data Sheet [MDS] evaluation of resident’s self-performance and staff-provided support in Activities of Daily Living [ADLs]. In the Topeka VA Community Living Centers [CLCs] (VA Nursing Homes), MDS data of resident functionality is gathered from nursing staff documentation. The aim of this study was to improve staff awareness of accurately capturing a Veteran’s ADLs through educational sessions describing the RUG-IV reimbursement algorithm, MDS data capture technique and provision of a simplified reference tool to help staff choose the appropriate score for self-performance and assistance. The secondary goal was improving a CLCs reimbursement by more accurately capturing a veteran’s level of assistance.

METHODS:
This prospective study of nursing staff gathered baseline data, and provided a brief educational session delivered at shift change with a cartoon reference tool visually describing levels of self-performance and assistance. Anonymous surveys administered before and after the intervention probed about awareness of the RUG, if ADLs factored into staffing needs, and usefulness of the intervention. There was also a comparison of the pre and post CLCs quarterly RUG reports.

RESULTS:
Nursing staff felt strongly that ADLs factor into CLC staffing needs (23/26), and that the MDS was important to a CLC’s budget (23/26). The intervention further solidified these views, and the awareness of the RUG-IV increased (9/26 to 26/26). Respondents felt the intervention was useful (25/26). Comparison of FY18Q3 and Q4 RUG reports stratified by ADLs showed trend of higher scores.

CONCLUSION:
Our intervention increased awareness and appreciation of the implications of accurate ADL documentation. This may reflect a trend on increased ADL scores captured on quarterly RUG. Although the days of the RUG-IV are numbered with the coming of the new Patient Driven Payment Model [PDPM], ADLs continue to be heavily weighted variables in this new iteration.
Differential Expression of Long Noncoding RNAs in Cocaine and HIV-1 Tat treated Pulmonary Smooth Muscle Cells

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Introduction
Noncoding RNAs play major role in regulation of pulmonary hypertension. Our previous study revealed co-exposure of HIV-1 proteins and cocaine downregulate bone morphogenetic receptor (BMPR)-2 protein in transgenic rat model and human pulmonary arterial cells (HPASMC) leading to enhanced proliferation. Later we observed down modulation of BMPR2 protein is post-transcriptional by microRNA-216a which was upregulated in combined treatment. Here, we have attempted to study role of long-noncoding RNAs (lncRNAs) in hyper proliferation of smooth muscle cells by HIV-1 and cocaine.

Methods
HPASMCs were treated with cocaine or cocaine and Tat (C+T) protein for 48 h followed by total RNA isolation for microarray expression profiling of mRNAs and lncRNAs by Arraystar Inc. To understand functional relevance of differentially expressed lncRNAs, “LncRNAs2Pathways” methodology (PMID:28425476) was employed across the set of differentially expressed lncRNAs identified in each treatment comparison.

Results
A total of 325 mRNAs and 2206 lncRNAs were found to be up-regulated (red dots) and 536 mRNAs and 3906 lncRNAs were down regulated (green dots)(p-value ≤ 0.05, fold change ≥1.5) in HPASMCs on C+T treatment compared to control as indicated in volcano plot. There was significant enrichment of differentially expressed mRNAs belonging to Ras and dilated cardiomyopathy signaling. The co-expression pairs of lncRNA and mRNA were calculated using lncRNAs with fold change ≥2.5, p-value ≤0.001 for C+T treatment compared to control. This identified 6265 pairs with Pearson correlation co-efficiency of ≥0.9 in combined treatment. The top 4 lncRNAs with fold change >7 namely BC045791, G043354, G028595, G082480 selected from this co-expression data were further analyzed using DAVID tool with corresponding paired mRNAs and leading to identification of PI3K-Akt and NFkB signaling pathways as potential targets of these lncRNAs. Furthermore, mapping of statistically significant (≤ 0.01) differentially expressed lncRNAs with fold change ≥2 onto coding-noncoding gene correlation network of lncRNA to mRNA identified oxidative phosphorylation as highly influenced signaling pathway in C+T HPASMCs.

Conclusion
Our preliminary studies reveal that C+T treatment significantly alter expression pattern of lncRNAs that are highly influencing signaling pathways critical to cellular growth. The work is being furthered to find detailed mechanistic roles of lncRNAs in HPASMC regulation.

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Chiclero’s Ulcer – A Case of Cutaneous Leishmaniasis in Kansas

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Introduction:
Cutaneous leishmaniasis is a disease caused by Leishmania protozoa and transmitted by sandfly vectors, with the majority of new cases occurring in the Middle East and Central and South America. We report a case of complicated cutaneous leishmaniasis diagnosed in an immigrant from Honduras and unique treatment with excisional therapy only.

Case Presentation:
A 22 year-old male with no medical history was referred to the University of Kansas Infectious Diseases clinic with a persistent left facial lesion. It started as a small “pimple” 6 months prior, then began growing for the next 3 months with development of a necrotic center and mild surrounding erythema. He was prescribed a course of oral antibiotics without improvement. There was no associated pain, drainage, fever, or other systemic symptoms. Examination revealed a 2x3 centimeter left pre-auricular lesion with well-defined borders and a large central necrotic eschar. There were no mucosal lesions or lymphadenopathy. CBC and CMP were normal.

The patient emigrated from Honduras 3 months prior to symptom onset. He traveled for two weeks, sleeping in the open air and having many insect bites. He crossed the border in Texas and spent three weeks in a detention center in Louisiana prior to moving to Kansas. A prior biopsy revealed abundant intracellular organisms with acute and histiocytic inflammation, most consistent with leishmaniasis. After consulting with the CDC and plastic surgery, the decision was made to excise the lesion for definitive diagnosis and perform a skin flap for optimal cosmetic outcome. Surgical pathology was consistent with leishmaniasis. A sample submitted to the CDC for PCR testing and DNA sequencing confirmed infection with Leishmania mexicana. Treatment with liposomal amphotericin B was attempted, however he could not tolerate the infusion despite pre-medicating with diphenhydramine and acetaminophen and slowing the infusion rate. The patient declined any further treatment options. In follow up, he has a hypertrophic scar but no evidence of recurrent infection.

Discussion:
Cutaneous leishmaniasis is an emerging infection to be aware of in travelers and migrants from endemic areas. Recognition and diagnosis of cutaneous leishmaniasis is important for determining disease severity and initiating treatment if indicated.
Title: Effect of Methlythioadenosine on TGF-β1-induced mucociliary dysfunction in human bronchial epithelial cells

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Objective: Cystic fibrosis (CF) is an autosomal recessive lung disease caused by mutations in cystic fibrosis transmembrane conductance regulator (CFTR). The severity of CF lung disease varies even amongst those homozygous for the most prevalent CFTR mutation (F508del). Heritability studies show non-CFTR modifier genes are responsible for the majority of this disease variability. Our airway epithelial transcriptomic studies in 134 CF subjects showed that increased expression of genes in the methionine salvage pathway (MSP), including methlythioadenosine phosphorylase (MTAP), was associated with worse lung disease severity. MTAP recycles, or reduces, methlythioadenosine (MTA), the key metabolite of the MSP. While MTA has been shown to be anti-inflammatory in multiple models, its role in CF and/or in the human airway is unknown. In this study, we set out to determine whether MTA could improve the mucociliary dysfunction induced by transforming growth factor beta1 (TGF-β1), a known genetic modifier of CF.

Hypothesis: We hypothesized that MTA could mediate physiologic effects to improve airway epithelial function impaired by an inflammatory stimulus by restoring innate host defense features such as airway surface liquid (ASL) volume and ciliary beat frequency (CBF).

Method: Fully differentiated normal human bronchial epithelial (NHBE) cells grown at air-liquid interface were stimulated using TGF-β1 (10 ng/mL) for 24 hours. To determine the effect of increasing MTA on ASL and CBF, we used increasing doses of MTA and Methylthio-DADMe-Immmucillin A (MTDIA, a small molecule inhibitor of MTAP). ASL was measured by meniscus scanning and CBF was measured using the SAVA system.

Results: MTA treatment (100 µM) significantly improved ASL volume and trended to increase CBF in NHBE cells exposed to TGF-β1. Treatment of NHBE cells with MTDIA (10 µM) trended to increase the loss of ASL volume and CBF induced by TGF-β1.

Conclusion: MTA and MTDIA improved TGF-β1-induced decreases in ASL and CBF in vitro, which would improve mucus hydration and mucociliary transport, and thereby be beneficial to airway cells. Future studies will evaluate the anti-inflammatory effects of MTA in NHBE cells and CF airway epithelial cells.
LEAP!Rx: Integrating Exercise as a Prescription within the Clinical and Clinical Trial Workflows of the Electronic Health Record and REDCap

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Introduction: Use of electronic health record (EHR) alerts at the point of care for research study recruitment is increasing. Studies have shown challenges, success, and the promise of these tools to increase study accrual. In addition, the use of REDCap in conjunction with EHR alerts to augment recruitment and data management has increased. This research study, entitled Lifestyle Empowerment for Alzheimer’s Prevention (LEAP! Rx) is a randomized, controlled trial of lifestyle modification education and support, delivered at community YMCAs.

Methods: In the LEAP! Rx trial we utilized the Epic EHR to design a point-of-care recruitment alert that displays to specific clinicians who have agreed to recruit participants for the study. The alert algorithm was based on study inclusion and exclusion criteria. The alert contains study information, as well as interactive options that will connect the patient to the study record the EHR and notify the study coordinator that there is a potential subject awaiting follow-up screening. EHR reporting tools assist the study team in managing the study cohort. Once an individual is identified as potentially eligible via the alert, they are screened, screening information is entered into REDCap. If a subject is eligible, randomization is performed in REDCap to assign group, stratified by the referring clinical practice and subject status is updated in the EHR to reflect patient status on study. Study data are captured in the REDCap database and use the public survey feature to facilitate exercise session data capture at the YMCAs. Additional custom coding in REDcap was performed to facilitate multiple choice selection for improved data validation.

Results: The EHR recruitment alert went live July 2018 and displays for 4 providers. As of 1/7/2019, the EHR alert has displayed for 125 patients. To date, 72 patients have been referred to the program. Of those, 48 were excluded (declined, ineligible, etc.), 11 are currently in screening, 13 were found eligible in baseline testing, 7 consented, and 6 are active in the program.

Conclusion: This study represents a method to utilize the EHR for clinical trial recruitment and integrate that work with an external data capture system such as REDCap.

References


Funding: NIH R01 AG052954-01A1 (Burns,Jeffrey M), 9/15/2017-3/31/2022, Prescribing Smart Aging: Integrating Health Systems with Community-Based Lifestyle Interventions.
Dietary Phosphate Restriction Attenuates Renal Cystic Disease in *pcy/pcy* Mice

**Authors:** Ogorchukwu F. Omede, Shiqin Zhang, Cassandra R. Johnson, Emily A. Daniel, Ishfaq Ahmed, Timothy Fields, Shahid Umar, Darren P. Wallace, Jason R. Stubbs

**Background:** Abnormalities in phosphate metabolism strongly predict future development and progression of chronic kidney disease (CKD); however, the mechanism remains undefined. Previously, we showed that dietary phosphate restriction reduced tubular injury in mice with glomerulonephritis. Here, we determined if dietary phosphate restriction slows renal cyst growth and fibrosis in *pcy/pcy* mice, a slowly progressive model of polycystic kidney disease (PKD).

**Methods:** At 7 weeks of age, *pcy/pcy* mice were randomized to receive either a control phosphate (0.54%) or low phosphate (0.02%) diet (n=10/group) until 20 weeks of age. All other major dietary constituents, including protein source and content were comparable between diets. Mice were sacrificed for measurement of kidney weight to body weight (KW/BW), cystic index (% cystic area), and renal expression of early markers of fibrosis.

**Results:** *Pcy/pcy* mice that received the low phosphate diet had a 25% lower KW/BW (low phosphate 2.9±0.3% vs. control 4.3±0.6%, P<0.001) and 30% lower cystic index (low phosphate 21.7±6.6% vs. control 31.5±4.4%, P<0.01; Figure 1). When examining the renal gene expression of markers of fibrosis, *pcy/pcy* mice fed the low phosphate diet had a 50% reduction in the expression of collagen 1α1 (P<0.05) and a 40% reduction in the expression α-smooth muscle actin (P<0.01).

**Conclusions:** Dietary phosphate restriction attenuates PKD progression and renal gene expression for early markers of fibrosis in *pcy/pcy* mice.

![Figure 1. Effect of dietary phosphate restriction on cyst burden in PKD mice. (A) Cross-sections of kidneys from 20-week-old *pcy/pcy* (PKD) mice receiving either a normal diet or phosphate-deficient diet (0.02% phos). (B) Kidney cystic index scoring from *pcy/pcy* mice receiving either normal or phosphate-deficient diet. (**P<0.01)**]
Microbial Blockade - Occlusive Wound Dressing

Stephen Waller, MD, Bart Kane, MD PhD

**Microbial Blockade** is a novel occlusive wound dressing designed to protect surgical or traumatic wounds from bacterial contamination. The patented release method allows use of a cyanoacrylate polymer (*i.e.* medical SuperGlue™) to bond the dressing to the skin and allow for the dressing’s subsequent removal without skin injury. Use of this bonding polymer not only provides an incomparable bacterial barrier to prevent bacterial wound contamination but also eliminates dressing ‘roll-up’ and creasing on uneven surfaces. Use of such a dressing could decrease incidence of surgical wound infections, including infections of underlying orthopedic hardware and implantable devices.

The key to the superiority of this occlusive dressing lies in the bonding adhesive and patented safe removal system. The dressing is designed to be bonded to the skin via a strong FDA-approved cyanoacrylate adhesive.

**Methods:** We tested the microbial barrier properties of two cyanoacrylate adhesives against six common pressure sensitive adhesives. Five standard human bacterial pathogens were utilized. All adhesive samples were placed on culture agar and contaminated with standard, high concentrations of bacteria.

**Results:** After 72 hours, bacteria were found to have penetrated 99.3% (149 of 150) of pressure sensitive adhesive samples. In sharp contrast, bacteria penetrated 0% (0 of 50) of cyanoacrylate adhesive samples at 72 hours.

**Conclusions:** Microbial Blockade is a novel occlusive wound dressing with antimicrobial barrier properties far superior to that of existing wound dressings. The dressing adhesive prevents bacterial ‘creep’ along the skin into the wound, ‘roll-up’ of the dressing edge and formation of creases. We believe use of such a dressing could decrease incidence of surgical wound infections, including infections of underlying orthopedic hardware and implantable devices. Next steps include developing a partnership with existing wound dressing manufacturer, particularly those who also manufacture orthopedic hardware, to move forward with prototype development and potential commercialization.
Common CLDN2 variants are associated with kidney stone risk and reduced claudin-2 expression in human tissue

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2- Laboratory of Genome Technology, Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan
3- Laboratory for Statistical Analysis, RIKEN Center for Integrative Medical Sciences, Kanagawa, Japan
4- Laboratory of Clinical Genome Sequencing, Department of Computational Biology and Medical Sciences, Graduate School of Frontier Sciences, University of Tokyo, Tokyo, Japan

Background: The majority of calcium reabsorption in the proximal tubule (PT) occurs by an unknown route, although many studies suggest it is a passive process. The claudin family of proteins are tight junction proteins that in part modulate paracellular permeability and passive reabsorption in the kidney. The isoform claudin-2 forms cation-selective pores in vitro and is highly expressed in the PT. We previously showed that Cldn2⁻/⁻ mice exhibit hypercalciuria and nephrocalcinosis, both of which are major risk factors for the development of kidney stones. We hypothesized that CLDN2 polymorphisms would associate with susceptibility for nephrolithiasis. To date, genome-wide association studies of nephrolithiasis have excluded CLDN2 from their analyses due to its location on the X chromosome.

Methods: Twelve SNPs in the CLDN2 locus passed our inclusion criteria and were assessed by logistic methods for disease association in two separate patient populations. Meta-analysis of the 2 studies was subsequently conducted using METAL with a total of 11,130 kidney stone cases and 187,639 controls. Using the dataset from the Genotype-Tissue Expression (GTEx) project, we analyzed cis-acting eQTL in the CLDN2 locus. GTEx has insufficient kidney samples for eQTL analysis, but human kidney cortex and pancreas both exclusively express the same transcript (ENST00000540876.1). Thus, we analyzed pancreatic claudin-2 expression in association with CLDN2 risk variants.

Results: Our findings show that 9 CLDN2 SNPs were associated with nephrolithiasis with p-values of 0.0462-0.0055. Given our findings in Cldn2⁻/⁻ mice, we predicted that CLDN2 risk variants for kidney stones would lead to reduced claudin-2 expression. In 6 of the 7 CLDN2 SNPs available for eQTL analysis using GTEx, nephrolithiasis risk alleles were strongly associated with decreased pancreatic claudin-2 expression.

Conclusion: Our present findings suggest that common CLDN2 variants lead to reduced claudin-2 expression and thereby increase the risk for human kidney stone formation.
Prognostic impact of BRAF V600E mutation in patients with non-metastatic colorectal cancer with microsatellite instability: A systematic review and meta-analysis

Authors: Sashidhar Manthravadi MD, Weijing Sun MD and Anwaar Saeed MD

Affiliation: Division of Oncology, University of Kansas Medical Center, Kansas City KS

Background: Colorectal cancer (CRC) displaying high levels of microsatellite instability (MSI-H) has been associated with improved survival in colorectal cancer. MSI-H CRC is also known to be enriched in V600E mutations in the BRAF gene (BRAF-Mut). BRAF-Mut is a known adverse prognostic factor in patients with non-metastatic MSI-low CRC. However, the prognostic role of BRAF V600E mutations in non-metastatic MSI-H CRC remains unclear.

Methods: Following PRISMA guidelines, a systematic review of PubMed and Embase was performed from inception through January 2018 to identify studies which described the impact of BRAF-Mut vs BRAF-wildtype on outcomes in patients with non-metastatic MSI-H CRC. Studies which included patients with metastatic CRC were excluded. Summary hazard ratios (HR) with 95% confidence intervals (CI) for overall survival (OS) and recurrence-free survival (RFS) were estimated using a random effects model and heterogeneity was estimated using the inconsistency index ($I^2$).

Results: After reviewing 988 reports, 8 studies which described the association between BRAF status and outcomes in non-metastatic MSI-H CRC were selected for inclusion. These were reported from Europe, North America and Asia. A total of 1164 patients with MSI-H CRC were included of whom 553 were found to carry BRAF V600E mutation. Data regarding RFS and OS for BRAF-Mut vs BRAF-Wild type was provided in 5 and 8 studies respectively. No association was found between BRAF-Mut and RFS in patients with non-metastatic MSI-H CRC (HR 1.13; 95% CI 0.77- 1.67, $I^2= 0\%$). In contrast to these findings, BRAF-Mut had an adverse impact on OS in patients with non-metastatic MSI-H CRC (OS= HR 1.53; 95% CI 1.15- 2.03, $I^2= 0\%$).

Conclusion: BRAF V600E mutation appears to have no association with disease recurrence but does correlate with adverse overall survival in patients with non-metastatic colorectal cancer with high levels of microsatellite instability. Clinical trials planned in the future must therefore consider adding BRAF status as a stratification factor.

<table>
<thead>
<tr>
<th>Name</th>
<th>Year</th>
<th>Location</th>
<th>BRAFMut</th>
<th>BRAFWt</th>
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<tr>
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<td>2008</td>
<td>USA</td>
<td>83</td>
<td>51</td>
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<td>France</td>
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<td>13</td>
<td>45</td>
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<tr>
<td>Kadowaki</td>
<td>2015</td>
<td>Japan</td>
<td>24</td>
<td>43</td>
<td>67</td>
</tr>
<tr>
<td>De Cuba</td>
<td>2016</td>
<td>Netherlands</td>
<td>89</td>
<td>45</td>
<td>134</td>
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<tr>
<td>Nakaji</td>
<td>2017</td>
<td>Japan</td>
<td>18</td>
<td>26</td>
<td>44</td>
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<tr>
<td>Taieb</td>
<td>2017</td>
<td>Europe, USA</td>
<td>201</td>
<td>204</td>
<td>405</td>
</tr>
</tbody>
</table>

Total | 553 | 601 | 1164 |

Table: Characteristics of included studies
Recurrence-Free Survival:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
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<tr>
<td>Nakaji</td>
<td>0.75 [0.02, 34.15]</td>
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<tr>
<td>Aparicio</td>
<td>1.45 [0.19, 11.11]</td>
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<tr>
<td>Kadowaki</td>
<td>2.46 [0.49, 12.35]</td>
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<tr>
<td>French</td>
<td>1.50 [0.70, 3.21]</td>
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<tr>
<td>Taieb</td>
<td>0.94 [0.58, 1.52]</td>
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<tr>
<td>Total (95% CI)</td>
<td>1.13 [0.77, 1.67]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 4 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)

Overall Survival:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
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<tr>
<td>Kadowaki</td>
<td>1.18 [0.23, 6.02]</td>
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<tr>
<td>Aparicio</td>
<td>1.08 [0.30, 3.84]</td>
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</tr>
<tr>
<td>Nakaji</td>
<td>0.64 [0.20, 2.10]</td>
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<tr>
<td>Popovic</td>
<td>1.48 [0.56, 3.91]</td>
<td></td>
</tr>
<tr>
<td>de Cuba</td>
<td>2.18 [0.93, 5.09]</td>
<td></td>
</tr>
<tr>
<td>French</td>
<td>2.90 [1.31, 6.42]</td>
<td></td>
</tr>
<tr>
<td>Gavin</td>
<td>1.76 [0.88, 3.52]</td>
<td></td>
</tr>
<tr>
<td>Taieb</td>
<td>1.26 [0.78, 2.04]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1.53 [1.15, 2.03]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 6.39, df = 7 (P = 0.49); I² = 0%
Test for overall effect: Z = 2.89 (P = 0.004)
Micro-RNA 216a Mediated Post-transcriptional Regulation of Bone Morphogenetic Protein Receptor 2 Expression in Cocaine and HIV Tat Exposed Pulmonary Smooth Muscle Cells.

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Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Kansas Medical Center, Kansas City, Kansas

Introduction
We earlier reported decrease in BMPR-2 protein but increase in BMPR-2 mRNA levels on exposure of human pulmonary arterial smooth muscle cells (PASMC) to combined treatment of HIV-1 protein(s) and cocaine (Dalvi., et al, 2013). Further, we reported a differential expression of miRNAs predicted to target BMPR-2 mRNA in human PASMCs treated with cocaine and HIV-Tat (Am J Respir Crit Care Med 189; 2014; A1206). Here, we hypothesize post-transcriptional regulation of BMPR-2 expression by these predicted miRNAs in cocaine and Tat treated cells.

Methods
Cells were transfected with antagonirs or mimics followed by BMPR-2 mRNA/protein and MTS proliferation analysis. To evaluate the miRNA’s ability to directly bind to BMPR-2 UTR, cells were transfected with BMPR2-3’UTR-luciferase plasmid in the presence or absence of either antagonirs or mimics of miR-216a or miR-301a. The cell culture supernatant was collected at 24h and 48h post transfection followed by dual luciferase assay.

Results
Inhibition of miR-216a and miR-301a by antagonirs in cocaine and Tat (C+T) treated human PASMC resulted in increased BMPR2 protein expression while the overexpression of the miRNAs by mimics decreased the BMPR2 protein levels when compared with un-transfected C+T treated cells. However, BMPR2 mRNA levels remained unchanged in C+T treated cells transfected with antagonirs but decreased in cells transfected with mimics. In addition, the cocaine and Tat mediated increase in the proliferation of human PASMC was observed to decrease upon transfection of cells with miR-216a and -301a antagonirs while transfection with the corresponding mimics resulted in further increase in the proliferation. Transfection of cells expressing BMPR2 3’UTR-luciferase with different concentrations of mimics against miR-216a and miR-301a resulted in a concentration dependent decrease in luciferase expression compared to cells transfected with scrambled controls; and this was prevented by co-transfection of mimics along with antagonirs. We also observed an increase in the levels of miR-19a, -21a,-216a, -301a in hyper-proliferative PASMCs isolated from HIV transgenic rats exposed to cocaine compared to cells isolated from HIV Tg or WT+/--cocaine groups. Transfection of rat cells from HIV-Tg +cocaine group rats with miR-19a and -216a antagonirs could prevent the increase in proliferation of these cells compared to wildtype.

Conclusion
Our initial findings suggest translation inhibition of BMPR2 protein by miR-216a and 301a. Increase in the levels of these BMPR-2 targeting miRNAs on combined exposure to HIV-protein(s) and cocaine may be involved in abrogation of BMPR-2 signaling leading to enhanced proliferation of pulmonary smooth muscle cells.

Funding
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Across the Continuum: How Inpatient Palliative Care Consultations are Reported in Hospital Discharge Summaries.

Nikki Miller 1 John Shuler 1 Deon Hayley, DO 1,2 Karin Porter-Williamson, MD 1 Jessica Kalender-Rich, MD 1,2

Department of Internal Medicine, University of Kansas School of Medicine 1 Landon Center on Aging, University of Kansas School of Medicine 2

Background
Inpatient Palliative Care Consultations (PCC) develop a patient-centered plan of care for patients with serious illness. Discharge summaries (DS) are an essential tool to maintain continuity across locations. This study was the second phase to look further into documentation of PCC in DS.

Methods
In retrospective chart review, DS were examined of patients who received inpatient PCC at the University of Kansas Hospital (July 2014-May 2015). The study included patients 18 years or older, discharged alive and without hospice.

Code words, developed by an expert panel, and related phrases were used to evaluate DS. They were categorized into Palliative Care (PC), Symptom Management, Hospice and Palliative Home Health, Decision Making and Plan of Care. We also identified communication between primary team and PC team and family meeting status in the PC consult.

Results
595 charts were reviewed: 53% female, ages 18-102 years (mean 66), average length of stay was 15 days and time from PCC to discharge was 9 days. 53% were Full Code, 41% were Do Not Resuscitate and 6% were Limited Attempt at Resuscitation. Services patients were discharged from: medicine (79%), surgery (13%) and burn (2%). Patients discharged to home (51%, 23% with home health, 28% without), skilled nursing facility (30%), long term acute care hospitals (12%), outside hospital (2%) and inpatient rehab (5%).

No code words were included in 21% of the DS. PC was mentioned in 65% and was the only code word in 7%. Symptom management was discussed in 36%, hospice and palliative home health in 17%, decision making and capacity in 32%, and plans of care in 39%. 92% of PC consults and notes documented communication with the primary team and 39% documented a family meeting. Of the 39% who documented a family meeting, 12% mentioned it in the DS.

Conclusions
More than one of five DS lacked mention of the completed PCC. As the main source of provider communication, DS need to reflect critical discussion points from the PCC to improve transitions of care. We propose mandating documentation of the PCC in the standard DS to improve quality of provider communication.
Epithelial Vasopressin Type 2 Receptors Regulate Fibrosis by a YAP Dependent Mechanism in ADPKD

Nidhi Dwivedi and Reena Rao

The Jared Grantham Kidney Institute, University of Kansas Medical Center, Kansas City, KS, USA

**Background:** Progressive tubulo-interstitial fibrosis accompanies cyst expansion in polycystic kidney disease (PKD) and is a major cause for loss of renal function and end stage renal disease. However, the mechanisms for development of renal fibrosis in PKD are currently unclear. A significant number of myofibroblasts, the primary producers of ECM are often found in the pericystic areas in PKD kidneys. We tested the hypothesis that cystic epithelial cells can activate interstitial myofibroblasts and thus modify the cystic microenvironment to promote fibrosis.

**Methods:** Renal tubular epithelial-specific vasopressin type-2 receptors (V2R) were stimulated or inhibited in pre-weaning and adult inducible conditional Pkd1 gene knockout mice with cystic kidneys. Wild type and PKD mice were treated with the V2R agonist dDAVP, or the antagonist OPC31260 by daily intraperitoneal injections for 3 days. 

**Results:** Treatment with dDAVP increased myofibroblast numbers and ECM deposition in PKD mouse kidneys, while OPC31260 had the opposite effect. Expression of connective tissue growth factor (CTGF), a matricellular protein, and its transcriptional regulator YAP were increased in the dDAVP treated PKD mouse kidneys. CTGF and YAP were expressed in mouse and human ADPKD renal cystic epithelium, and CTGF secreted by cultured human ADPKD epithelial cells induced myofibroblast activation and migration in vitro. In contrast, YAP inactivation by pharmacological inhibition or renal tubule specific gene deletion suppressed CTGF production and cyst expansion in vitro, and the development of fibrosis in Pkd1 knock out mice.

**Conclusions:** These results suggest that epithelial specific V2R stimulation can induce YAP dependent CTGF production to activate interstitial myofibroblasts and renal fibrosis in PKD.
Balloon-occluded retrograde transvenous obliteration (BRTO) versus transjugular intrahepatic portosystemic shunt (TIPS) for treatment of gastric varices due to portal hypertension: A meta-analysis

Venkat Nutalapati, Madhav Desai, Sravan Jeepalyam, Swathi Paleti, Mojtaba Olyaee, Amit Rastogi

Background:

Gastric varices (GVs) are a major complication of portal hypertension, developing in 20% of patients afflicted. Although gastric variceal bleeding (GVB) is less common than esophageal variceal bleeding, the severity of GVB is often greater (requiring more transfusions), and thus morbidity and mortality rates (45–55%) are higher. Less invasive endovascular treatments such as balloon-occluded retrograde transvenous obliteration (BRTO) and transjugular intrahepatic portosystemic shunt (TIPS) have been used to overcome the limitations of endoscopic treatment and shunt surgery. At present, there are individual and regional differences in the use of BRTO or TIPS for management of patients with GVs.

Aim:

We performed a meta-analysis to compare the feasibility, efficacy and safety BRTO and TIPS for treatment of GVs due to portal hypertension.

Methods:

A comprehensive search for randomized controlled trials and comparative studies looking at BRTO and TIPS for treatment of GVs due to portal hypertension since the inception of databases (PubMed, Embase, Cochrane Library and Google scholar). Case reports/series and review articles were excluded, along with studies lacking comparative arms. RevMan 5.3 software was used for statistical analysis, random effects model. The primary endpoints evaluated were technical success rate, hemostasis rate, incidence rate of postoperative rebleeding, incidence rate of hepatic encephalopathy, and postoperative procedure-related complication. Pooled rates of study outcomes were compared for BRTO vs TIPS. Outcomes were reported as pooled odds ratio (OR) with 95% confidence intervals (CI) with statistical significance (p <0.05).

Results:

Eight studies (N=8) were included in the meta-analysis. There was no difference in pooled technical success rate (OR, 0.61; 95% confidence interval [CI], 0.11-3.44; P = 0.58), hemostasis rate (OR, 3.41; 95% CI, 0.33-35.40; P = 0.30), and postoperative procedure-related complications (OR, 1.87; 95% CI, 0.58-6.02; P = 0.29). However, BRTO had a lower incidence rate of post-operative rebleeding (OR, 0.33; 95% CI, 0.19-0.57; P =< 0.001) and a lower rate of postoperative encephalopathy (OR, 0.06; 95% CI, 0.02-0.14; P < 0.00001).

Discussion:

BRTO showed similar technical success as TIPS with lower rebleeding rates and post procedure hepatic encephalopathy rates. Based on these results, BRTO should be considered as a primary procedure for treatment of GVs due to portal hypertension.
EFFECT OF DYNAMIC POSITION CHANGES ON ADENOMA DETECTION RATE DURING COLONOSCOPE WITHDRAWAL: A META-ANALYSIS

Venkat Nutalapati, Sravan Jeepalyam, Madhav Desai, Ajay Bansal, Mojtaba Olyaee, Amit Rastogi

Background:
Adenoma detection rate (ADR) is an important quality metric of colonoscopy. Higher ADR correlates with lower incidence of interval cancer. ADR is variable between endoscopists and depends upon the withdrawal technique amongst other factors. Adequate luminal distension of the colon is an important component of good withdrawal technique. Dynamic position changes keeping the colonic segment being inspected at a higher position helps with luminal distension during the withdrawal phase. This entails left lateral position for inspecting the ascending colon, supine position for transverse colon and right lateral for the descending and sigmoid colon. However, this is not routinely practiced.

Aim:
We performed a meta-analysis to study the impact of dynamic position changes during withdrawal phase of colonoscopy on ADR

Methods:
A comprehensive search of MEDLINE, EMBASE, Scopus, Cochrane Database was conducted from each database’s inception to search for studies comparing dynamic position changes during colonoscope withdrawal with static left lateral position. The primary outcome of interest was ADR. Other studied outcomes were polyp detection rate (PDR) and withdrawal time. Outcomes were reported as pooled odds ratio (OR) with 95% confidence intervals (CI) with statistical significance (p <0.05). RevMan 5.3 software was used for statistical analysis.

Results:
A total of 6 studies were included in our analysis with 2860 patients. Of these, dynamic position change was implemented in 1177 patients while 1183 patients served as the controls. ADR was significantly higher in the dynamic position change group with pooled OR 1.36 (95% CI, 1.15-1.61; p <0.01) Figure 1. There was low heterogeneity in inclusion studies (I^2=0%). PDR was not significantly different between the 2 groups with a pooled OR=1.32 (95% CI, 0.9-1.93; p=0.16) Figure 2. Mean withdrawal time in the dynamic position change group was 12.43 min while it was 11.46 min in the control group.

Conclusion:
Dynamic position changes during the withdrawal phase of colonoscopy can increase the ADR compared to static left lateral position. This is potentially due to the improved luminal distension by position change whereby the segment of colon being inspected is brought to a higher position. This is a easy and practical technique to improve ADR.

Forest Plot
ADR
### PDR

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<td>East 2011</td>
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<td>Ou 2014</td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1177</strong></td>
<td><strong>1183</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

**Total events**: 490, 408

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 1.79, df = 5 (P = 0.88); I^2 = 0$

Test for overall effect: $Z = 3.57 (P = 0.0004)$

### PDR

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<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>566</strong></td>
<td><strong>572</strong></td>
<td><strong>100.0%</strong></td>
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</table>

**Total events**: 302, 284

Heterogeneity: $\tau^2 = 0.06; \chi^2 = 5.03, df = 3 (P = 0.17); I^2 = 40$

Test for overall effect: $Z = 1.41 (P = 0.16)$
An Interprofessional Simulation: Improving Transitions of Care and Reducing Medical Errors Across the Spectrum of Care

Crystal Burkhardt¹, Candice Coffey², Jessica Kalender-Rich²

1. University of Kansas, Pharmacy Practice
2. University of Kansas Medical Center

**Background** Transitions of care from hospital to home are fraught with opportunities for error, particularly with medications. Accreditation bodies recognize the importance in instilling the skill of identifying and communicating such errors across the professions in order to address this public health concern.

**Methods** A simulated educational experience for pharmacy and medical students to emphasize the importance of interprofessional (IP) collaboration in this process was developed and implemented using standardized patient actors (SPA). Students completed pre-learning overviewing medical error disclosure. Additionally, pharmacy students were provided patient materials in order to complete a medication reconciliation from a recorded a SPA encounter with a community pharmacist following a patient’s hospital discharge. Pharmacy and medical students communicated via a telehealth conference encounter to discuss a plan of care to correct errors and optimize medications during the care transition. Faculty debriefed students regarding their IP experience following the simulation. Quantitative data from a student completed pre- and post-simulation 5-point Likert scale survey were evaluated. Qualitative data from the simulation debriefs were evaluated for thematic findings.

**Results** One-hundred-seventy-three students completed the pre-simulation survey which was compared to the first pilot group of 29 students who completed the post-simulation survey. Students reported statistically significant improvements in their confidence in use of telehealth technology to communicate with other professionals as well as in disclosing medical errors (p<0.005). Students did not report a significant change in their perception of the role of the community pharmacist as a member of the IP team, but did report improved understanding of what medication therapy management is as performed by the pharmacist (p<0.005). Themes of team structure, leadership, and communication emerged in the qualitative review.

**Conclusion** This simulation afforded health professional students the opportunity to increase their confidence in communicating an error and gain insight into telehealth as an alternative format of IP team communication, while increasing their understanding of care provided by community pharmacist.
Medical Student Reflections After a Skilled Nursing Experience – Words to Grow On

D Zwahlen, MD\textsuperscript{1,3}; J Kalender-Rich, MD\textsuperscript{2,3}; C Coffey, MD\textsuperscript{2,3}

University of Kansas – School of Medicine: Dept of Family Medicine\textsuperscript{1}, Dept of Internal Medicine\textsuperscript{2}, Landon Center on Aging\textsuperscript{3}

Background
Curricular changes recently shifted Geriatric content from a dedicated clerkship to an embedded longitudinal format. A required skilled nursing facility (SNF) experience focused on care of the post-operative patient is now included in the surgical clerkship. Each student spends one half day at a SNF with a Geriatric physician preceptor. The student performs a routine SNF visit that includes discussing the patient with the interprofessional team, writing a progress note and rounding on the patient. We sought assurance that this hands-on SNF experience was relevant to the students’ ongoing education.

Methods
We evaluated the SNF experience using an open-ended reflection that asked about differences between SNF and hospital care and how the SNF visit may impact their care of future patients. All reflections were de-identified and coded individually by three faculty geriatricians. Coding categories include positive or negative valuation by the student; interprofessional roles (IPR); systems analysis (SA); transitions of care (TC); healing process (HP); medication management (MM); self-reflection by the student (SR); patient education (PE) and value of patient contact time (VT). The three geriatricians created a consensus document of the coded reflections based on the agreement of at least two of the three and final codes were entered into a spreadsheet.

Results
Reflections from two clerkships were reviewed (n=43 students). Forty-two students (97.7%) identified the experience as positive. The most common themes were self-reflection (42, 97.7%), systems analysis (40, 93%) and the healing process (32, 74.4%). The theme least commonly experienced was medication management (7, 16.3%). Others were as follows: transitions of care (29, 67.4%), interprofessional roles (22, 52.4%), patient education (17, 39.5%), and the value of patient contact time (15, 34.9%).

Conclusion
The SNF experience has been positive for students and should be maintained. The experience has led to self-reflection, systems awareness, and a better understanding of the healing process. This format of feedback from students can be used longitudinally to assess the quality and impact of the SNF experience.
The Hidden Problem List: Assessment of Older Adult Health Records in Search of the Real Patient 2.0

Coffey C¹, Hayley D¹

¹Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS

Background:

Problem Lists (PL) should communicate essential elements of health status and are a tool for clinical decision-making. PLs should improve the quality of the health record by adding meaning to it. However, PL content is not standardized and completeness varies. If PLs are not reflective of health status they can have potential for adverse consequences. We examined effectiveness of PLs at reflecting health status of older patients. We determined; a) how common specific geriatric conditions are, as recorded in progress notes; b) how often these conditions are present in the PL after consultation; and c) which conditions showed discrepancies between note content and PLs.

Methods:

A consensus list of 18 conditions that capture geriatric health status was created and used in a pilot study at a VA geriatric assessment clinic (GAC). In the current study the consensus list was used to analyze notes at an academic GAC July to December 2016. Presence or absence of each condition and discrepancy between note content and PL entry was analyzed.

Results:

23 patients were seen in the academic GAC from July through December 2016 and their electronic health records were reviewed. Most common conditions mentioned in provider note were cognitive impairment (19/23) and adverse drug effect (19/23). Fall risk and cognitive impairment were recorded in the in PL most often (7/23 and 16/23 respectively). Most of the time when fall risk was listed in the note, it was also in the PL (16/19). 46 health records were reviewed in the pilot study at a VA medical center. Cognitive impairment was found in 42 notes but only in 27 PLs. Dependence on a caregiver and noncompliance with treatment were found in 28 and 26 notes but 0 and 1 of the PLs.

Conclusion:

Conditions other than cognitive impairment were generally missing from PLs. Health records that do not communicate cognition and function may portray a robust perception of the “virtual patient”, with potential adverse consequences. Using these results we will develop tools that make PLs more reflective of geriatric patient’s health status.
Perceptions of Older Adults and Their Family Members on Driving Alternatives: A Comparative Analysis

D Malis; C Coffey; A Koptelova; D Hayley.

University of Kansas School of Medicine, Kansas City, KS

Background: Despite more health problems, many older adults continue to drive—in part due to perceived lack of acceptable transit alternatives. Older adults in cities rely on private vehicles 90% of the time even when other options may be available (Glasgow 2000). Many older adults rely on friends and family despite a growing popularity for alternatives such as “ride-sharing” or “ride-hailing” services. We sought to assess differences in perceptions of driving alternatives between older adults and families and to determine how comfortable each are in coordinating transportation via technology.

Methods: Dyads of older adult drivers and an adult family member were recruited from Geriatrics clinics for focus groups. Each set completed a questionnaire including demographic data, current driving status, knowledge of transportation options available and willingness to use technology for transportation assistance. Older adults and their family were divided into 2 groups where parallel semi-structured questions were asked regarding driving perceptions. The responses were recorded, transcribed and analyzed using coding searching for thematic findings, quantified and correlated between groups.

Results: Two focus groups of 4 dyads were recruited. All older adults reported driving more than 30 miles/week but 3 of 4 family members reported they drove less than 10 miles/week. Both groups had 3 of 4 respondents list transportation alternatives; however, none of the respondents felt comfortable coordinating transportation with technology. Major themes from focus group discussions describing the older adult’s driving included: safety, health related problems and emotions including fear and stress. When asked about use of technology-assisted driving applications, family responses were more negative (16) than positive (12) as opposed to older adults’ which were less negative 4 and 7 respectively.

Conclusions: We found important differences between older adults and their family regarding current driving, concerns about driving habits, views of alternatives available and comfort using technology. We found neither older drivers nor their family were comfortable using other forms of transportation such as public transportation, or taxis. Similarly, there was a paucity of interest in using technology to coordinate transportation. In addition, neither group was confident they had the skills to use the technology.
Outcomes in Polycystic Kidney Disease
Composite endpoints in ADPKD studies: A guide for best practices

Reem Mustafa, M.D., Ph.D., MPH, David Baron, Ph.D., Frank Czerwiec, M.D., Ph.D., Alan Yu, M.B, B.Chir. Ronald Perrone, M.D. for the Polycystic Kidney Disease Outcome Consortium (PKDOC) composite outcomes subcommittee

**Introduction:** There is considerable inconsistency in the outcomes reported in Autosomal Dominate Polycystic Kidney Disease (ADPKD) and how they are measured. In this article, we aim to highlight the appropriateness of different outcomes to be included as a component in a composite outcome.

**Methods:** We developed guidance including a summary table for components of the composite end points in ADPKD. We utilized the results of a systematic review and discussions among the PKDOC composite endpoint subcommittee. The subcommittee consists of Scientists, clinicians, methodologists, manufacturers, patients, advocacy groups representatives, and critical path institute representatives, all with experience in ADPKD. The investigators assessed the face validity of the suggested guidance and used an iterative approach of feedback, revision, and testing.

**Results:** Table 1 summarizes outcomes that are reported in ADPKD studies and the different ways they can be measured. It also explores pros and cons for including them as part of a composite outcome for ADPKD studies.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Feasibility of collecting data</th>
<th>Event frequency</th>
<th>Acceptability to regulators</th>
<th>Previous body of evidence in a clinical area</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Yes</td>
<td>rare</td>
<td>Yes</td>
<td>Commonly reported as a component of a composite</td>
<td>- Likely more appropriate to use overall mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Disease specific mortality requires clear definitions.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Death rate will depend on baseline risk of mortality in the population of interest, which is low in ADPKD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Should be considered but may not apply in all cases (e.g. children).</td>
</tr>
<tr>
<td>ESRD including preemptive transplant</td>
<td>Yes</td>
<td>Varies depending on genotype, rate of progression and</td>
<td>Yes</td>
<td>Commonly reported as a component of a composite</td>
<td>- Enrichment strategies are useful to increase the event rate of the outcome.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Clear definitions of ESRD are necessary.</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Feasibility of collecting data</td>
<td>Event frequency</td>
<td>Acceptability to regulators</td>
<td>Previous body of evidence in a clinical area</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------------------------------</td>
<td>------------------------------------------------------</td>
<td>----------------------------</td>
<td>----------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>Yes</td>
<td>Varies; Can be affected by patients’ history</td>
<td>Yes</td>
<td>Reported as an outcome but not often part of a composite</td>
<td>Hospitalization due to disease specific Interventions or complications should be very clearly defined and adjudicated.</td>
</tr>
</tbody>
</table>
| Worsening kidney function        | Yes                            | Varies/ frequent                                     | Yes                        | Commonly reported as a component of a composite | -Reported using different measures (e.g. doubling of serum Cr, 50% reduction in eGFR, reduction of eGFR beyond a certain threshold)  
-Important to note that the pattern of treatment effects on GFR must be examined, specifically acute effects on eGFR  
-Need to be aware of hyperfiltration as a potential confounder to the results of kidney function                                                                                                                                 |
| Hypertension                     | Complicated if agent affects BP and by concomitant anti-hypertensive use | frequent                                             | Accepted surrogate          | Reported as an outcome but not often part of a composite | -could be unreliable unless very clearly defined.  
-Reported using different measures (e.g. SBP, DBP, worsening hypertension as defined by “intensified therapy”)  
- It is important to include the actual BP value                                                                                                                                                        |
<p>| Chronic or acute pain / Medication | ? lack of reliable and responsive tools to assess pain and identify | Varies/ frequent                                      | ?                          | Reported as an outcome but not part of a composite | -Reported using different measures (e.g. significant kidney pain necessitating medical leave, pharmacologic treatment or pharmacologic treatment or medication) |</p>
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Feasibility of collecting data</th>
<th>Event frequency</th>
<th>Acceptability to regulators</th>
<th>Previous body of evidence in a clinical area</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Kidney Volume</td>
<td>Varies/ requires CT or MRI</td>
<td>Varies</td>
<td>Varies</td>
<td>Reported as an outcome but not part of a composite</td>
<td>- Challenging to distinguish Kidney pain - Earlier biomarker than worsening kidney function - Usually reported as % change of TKV over different periods</td>
</tr>
<tr>
<td>Activities of Daily Living/Quality of life</td>
<td>Yes/ requires validated tools</td>
<td>Varies</td>
<td>Yes when using validated tools</td>
<td>Reported as an outcome but not part of a composite</td>
<td>- Many different ADLs could be measured using validated tools. - There are also “accepted” patient reported outcome measures that should be considered</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Varies/ Complicated by concomitant medication use and variability in ways to measure it</td>
<td>Varies</td>
<td>No</td>
<td>Inconsistent reporting</td>
<td>- Not a common feature of ADPKD - Reported using different measures (e.g. Urine protein/Creatinine ratio, time to the doubling of the baseline urine protein-to-creatinine</td>
</tr>
<tr>
<td>Radiological appearance of the kidney</td>
<td>No</td>
<td>Varies</td>
<td>No</td>
<td>Not often reported and is not part of a composite</td>
<td>- Technology not mature and validated. “Textural analysis.”</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Feasibility of collecting data</td>
<td>Event frequency</td>
<td>Acceptability to regulators</td>
<td>Previous body of evidence in a clinical area</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------------</td>
<td>-----------------</td>
<td>-----------------------------</td>
<td>---------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Girth                          | Yes/ requires validated tools  | Varies          | Yes when using validated tools | Not often reported and is not part of a composite | - Could be well measured with a PRO  
- Multiple factors affect Girth including liver size.  
- Organ enlargement is only a measure of late disease  
- May be considered cosmetic |
| Kidney stones and Kidney infections | Yes                           | Varies but relatively infrequent | Yes (clinically meaningful) | Not often reported and is not part of a composite | - Infrequent and may not be a good component in a composite |
| Cardiovascular outcomes        | Yes                           | Varies depending on comorbidities but relatively infrequent | Yes                          | Not often reported and is not part of a composite | - Unlikely to occur in early ADPKD disease  
- May be considered a safety endpoint depending on the agent being investigated |

**Conclusion:** Composite end points will continue to be used in ADPKD studies and may be more utilized in light of new approved treatments. Understanding the unique considerations about the different components and their use in ADPKD studies is essential in developing high quality evidence that will appropriately assess the short and long term effects of different interventions.
EMPOWER PKD—A patient engagement effort setting priorities

Reem Mustafa, MD, PhD, MPH, Mohamad A Kalot, MD, Mohammed Al Khatib, MD, Nedaa Husainat, MD, Kim Kimminau, PhD, Crystal Lumpkins, PhD, Alan Yu, MD

Introduction

Polycystic kidney disease (PKD) is a rare genetic disease that causes permanent worsening kidney function. PKD is the most common genetic cause of chronic kidney disease. We engaged with PKD patients and families to “Establishing Meaningful Patient-centered Outcomes With Relevance for patients with PKD” (EMPOWER PKD). The first phase of this initiative focused on identifying the most important health outcomes, discussing insurability issues, and exploring patients’ activation and engagement.

Methods

We utilized semi-structured focus groups with a pre-piloted guide which allowed for conversational flow and consistency. We have conducted seven focus groups with patients and caregivers, and one with clinicians. During each group, participants identified important outcomes and used a nominal, multi-voting technique to prioritize them. We conducted a qualitative thematic analysis using grounded theory.

Results

Seventy six patients and caregiver and 8 clinicians and researchers participated in the focus groups. Of these, 59 (78%) reported having PKD, and 11 (15%) reported being caregivers. The mean age was 53.3 years (range 19-80 years). The participants included 84% white, 7% African American, 5% Latino, and 59% were female.

Seven focus groups yielded 425 votes and 38 important outcomes that can be classified into six categories: kidney health, lifestyle, comorbidities, psychological impact, family and awareness, and mortality. The outcomes that were most valued include slowing the progression/symptoms of the disease and keeping kidneys healthy, and diet modifications. Patients where less concerned about mortality than they were about their kidney health.

We summarized discussion regarding the impact PKD has on patients and families using the following domains: issues affecting decision-making, daily living impact, psychological impact, testing dilemmas, misconceptions, healthcare related issues, insurability, and activation/engagement. While the psychological impact of PKD was not ranked as the most important outcome to be tested in studies using the multi-voting technique, it has emerged as a leading theme during the qualitative analysis.

Conclusions

It is important to be aware that patients’ views and values have pivotal effects on care especially now that a treatment has been approved. While early diagnosis and detection is usually important, “labelling” someone with PKD hinders patients’ participation in care and research.
Analyzing the effect of Notch inhibition on the progression of Polycystic Kidney Disease

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Departments of Internal Medicine1, Department of surgery2 and Biochemistry and Molecular Biology2, The Jared Grantham Kidney Institute, University of Kansas Medical Center

Introduction: Signaling pathways activated by loss of function mutation in polycystic kidney disease (PKD) constitute important targets of therapy for PKD. We have recently shown an activation of the Notch3 pathway in PKD. The expression of Notch3 correlated with cell proliferation in the renal cystic epithelium.

Methods: To determine the in vivo effect of Notch inhibition in PKD, we selected two repurposed drugs Quinomycin A (Quin) and Ciclopirox-olamine (CPX) both of which have been shown recently to inhibit the Notch pathway and ameliorate progression of cancer. First, we tested the in vitro efficacy of these drugs. We then intraperitoneally injected CPX (10mg/kg body weight), or vehicle, in 21 day old mice. Quin (10 mg/kg body weight) was injected similarly.
Studies consisted of 6 male and 6 female mice in each of the four groups: WT-vehicle, WT-drug, PKD1RC/RC/PKD2+/−- vehicle and PKD1RC/RC/PKD2+/−- drug. Mice were euthanized after 27 days of treatment. Kidneys and blood were harvested for further studies.

Results: A concentration of 0.2 mM CPX was found safe for ADPKD cells in culture. CPX was able to reduce the size of ADPKD cysts grown in 3D collagen gels. Treatment of PKD mice with CPX or Quin for 27 days both resulted in a significant reduction in PKD progression. Normal mice were not affected by either of these drugs. Histological analysis revealed a significant decrease in the percent cystic index. Blood urea nitrogen levels showed a decreasing trend with CPX and Quin treatment. Both treatments were associated with decreased cell proliferation of the cyst lining epithelial cells.

Conclusions: Both CPX and Quin have been shown to target Notch signaling. Further studies will be required to determine the exact mechanisms by which they confer protection in PKD. Nevertheless Ciclopirox-olamine and Quinomycin A may constitute alternate drugs of choice for PKD in the clinic.
Differential pathogenic roles of Notch4 and Notch3 in the progression of HIV associated Nephropathy.

Jessica Idowu¹, Trisha Home¹, Sireesha Yerrathota¹, Timothy Fields² and Madhulika Sharma¹.

Department of Internal medicine (Nephrology)¹ and Department of Pathology², Kansas University Medical Center, KS, 66160

Background: Notch pathway activation plays a central role in pathogenesis of many glomerular diseases. We have previously shown that Notch4 and Notch3 were up-regulated in various renal cells in HIVAN patients and rodent models of HIVAN. Notch inhibition by gamma secretase inhibitors ameliorated disease progression in Tg26 mouse model of HIVAN. Since, gamma secretase inhibitors are associated with toxicity in clinics, here we explore the individual effects of Notch4 and Notch3 inhibition on HIVAN pathogenesis.

Methods: Tg26 mice were bred with mice deleted for intracellular domain of Notch4 and Notch3 separately to generate Tg26 mice with Notch4 deletion (Tg26/N4del) and Notch3 deletion (Tg26/N3 null) respectively. The effect of Notch4 and Notch3 deletion in Tg26 mice was determined by analyzing renal function, histology, cell proliferation/podocyte differentiation and inflammatory markers.

Results: Deletion of both Notch4 and Notch3 in Tg26 mice separately, significantly decreased the mortality rate and reduced kidney injury in Tg26 mice. While, Notch4 deletion in male Tg26 mice reduced kidney injury, controlled cell proliferation, cell differentiation and inflammatory response of NF kappa B positive cells in Tg26 mice, it was not enough to significantly reduce proteinuria and blood urea nitrogen levels. In contrast Notch3 deletion appeared to be effective in controlling proteinuria and blood urea nitrogen levels in Tg26 mice. In addition, histological studies indicated a significant improvement in glomerulosclerosis, tubulo-interstitial fibrosis and inflammatory response in Notch3 deleted Tg26 mice. More studies are required to reveal subtle roles of Notch4 and Notch3 activation in HIVAN.

Conclusion: Our study supports a non-redundant role of Notch4 and Notch3 in HIVAN pathogenesis and suggests therapeutic implication of Notch3 and Notch4 inhibition in HIV associated nephropathy.
EUS vs ERCP as primary modalities for palliation of malignant biliary obstruction: A systematic review and meta-analysis

Venkat Nutalapati, Sravan Jeepalyam, Madhav Desai, Ajay Bansal, Mojtaba Olyaei, Amit Rastogi

Background:
ERCP and biliary stenting has been used for palliation of malignant biliary obstruction. Endoscopic ultrasound-guided biliary drainage (EUS-BD) can help in biliary decompression when ERCP fails. Whether EUS can be used as the primary methods for biliary decompression instead of ERCP in malignant biliary obstruction (MBO) in unclear.

Aim: We performed a systematic review and meta-analysis comparing ERCP versus EUS for the primary management of MBO.

Methods:
A comprehensive search of MEDLINE, EMBASE, Scopus, Cochrane Database was conducted from each database’s inception (2000-2018) to search for comparative studies of ERCP versus EUS in the primary decompression of malignant biliary obstruction, excluding studies that did not have comparative arms, different outcomes, different clinical entities. The primary outcome of interest was technical success, which was defined as the placement of the metal stent across the stricture site via the papilla (ERCP) or across the stomach or the duodenum (EUS-BD), along with the flow of the contrast medium and/or bile through the stent. Other studied outcomes were clinical success rate at 2 and 4 weeks, rate of pancreatitis and overall adverse events (AEs) post procedure. Outcomes, were reported as pooled odds ratio (OR) with 95% confidence intervals (CI) with statistical significance (p <0.05) using random effects.

Results:
Five studies including three randomized controlled trials and two retrospective studies with a total of 538 patients were included, 303 patients in the ERCP arm vs 235 in the EUS arm. How many patients in each arm. There was no difference between ERCP and EUS in technical success (OR 0.80, 95% CI 0.25-2.52, P=0.70). There was significant heterogeneity (I²=80%). Similarly, there was no difference among ERCP and EUS regarding clinical success at 2 (OR, 1.05; 95% CI, 0.55-2.00; P = 0.88), or at 4 weeks (OR, 1.41; 95% CI, 0.24-8.24; P = 0.70). However, EUS performed better than ERCP regarding rates post procedure pancreatitis (OR, 6.46; 95% CI, 1.44-28.84 P = 0.01). There was no difference in overall adverse events – OR, 1.06; 95% CI, 0.50-2.22; p = 0.88). See figures 1 and 2.

Conclusion:
This meta-analysis shows that EUS-BD is comparable to ERCP as the primary modality for successful palliation of MBO. Given the similar technical and clinical success rates, and lower risk of post procedure AEs including post procedure pancreatitis, EUS may become a viable and attractive alternative to ERCP for the palliation of MBO.
Forest Plots

**Figure 1: Technical Success and Clinical Success**

### Pancreatitis Rate

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ERCP Events</th>
<th>Total Events</th>
<th>EUS Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bang JY 2018</td>
<td>31</td>
<td>32</td>
<td>33</td>
<td>33</td>
<td>7.6%</td>
<td>0.32 [0.03, 3.27]</td>
</tr>
<tr>
<td>Dhir Y 2014</td>
<td>95</td>
<td>93</td>
<td>104</td>
<td>104</td>
<td>43.5%</td>
<td>1.25 [0.48, 3.15]</td>
</tr>
<tr>
<td>Harrada T 2017</td>
<td>52</td>
<td>54</td>
<td>61</td>
<td>64</td>
<td>43.6%</td>
<td>1.07 [0.40, 2.84]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>199</td>
<td>201</td>
<td>289</td>
<td>221</td>
<td>100.0%</td>
<td>0.46 [1.44, 26.84]</td>
</tr>
</tbody>
</table>

Total events 178, 179
Heterogeneity: Tau² = 0.00, Chi² = 1.13, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.44 (P = 0.01)

### Overall Adverse Rates

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ERCP Events</th>
<th>Total Events</th>
<th>EUS Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bang JY 2018</td>
<td>32</td>
<td>30</td>
<td>33</td>
<td>33</td>
<td>18.0%</td>
<td>1.60 [0.25, 10.25]</td>
</tr>
<tr>
<td>Dhir Y 2014</td>
<td>98</td>
<td>97</td>
<td>104</td>
<td>104</td>
<td>43.5%</td>
<td>1.18 [0.38, 3.63]</td>
</tr>
<tr>
<td>Park WH 2018</td>
<td>55</td>
<td>60</td>
<td>61</td>
<td>64</td>
<td>31.8%</td>
<td>0.81 [0.16, 2.28]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>214</td>
<td>216</td>
<td>289</td>
<td>221</td>
<td>100.0%</td>
<td>1.06 [0.50, 2.22]</td>
</tr>
</tbody>
</table>

Total events 199, 200
Heterogeneity: Tau² = 0.00, Chi² = 1.20, df = 3 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.36)
IMPACT OF FEEDBACK ON ADENOMA DETECTION RATE: A SYTEMATIC REVIEW AND META-ANALYSIS

Venkat Nutalapati, Sravan Jeepalyam, Madhav Desai, Ajay Bansal, Mojtaba Olyaee, Amit Rastogi

Background
Adenoma detection rate (ADR) is one of the most important quality indicators of colonoscopy. Benchmarks for ADR have been established - > 30% in males and >20% in females undergoing screening colonoscopy. Factors affecting ADR include quality of bowel prep, withdrawal times, inspection technique, distal attachment devices and educational interventions and training. Monitoring ADR and providing feedback to the endoscopist has also been shown to positively impact the ADR of endoscopist.

Aim: We performed a meta-analysis to determine the effect of feedback (report cards, quality improvement project, score cards) on ADR and polyp detection rate (PDR).

Methods
A comprehensive search of MEDLINE, EMBASE, Scopus, Cochrane Database was conducted from each database’s inception to search for comparative studies that employed feedback (in the form of score cards, report cards, quality improvement projects) vs no-feedback (control group) to same group of endoscopists being followed post feedback. The primary outcome of interest was ADR before and after feedback among same group of endoscopists. Other studied outcomes were PDR. Outcomes were reported as pooled odds ratio (OR) with 95% confidence intervals (CI) with statistical significance (p <0.05). RevMan 5.3 software was used for statistical analysis.

Results
A total of 9 studies were included for analysis, with a total of 64875 subjects. Mean age 59.4 years (reported in 7 studies), with 50.4% males. There were 43052 in the feedback group versus 19184 in the control group. Feedback was provided by means of quality training in 2 studies, 3- or 4-month report cards in 5 studies, yearly report card in 2 studies.

ADR percentage was 33.5% in the feedback group and 28.1% in the control group. ADR was significantly higher in the feedback group, pooled OR = 1.40; 95% CI 1.24-1.58; (p<0.01). Substantial heterogeneity was noted in included studies (I²=86%). Feedback also improved the PDR with a pooled OR = 1.47; 95% CI 1.29-1.68; with heterogeneity of (I²=82%).

Conclusion
Monitoring the ADR and providing feedback to the endoscopist in any form leads to improvement in ADR and PDR. This represents an easy and effective way of improving the ADR of endoscopists especially those whose are not achieving the recommended benchmarks.
### Forest Plot

#### PDR

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Feedback Events</th>
<th>Total Events</th>
<th>No feedback Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdur-Razi 2015</td>
<td>8368</td>
<td>14859</td>
<td>1284</td>
<td>2627</td>
<td>25.7%</td>
<td>1.34 [1.13, 1.58]</td>
<td></td>
</tr>
<tr>
<td>Gurudu 2018</td>
<td>634</td>
<td>1057</td>
<td>266</td>
<td>555</td>
<td>18.3%</td>
<td>1.63 [1.32, 2.00]</td>
<td></td>
</tr>
<tr>
<td>Sey 2017</td>
<td>421</td>
<td>813</td>
<td>510</td>
<td>1133</td>
<td>20.0%</td>
<td>1.31 [1.10, 1.57]</td>
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<td>Wallace 2015</td>
<td>5290</td>
<td>8673</td>
<td>3665</td>
<td>7480</td>
<td>31.4%</td>
<td>1.63 [1.53, 1.73]</td>
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<tr>
<td>Total (95% CI)</td>
<td>25442</td>
<td>11795</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>1.47 [1.29, 1.68]</td>
<td></td>
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<tr>
<td>Total events</td>
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<td>5725</td>
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Heterogeneity: $\tau^2 = 0.01; \chi^2 = 16.25, df = 3 (p = 0.001); I^2 = 82%$

Test for overall effect: $Z = 5.77 (p < 0.00001)$

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#### ADR

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<th>Study or Subgroup</th>
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<th>Total Events</th>
<th>No feedback Events</th>
<th>Total Events</th>
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<th>Odds Ratio M-H, Random, 95% CI</th>
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<td>232</td>
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<td>258</td>
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<td>684</td>
<td>2444</td>
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<td>1.64 [1.47, 1.84]</td>
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<td>13157</td>
<td>698</td>
<td>4353</td>
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<td>Sey 2017</td>
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<td>7480</td>
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Heterogeneity: $\tau^2 = 0.02; \chi^2 = 50.40, df = 7 (p < 0.00001); I^2 = 96%$

Test for overall effect: $Z = 5.38 (p < 0.00001)$
Cryptococcal meningitis is a cause for cross-reactivity in cerebrospinal fluid assays for anti-Histoplasma, anti-Coccidioides, and anti-Blastomyces antibodies.

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² Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA
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⁵ Division of Infectious Diseases, Department of Medicine, Indiana University, Indianapolis, IN, USA
⁶ Division of Infectious Disease, Department of Medicine Johns Hopkins, Baltimore, MA
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⁸ Division of Infectious Disease and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN, USA

Abstract
Background/Objectives: Antibody detection is commonly used for diagnosis of histoplasmosis, cross-reactions have been recognized due to endemic mycoses but not cryptococcosis. We observed cross-reactions in an anti-Histoplasma antibody enzyme immunoassay (EIA) in the cerebrospinal fluid (CSF) from a patient with cryptococcal meningitis and sought to assess the risk for cross-reactive anti-Histoplasma antibodies in persons with cryptococcal meningitis.

Methods: An anti-cryptococcal antibody EIA was developed to measure CSF antibody response in HIV-infected subjects from Kampala, Uganda and previously healthy, HIV-negative subjects at the National Institutes of Health (NIH) with cryptococcal meningitis. Specimens were tested for cross reactivity in assays for IgG anti-Histoplasma, anti-Blastomyces, and anti-Coccidioides antibodies.

Results: Among 61 subjects with cryptococcal meningitis (44 Kampala cohort, 17 NIH cohort), elevated CSF anti-cryptococcal antibody levels existed in 38% (23/61). Of the 23 CSF specimens containing elevated anti-cryptococcal antibodies, falsely positive results were detected in antibody EIAs for histoplasmosis (8/23, 35%), coccidioidomycosis (6/23, 26%), and blastomycosis (1/23, 4%). Overall, 2% (2/81) of control CSF specimens had elevated anti-cryptococcal antibody detected, both from Indiana.

Conclusions: Cryptococcal meningitis may cause false-positive results in the CSF for antibodies against Histoplasma, Blastomyces and Coccidioides. Fungal antigen testing should be performed to aid in differentiating true and false positive antibody results in the CSF.

Funding: This study was supported, in part, by the Intramural Research Program of the National Institute of Allergy and Infectious Diseases, National Institutes of Health (AI001123, AI001124) as well as extramural grants from the National Institute of Allergy and Infectious Diseases (T32AI055433, U01AI089244, UO1AI109657, RO1 AI059681, and RO1AI127704).
Delta-like 1 protein, vitamin D binding protein, and fetuin for detection of *Mycobacterium tuberculosis* meningitis

Nathan C Bahr MD, MA¹,²,³, Ryan Halupnick¹, Grace Linder¹, Reuben Kiggundu MBChB², Henry W Nabeta MBChB², Darlisha A Williams MPH¹,², Abdu K Musubire MMed², Bozena M Morawski PhD, MPH⁴, Srinand Sreevatsan PhD, MVSc, MPH⁴, David B Meya MMed, PhD¹,², Joshua Rhein MD¹,², David R Boulware MD, MPH¹

**Affiliations:**
1 Division of Infectious Diseases and International Medicine, Department of Medicine, University of Minnesota, Minneapolis, MN, USA
2 Infectious Diseases Institute, Makerere University, Kampala, Uganda
3 Division of Infectious Diseases, Department of Medicine, University of Kansas, Kansas City, KS, USA.
4 College of Veterinary Medicine, University of Minnesota, Minneapolis, MN, USA

**Abstract:**
**Background:** Tuberculosis meningitis (TBM) diagnosis is difficult, new biomarkers are needed. We evaluated the diagnostic utility of delta-like 1 protein (DLL1), vitamin D binding protein (VDBP), and fetuin.

**Methods:** Biomarker concentrations were measured by ELISA in cryopreserved cerebrospinal fluid from 139 HIV-infected Ugandans with suspected meningitis. TBM was diagnosed by GeneXpert MTB/Rif or culture. Cohort diagnoses included TBM (n=22), cryptococcal (n=71), or aseptic meningitis (n=16), and no meningitis (n=30).

**Results:** DLL1 (cutoff value 1150 pg/mL) provided 32% sensitivity and 98% specificity. Adding fetuin, cryptococcal antigen, and interferon gamma resulted in sensitivities of 36%, 63%, and 76% with specificities of 98%, 90%, and 92%, respectively. VDBP (cutoff value 2.0 μg/mL) provided 81% sensitivity and 68% specificity while fetuin (cutoff value 2 μg/mL) provided a sensitivity of 86% and specificity of 68%.

**Conclusions:** CSF DLL1, VDBP, and fetuin exhibited fair diagnostic performance for TBM diagnosis.

**Funding:** This research was made possible through support from the Fogarty International Center (R25TW009345), the National Institute of Neurologic Diseases and Stroke (R01NS086312) and the National Institute of Allergy and Infectious Diseases (U01AI089244).
Title: Endothelial HIF-1 mediates protection from acute kidney injury in the context of endothelial PHD2 loss

Ratnakar Tiwari, Ganeshkumar Rajendran, Michael P. Schonfeld, Rafael Torosyan, Timothy Fields and Pinelopi P. Kapitsinou

Background: Prolyl-hydroxylases (PHDs) have emerged as safeguards of cellular metabolism by virtue of their oxygen sensing function, which enables them to regulate the activity of hypoxia-inducible factors (HIF). We previously reported that loss of endothelial PHD2 protected from renal ischemia reperfusion injury (IRI) but the molecular mechanisms remain undefined. Here, we investigated the contribution of HIF in renoprotection induced by endothelial PHD2 loss and examined the impact of HIF-activation in endothelial cell (EC) metabolism.

Methods: Endothelial cell specific HIF activation was achieved by crossing Vecadherin (Cdh5)-Cre transgenics to Phd2 floxed mice (ePHD2), while the contribution of each HIF isoform was assessed by generating double mutants lacking PHD2 and HIF-2 (ePHD2HIF2) or PHD2 and HIF-1 (PHD2HIF1). IRI was induced by unilateral renal artery clamping. Functional metabolic analysis in ECs was performed by a Seahorse Extracellular Flux Analyzer.

Results: Deletion of HIF-1 in endothelial PHD2 deficient background completely reversed the renoprotection conferred by endothelial PHD2 loss as indicated by histological injury scores and Kim1 mRNA levels in kidney homogenates (Day 3 post IRI, n=8 mice). In contrast, double ePHD2HIF2 mutants had attenuated kidney injury with ~1.7 fold down-regulation in Kim1 transcript levels compared to controls. Ly6B.2 staining showed comparable inflammatory cell infiltration in ePHD2HIF1 injured kidneys with Cre-, while ePHD2HIF2 kidneys had significantly less Ly6B.2^+ve area than their corresponding controls. Metabolomic analysis of ECs exposed to PHD inhibitor revealed significant increase in glycolytic metabolites with simultaneous reduction in TCA cycle metabolites suggesting that HIF activation led to glycolytic shift and suppression of mitochondrial metabolism, which was validated by bioenergetic measurements. On the other hand, preconditioning of ECs with PHD inhibitor reversed the defects in mitochondrial metabolism triggered by hypoxia-reoxygenation.

Conclusions: Our data establish that HIF-1 but not HIF-2 is required in endothelial PHD-2 mediated renoprotection. Furthermore, our studies show that the PHD/HIF axis regulates EC metabolism with potential critical consequences in response to ischemic injury.
The D2d Study: Will Vitamin D slow the progression from Prediabetes to Diabetes?

David C. Robbins MD, Erica Lower CSC for the D2D Study

OBJECTIVE

Observational studies suggest that vitamin D may lower the risk of type 2 diabetes. However, data from long-term trials are lacking. The Vitamin D and Type 2 Diabetes (D2d) study is a randomized clinical trial designed to examine whether a causal relationship exists between vitamin D supplementation and the development of diabetes in people at high risk for type 2 diabetes.

RESEARCH DESIGN AND METHODS

D2d was designed with support from a U34 planning grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The final protocol was approved by the D2d Research Group, the data and safety monitoring board, and NIDDK. Key eligibility criteria are age ≥30 years, BMI of 24 (22.5 for Asian Americans) to 42 kg/m\(^2\), increased risk for diabetes (defined as meeting two of three glycemic criteria for prediabetes established by the American Diabetes Association [fasting glucose 100–125 mg/dL (5.5–6.9 mmol/L), 2-h postload glucose after 75-g glucose load 140–199 mg/dL (7.7–11.0 mmol/L), hemoglobin A\(_1c\) 5.7–6.4% (39–46 mmol/mol)]), and no hyperparathyroidism, nephrolithiasis, or hypercalcemia. D2d participants are randomized to once-daily vitamin D\(_3\) (cholecalciferol 4,000 IU) or placebo and followed for an average of 3 years. The primary end point is time to incident diabetes as assessed by laboratory criteria during the study or by adjudication if diagnosed outside of D2d. Recruitment was initiated at the end of 2013.

2423 individuals with prediabetes were evenly randomized to take placebo or 4000 IU of vitamin D daily. The average age of the participant at entry was 59.4±9.9y, 44.8% of whom were women, 43.7% were nonwhite, and BMI was 32.1±4.5. Mean vitamin D level at entry was 28.5 (10.4) ng/mL. Entry mean HgbA1c was 5.9±0.2% and the fasting and 2 hr glucose was 108±7 and 137±34, respectively. Using an intention to treat analysis, data from 100% of the volunteers will be analyzed. 124 of the participants were enrolled at the KU site. Overall participant retention/5y was in excess of 95%. There were no serious adverse events related to the study medication. Data collection was closed in Fall of 2018. Data cleaning and analysis are underway, and final results will be embargoed until June 7, 2019. D2d will present its findings to the American Diabetes Association Scientific Convention in a 1-hour plenary session.

CONCLUSIONS

D2d tested whether vitamin D supplementation is safe and effective at lowering the risk of progression to diabetes in people at high risk for type 2 diabetes. The study reached its recruitment goals, had very high retention and the recommended daily dose of vitamin D appeared to be safe.
Dual Hit of HIV-1 and Opioids Promote Oxidative Stress mediated Pulmonary Endothelial Dysfunction

H Sharma, S Agarwal, L Chen, J Allen, N.K Dhillon

Introduction: HIV-related pulmonary hypertension is one of the serious non-infectious cardiovascular complications in HIV-infected individuals, especially among intravenous drug users (IVDUs). We previously demonstrated that opioids in combination with viral protein(s) result in the reactive oxygen species (ROS) mediated induction of autophagy in pulmonary endothelial cells leading to shift in the cells from apoptosis to apoptosis-resistant proliferative status associated with the angio-proliferative remodeling observed in PAH. Here, we now delineate the major sources of HIV-1 and morphine induced oxidative burst and their role in the development of PAH using in-vivo model.

Methods: HPMECs were treated with morphine and HIV-Tat (M+T) in the presence or absence of ROS scavengers followed by measurement of ROS. Mitochondrial specific superoxide radicals were measured using MitoSOX dye and the ratio of mitochondrial DNA to nuclear DNA was determined by qRT-PCR. To assess the in-vivo effect of HIV-1 and morphine on pulmonary vascular dysfunction, male HIV-Tg/WT Fischer rats (n=7-13 per group) were administered 10 mg/kg bodywt. Morphine/saline daily IP for 21 days. Right ventricle systolic pressure (RVSP) and Fulton Index (RV/LV+Septum ratio) were measured along with immunohistochemical analysis of lungs.

Result: Increased oxidative stress in HPMECs in response to combined treatment of morphine and tat (M+T) was contributed by mitochondria, NADPH oxidase as well as xanthine oxidase. Decrease in ROS production of M+T treated cells on pre-treatment with specific ROS scavenger viz., Mitotempo (mitochondria), VAS3947 (NADPH oxidase) and allopurinol (Xanthine oxidase) was observed. However, M+T mediated early apoptosis and late hyper-proliferation of HPMECs was prevented only in presence of NADPH oxidase inhibitor. Parallely, we also observed elevated mitochondrial specific ROS at 2hr and increased mitophagy at 3h followed by increase in total mitochondrial mass after 4-6h of MT treatment. Further, we observed significant increase in RVSP and RV hypertrophy in HIV-Tg rats exposed to morphine compared to WT-saline rats. In addition, immuno-histochemical analysis showed significant pulmonary vascular remodelling including endothelial proliferation in the lung-sections from HIV+morphine rats.

Conclusion: Our findings suggest NADPH oxidase specific ROS role in autophagy-dependent increased proliferation of morphine and Tat treated HPMECs. Further our in-vivo findings provide evidence of potentiation of PAH development with the dual hit HIV-1 and opioids.
Sugen-Morphine (SuMo) Rat Model for Pulmonary Arterial Hypertension

Stuti Agarwal, Zachery Harter, Ling Chen, Julie Allen, Tyler Nguyen, Navneet Dhillon
University of Kansas Medical Center, Kansas City, KS/USA

Rationale: Pulmonary arterial hypertension (PAH) is a deadly disease typically associated with pulmonary vascular remodeling and right ventricle failure. The most prevalent animal model available for PAH is Sugen/hypoxia in which Sugen, a VEGFR antagonist primarily causes initiation of endothelial injury and later proliferation of apoptosis-resistant endothelial cells (ECs). This is one of the characteristic attributes of severe pulmonary hypertension leading to formation of angio-obliterative lesions and development of exaggerated PAH. Previously, we have reported that multiple-hit of morphine with HIV-infection accentuates pulmonary vascular remodeling characterized by formation of neo-intimal fibrotic/plexiform lesions in SIV-infected rhesus macaques. In addition, we have shown that chronic exposure to morphine and HIV-protein causes initial endothelial apoptosis followed by proliferation in primary HPMVECs that corresponded with initial inactivation and later increase in total VEGFR/VEGFR phosphorylation. Therefore, we hypothesize that Sugen with second hit of morphine can act as a better strategy to induce severe PAH in rats which may serve as an alternative animal model of PAH.

Methods: Male Sprague-Dawley rats (n=7-10/group) were subcutaneously administered 20mg/kg Sugen5416 once and morphine (10mg/kg) intraperitoneally daily for 35 days (SuMo group) or Sugen alone or morphine alone group. Right ventricle (RV) hemodynamic measurements and RV hypertrophy were assessed. Immunohistochemistry (IHC) was performed to analyze vascular remodeling using von Willebrand factor (vWF), smooth muscle actin (SMA) and Ki67 (cell proliferation marker) antibodies.

Results: Mean pulmonary arterial pressure (mPAP) and right ventricle systolic pressure (RVSP) was found significantly higher in rats from Sugen-morphine group when compared to Sugen or morphine alone rats. The Fulton Index (RV/LV+Septum ratio) was also higher in Sugen-Morphine group and positively correlated with RVSP. Immuno-histochemical analysis of lung-sections from SuMo group showed significant pulmonary vascular remodeling including medial and neo-intimal hypertrophy mainly in large vessels, obliteration of vessels due to endothelial proliferation, particularly in small vessels of size <50μm and formation of plexiform lesions, characteristic of PAH. The endothelial cells in the remodeled vessels also demonstrated high expression of Ki67.

Conclusion: Our findings support dual hit of Sugen and morphine as a potential optional strategy to induce significant pulmonary vascular remodeling and development of severe PAH pathology in rats similar to existing models of PAH like Sugen/hypoxia.

Funding: This work was supported by NIH grants: RO1 DA034542, RO1 DA040392, R01 HL129875
EVANS SYNDROME PRESENTING AS PANCYTOPENIA AND IMMUNOCOMPROMISED STATUS

Authors: Mohamad Alhoda Mohamad Alahmad1, Kurschner Pillai2
1 KUMC, KS
2 Mercy Health: St Vicent Medical Center, Toledo, OH

Introduction
Evans syndrome is a rare idiopathic hematological disease that consist of autoimmune thrombocytopenia, hemolytic anemia and neutropenia. Diagnosis can be challenging as it is by exclusion of other etiologies.

Case Presentation
A 67-year-old gentleman with past medical history of benign thymoma status post resection in 2014 and Atrial fibrillation (on Pradaxa) presented with weakness and fatigue, weight loss.

Symptoms started 3 months ago when he had reactivation of Herpes Zoster and gradually got worse. He was admitted for viral pneumonia 1 month prior to presentation. Patient reported weight loss of 70 lbs over last 4 months. On admission, Pancytopenia was prominent with hemoglobin of 5.5 mg/dL, WBC of 2000/microL and platelets of 11000/microL. Work up showed immunoglobulins deficiency and autoimmune hemolytic anemia suggested by indirect bilirubinemia, peripheral smear and positive DAT antibodies. Bone Marrow biopsy showed mature trilineage hematopoiesis with megakaryocytic and erythroid hyperplasia. Patient was treated with steroids with significant improvement clinically and in laboratory studies.

Discussion
Evan Syndrome is characterized by autoimmune phenomena. The presentation of this syndrome varies based on other hematological disorder that are associated with it.

We propose that the reactivation of hepes-zoster was the early manifestation in our case. This was associated with fatigue and weight loss and followed by pancytopenia. Supportive evidence includes chronic indirect bilirubinemia, the pathology report and clinical improvement with steroid therapy. The fatigue can be attributed to anemia and the immunocompromised status is related to neutropenia and acquired immunoglobulin deficiency.
Title: Severe Gabapentin Toxicity After Acute Kidney Injury in Hospitalized Patient with Acute Pain

Authors: Mohamad Alhoda Mohamad Alahmad, MD 1; Antonio Perez MD, MBA 2; J. Bradley Williams, PharmD 3; Emer Joyce, MD, PhD 2
1Internal Medicine, KUMC, KS.
2Department of Cardiovascular Medicine, Heart and Vascular Institute, , Cleveland Clinic, Cleveland, OH
3 Department of Pharmacy, Cleveland Clinic, Cleveland, OH

Introduction: The use of gabapentin, a gamma-aminobutyric acid analog, to treat acute pain is increasing in frequency as a means of sparing high dose opioid administration. Clinicians may be less familiar with the potential toxicities associated with gabapentin. Herein, we present a case of gabapentin toxicity precipitated by worsening kidney function after intravenous contrast which resulted in severe mental status changes and respiratory depression.

CASE DESCRIPTION: 47-year-old lady, with past medical history of type 1 diabetes mellitus and end-stage ischemic cardiomyopathy status post left ventricular assist device (LVAD) presented with fever, right groin pain and purulent discharge from prior vascular cannulation site.

At presentation, patient was alert, oriented and hemodynamically stable with low grade fever. Abdominal/pelvic CT with intravenous contrast revealed abscess collection in the right groin, site of prior vascular cannulation. Vancomycin was started and patient underwent incision and drainage.

Postoperatively, patient complained of progressive surgical site pain. Gabapentin, a home medication, was increased from 600 mg TID to 800 mg TID. Unfortunately, patient experienced acute kidney injury in setting of IV contrast administration; her creatinine increased from 0.72 to 3.2 over 5 days. On day 4, patient developed depressed mental status with myoclonus. EEG showed generalized, slow waveforms consistent with diffuse encephalopathy. She further developed respiratory depression with mildly elevated PaCO2, which improved with BiPAP.

Head CT showed no acute CVA. LVAD was stable throughout. Gabapentin was discontinued due to concern for acute toxicity, and blood testing confirmed toxic range level (42 µg/mL, therapeutic range 2-20 µg/mL).

Patient was initiated on intermittent hemodialysis with complete recovery in mental and respiratory status on day 3.

DISCUSSION: Gabapentin is widely prescribed for neuropathic pain. It can also be used for post-operative acute pain management. It is excreted via the kidneys; therefore, dose adjustment based on creatinine clearance is required. Gabapentin should be avoided in rapidly progressive acute renal failure, as occurred in this case. Common symptoms of gabapentin toxicity include are dizziness, drowsiness, and GI discomfort. In severe cases, respiratory depression can result. Gabapentin can be cleared via hemodialysis.

Conclusion: While gabapentin can be an appropriate alternative to opioids in many patients with acute pain, it should be avoided in patients with rapidly worsening acute renal failure. Urgent dialysis can successfully reverse gabapentin toxicity in patients with renal failure.
Diagnostic accuracy of Xpert MTB/Rif Ultra for TB Meningitis in HIV-infected adults: a prospective cohort study

Nathan C Bahr MD MA 1,2, Edwin Nuwagira MBChB 3, Emily E Evans BS 3, Fiona V Cresswell MBChB 4,5, Philip V Bystrom BA 1,3, Adolf Byamukama BMLS 3, Sarah C Bridge BS 1,3, Ananta S. Bangdiwala MS 1, David B Meya MMed PhD 1,4, Claudia M Denkinger MD PhD 6, Conrad Muzoora MBChB MMed 3, David R Boulware MD, MPH 1 on behalf of the ASTRO-CM Trial Team.

Affiliations:
1 University of Minnesota, Minneapolis, MN, USA
2 University of Kansas, Kansas City, KS, USA
3 Mbarara University of Science and Technology, Mbarara, Uganda
4 Infectious Disease Institute, Makerere University, Kampala, Uganda
5 Brighton and Sussex Medical School, Brighton, United Kingdom
6 FIND, Geneva, Switzerland

Abstract:
Background: World Health Organization recommends Xpert MTB/Rif as initial diagnostic testing for TB meningitis. However, diagnosis remains difficult with sensitivity of Xpert ~50-70% and culture ~60%. We evaluated the diagnostic performance of the new Xpert MTB/Rif Ultra (Xpert Ultra) for TB meningitis.

Methods: We prospectively evaluated 129 HIV-infected adults with suspected meningitis for TB in Mbarara, Uganda from March 2015 through November 2016. We centrifuged CSF, re-suspended the pellet in 2mL CSF, and tested 0.5mL with Mycobacteria growth indicator tube culture, 1mL with Xpert, and cryopreserved 0.5mL, later tested with Xpert Ultra (Cepheid, Sunnyvale, CA). We assessed diagnostic performance against uniform clinical case definition or a composite reference standard of any positive CSF TB test.

Results: 23 participants were classified as probable/definite TB meningitis by uniform case definition, excluding Xpert Ultra results. Xpert Ultra sensitivity was 70% (16/23) for probable/definite TB meningitis compared with 43% (10/23) for Xpert and 43% (10/23) for culture. By composite standard, TB meningitis was detected in 17% (22/129). Xpert Ultra had higher sensitivity of 95% (21/22) than either Xpert 45% (10/22; P<0.001) or culture 45% (10/22, P=0.003) for TB meningitis. Of 21 participants positive by Xpert Ultra, 13 were positive by culture and/or Xpert, and 8 were only Xpert Ultra positive. Of those eight, three were categorized as probable and three possible TB meningitis. Testing >6mL of CSF was associated with detecting TB more often than <6mL (26% vs 7%; P=0.014).

Conclusions: Xpert Ultra detected significantly more TB meningitis than either Xpert or culture.

Support: This research was supported by the National Institute of Neurologic Disorders and Stroke and the Fogarty International Center at the National Institutes of Health (R01NS086312, R25TW009345); the National Institute of Allergy and Infectious Disease (T32AI055433); the United Kingdom Medical Research Council/DFID/Wellcome Trust Global Health Trials award (MR/M007413/1); as well as the Doris Duke Charitable Foundation through a grant supporting the Doris Duke International Clinical Research Fellows Program at the University of Minnesota.
Eosinophilic meningitis due to infection with *Paragonimus kellicotti*

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2: Infectious Diseases Specialty Clinic, CoxHealth, Springfield, MO, USA

3: Department of Neurology, University of Kansas, Kansas City, KS, USA

4: Vascular Neurology & Neurointerventional Surgery, CoxHealth, Springfield, MO, USA

5: Infectious Diseases Division, Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA

**Abstract:**

*Paragonimus kellicotti* is an emerging pathogen in the United States with 19 previously reported cases, most in Missouri. Pulmonary symptoms with eosinophilia are most common though one case did involve the central nervous system with few symptoms. We describe the first two cases of eosinophilic meningitis due to *Paragonimus kellicotti*. The diagnoses are supported by a history of ingestion of crayfish from bodies of water known to be endemic for *P. kellicotti*, positive Western blot antibody testing (serum and CSF) and negative tests for other causes of eosinophilic meningitis. In conclusion, these cases suggest that *P. kellicotti* can cause eosinophilic meningitis and that infections with this parasite may be associated with CNS disease. Though most cases of infection due to *P kellicotti* been described in Missouri, clinicians throughout the central United States and Canada need to consider this pathogen.

**Figure 1: MRI Brain images and Western Blot Testing**

Figure 1a is from hospital day two, patient one, and shows a non-enhancing tubular structure from the left midbrain to the right centrum semi-ovale, crossing the corpus callosum.
Figure 1b comes from patient two on admission and shows tubular foci of subcortical enhancement within the right frontal lobe extending across the corpus callosum.
Figure 1c shows combined western blot results from serum and CSF specimens from patient 1. 1: negative serum control, 2: positive serum control, 3: Patient serum sample, 4: negative CSF control, 5: Patient CSF sample. A: 36 kDa band, B: 26 kDa band, C: 24 kDa band
Fanconi Syndrome and Tenofovir Alafenamide (TAF): A Case Report

Nathan C Bahr MD¹, Sri G Yarlagadda MD²

Affiliations:
1: Division of Infectious Diseases, Department of Medicine, University of Kansas, Kansas City, KS, USA.
2: Division of Nephrology and Hypertension, Department of Medicine, University of Kansas, Kansas City, KS, USA

Introduction: In the United States tenofovir disoproxil fumarate (TDF) has been almost completely replaced by tenofovir alafenamide (TAF) to treat human immunodeficiency virus (HIV) infection and to treat chronic hepatitis B infection. This change occurred in part because TAF causes less injury to the kidney than TDF.

Case Report: A 54 year-old man with HIV infection came to our institution to establish care. In 1994, he had been diagnosed elsewhere with HIV, and for the 10 years before coming to our institution his HIV had been well controlled on anti-retroviral regimens that contained TDF. His serum creatinine 3 months prior to the transfer of care was 0.59 mg/dL and his antiretroviral regimen was TDF/emtricitabine + darunavir/ritonavir + raltegravir based on his resistance profile. His previous provider switched his TDF to TAF to avoid chronic toxicities from TDF. When we first saw him 2 months after the medication change, his initial creatinine was 5.56 mg/dL (Table). We admitted him to the hospital and discontinued all his antiretroviral medications, his renal function rapidly recovered. The results of many of his laboratory studies are shown in the Table. No additional nephrotoxic agents were identified. The combination of hypokalemia, non-anion gap acidosis, glucosuria, and borderline-low-normal phosphorus in the setting of acute kidney injury was consistent with Fanconi Syndrome. Two weeks after his initial presentation we started an antiretroviral regime based on previous resistance patterns that did not contain tenofovir, and he rapidly achieved viral control.

Discussion: Fanconi syndrome is a well-known complication of TDF. Others have reported renal injury related to TAF in 3 patients. One patient was an intentional overdose without tubular injury, another patient had evidence of chronic tenofovir-induced tubular injury in addition to acute kidney injury from other causes, and the last patient had evidence of tubular injury with TAF but only after the patient started a regimen for treating hepatitis C that contained ledipasvir, which can increase tenofovir levels. To our knowledge, the case we are describing here is the first report of Fanconi syndrome due to TAF alone.

Table. Laboratory Values in Relation to Presentation

<table>
<thead>
<tr>
<th>Time from presentation</th>
<th>Body Fluid</th>
<th>Cr</th>
<th>UN</th>
<th>NA</th>
<th>K</th>
<th>CO₂</th>
<th>Phos</th>
<th>Prot</th>
<th>pH</th>
<th>Glu</th>
<th>WB C</th>
<th>RB C</th>
</tr>
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<tbody>
<tr>
<td>- 3 months</td>
<td>Blood</td>
<td>0.59</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Day 0</td>
<td>Blood</td>
<td>5.5</td>
<td>22</td>
<td>132</td>
<td>2.8</td>
<td>19</td>
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<tr>
<td>Day</td>
<td>Test Type</td>
<td>Value1</td>
<td>Value2</td>
<td>Value3</td>
<td>Value4</td>
<td>Value5</td>
<td>Value6</td>
<td>Value7</td>
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<tr>
<td>Day +1</td>
<td>Blood</td>
<td>5.3</td>
<td>22</td>
<td>132</td>
<td>2.9</td>
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<td>3.1</td>
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<td>Day +1</td>
<td>Urine</td>
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<td>1+</td>
<td>0-2</td>
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<tr>
<td>Day +4</td>
<td>Blood</td>
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<td>16</td>
<td>141</td>
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<td></td>
</tr>
<tr>
<td>Day +25</td>
<td>Blood</td>
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<td>8</td>
<td>136</td>
<td>3.6</td>
<td>23</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Day +48</td>
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<td>1.3</td>
<td>8</td>
<td>132</td>
<td>3.3</td>
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<td></td>
<td></td>
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<tr>
<td>Day +104</td>
<td>Blood</td>
<td>1.1</td>
<td>8</td>
<td>131</td>
<td>4.3</td>
<td>24</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Central Venous Oxygen Saturation (ScvO2) is Poorly Predicted by Serum Lactate in ICU Patients

Roshan Bisarya, Deena Shaath, Arman Pirzad, MD, Lewis Satterwhite, MD, Lucas Pitts, MD
Steven Simpson, MD

Introduction/Hypothesis:
A topic of debate in critical care medicine involves the relationship between serum lactate and ScvO2. Current consensus guidelines argue that low tissue oxygenation, as evidenced by a low ScvO2, should result in increased lactate production through anaerobic metabolism. However, elevated lactate could also be due to reduced lactate elimination or enhanced aerobic glycolysis through epinephrine release. Hypothesis: Serum lactate inversely correlates with ScvO2 in critically ill patients.

Methods:
Single center, retrospective cohort study in an urban academic medical center from 3/2007 – 3/2017. Entry criteria included age ≥ 18 years and ScvO2 or SvO2 analysis made +/- 1 hour from a lactate measurement. Central venous and mixed venous blood gases, serum lactate, serum cortisol as a surrogate for epinephrine, and markers of renal and hepatic function were collected from patient data. ICD-9 and ICD-10 codes determined if the patients were diagnosed with sepsis or shock. The correlation between lactate and ScvO2 was analyzed using simple linear regression models.

Results:
2,062 patients were included in the study. Lactate and ScvO2 were poorly correlated (r² = 0.0041, n = 2,348, p=0.0019). When eliminating patients with high adrenal activation (cortisol ≥ 25 μg/dL), lactate and ScvO2 showed an r² = 0.0140 (n = 268, p = 0.053). In patients with tissue hypoxia (ScvO2 ≤ 65%), lactate and ScvO2 had an r² = 0.0431 (n = 613, p < 0.001). In patients with normal liver (AST ≤ 40 U/L) and kidney (creatinine ≤ 1.2 mg/dL) function, lactate and ScvO2 had an r² = 0.0517 (n = 284, p < 0.001). In cardiogenic shock patients, lactate and ScvO2 had an r² = 0.0064 (n = 77, p = 0.49). In septic shock patients, lactate and ScvO2 had an r² = 0.0037 (n = 508, p = 0.17).

Conclusions:
In critically ill patients, lactate showed no predictive ability for ScvO2, even after eliminating patients with high adrenal activation, normoxia, or normal kidney and liver function. Lactate and ScvO2 should not be assumed to be interchangeable markers of tissue oxygenation.
An exploration of ontology-based EMR data abstraction for diabetic kidney disease (DKD) prediction

Xing Song, PhD1, Lemuel R. Waitman, PhD1, Yong Hu, PhD2, Alan S.L. Yu, MD3, David Robbins, MD4, Mei Liu, PhD1,
1University of Kansas Medical Center, Department of Internal Medicine, Division of Medical Informatics, Kansas City, KS, USA; 2Jinan University, Big Data Decision Institute, Guangzhou, PRC; 3University of Kansas Medical Center, Division of Nephrology and Hypertension and the Kidney Institute, Kansas City, KS, USA; 4University of Kansas Medical Center, Diabetes Institute, Kansas City, KS, USA

Introduction

The wide adoption of EMRs has enabled unbiased data-driven approaches utilizing a broader spectrum of clinical features to improve disease predictions. One of the key challenges is to determine the granularity at which features should be represented. In this work, we investigated how the varying data-granularity, abstracted from the built-in hierarchical ontology within i2b2 framework, would affect predictions and knowledge-discovery for DKD.

Methods

DKD was defined as diabetes with presence of microalbuminuria or impaired glomerular-filtration-rate. For each patient, we extracted observations from 11 data types (Alerts, Demographics, Diagnoses, History, Labs, Medications, Procedures, Orders, Reports, UHC, Visit-Details) at least 6 months prior to DKD onset or last normal eGFR/albumin, and collected ontology path for each medication and diagnosis (denoted as “LEV_X”, where X=1,…,6 with “6” being “finest”). We exhaustively trained 36 Gradient-Boosting-Machines over all combinations of Medications and Diagnoses representations and used validation AUROC for performance comparisons. Feature importance is calculated as “cumulative improvement of AUROC attributable to a feature”.

Results

A retrospective cohort of 20,718 patients were selected with 38.6% DKDs. Initially, a total of 96,605 finest features were extracted (2,524 selected) to build a baseline model, achieving an AUC of 0.86 (95% CI: 0.85 – 0.87). Due to the “curse of cardinality”, only 700 (out of 40,000) Medications and Diagnoses features got selected contributing to less than 10% of AUC improvement and typically low importance ranks. As we rolled up the features to coarse-grained terms, we observed significant changes on feature rankings (illustrated by examples in Figure 1): a) it pushed the Medication features to better rankings when we rolled the concepts up to LEV_2 but not necessarily higher; b) increasing granularity of Diagnoses features that carry more specific information could collectively strengthen the impact of Diagnoses.

Conclusion

We have identified the utility of the i2b2-specific hierarchical structure as a valuable but under-exploited resource for representing expert knowledge and facilitating interpretable data abstraction. Our experiments have shown great promises on improving DKD predictions by fully
exploiting the diversity of EMR data and have potential implications for future EMR-based studies by stressing on the role of data-representation in knowledge-discovery.

**Funding Sources**

This research was partially supported by the Major Research Plan of the National Natural Science Foundation of China (Key Program, Grant No. 91746204), the Science and Technology Development in Guangdong Province (Major Projects of Advanced and Key Techniques Innovation, Grant No.2017B030308008), and Guangdong Engineering Technology Research Center for Big Data Precision Healthcare (Grant No.603141789047). The dataset used for analysis described in this study was obtained from KUMC’s HERON clinical data repository, which was supported by institutional funding and by the KUMC CTSA grant UL1TR002366 from NCRR/NIH.
Figure 1 – Examples of important Medications and Diagnoses features with various levels of granularity
Visualization of Clinical Pathways for Severe Sepsis Patients

Xing Song, PhD¹, Mei Liu, PhD¹, Lemuel R. Waitman, PhD¹, Anurag Patel, MD³, Steven Q. Simpson, MD²
¹University of Kansas Medical Center, Department of Internal Medicine, Division of Medical Informatics, Kansas City, KS, USA; ²University of Kansas Medical Center, Department of Internal Medicine, Pulmonary and Critical Care Division, Kansas City, KS, USA;

Introduction

Electronic Medical Records (EMRs) contain adequate timestamped data for identifying the critical events describing how severe sepsis evolves over time with or without timely treatments. To better understand the current clinical pathways in adherence to the recommended care guidelines, we proposed a process mining technique to summarize and visualize the interactive behaviors of sepsis alerts and treatments in temporal order.

Methods

Among a retrospective cohort of adult patients admitted through a tertiary ED from 11/07-12/17, we collected onset times of sepsis “Alerts”: i) suspected infection (SI), ii) Systemic Inflammatory Response Syndrome (SIRS) and, iii) different sites of acute organ dysfunctions (OD), by following the Sepsis-1,2 criteria; and timings of “Treatments”: i) initial lactate, ii) blood culture order, iii) antibiotics administration, and iv) initiation and completion of bolus, by following the SSC 3-hour bundle definition. We created the “event logs” by arranging these timestamped entries in sequential order, properly aggregated the data and used Sankey diagram to visualize the pathways and effects on severe sepsis onset defined as the last occurrence of SI, 2 SIRS, and first OD.

Results

Among 15,616 eligible encounters, we identified 2,538 distinct non-trivial clinical pathways. Figure 1 displayed part of the Sankey diagram, which is a directed-acyclic-graph capturing all event paths from triage start to severe sepsis onset or the last identified events for no progression to severe sepsis within 48 hours (see link for full graph). As diverse as the pathways are, our integration and visualization strategy could help recognize certain patterns: a) Leading indicators: e.g., a majority of our cohort came in with suspected infection or 2 SIRS, which led to more conformed response and better outcome for former, but not latter; b) Treatment effectiveness: e.g., the outcomes flowing out of a treatment node usually turns out to be better, especially for early administration of antibiotics (ABX).

Conclusion

We introduced a temporal pattern mining technique and visualization that aggregated disease evolution statistics by integrating both symptoms and medical interventions for severe sepsis patients. This preliminary study showed promise in understanding current treatment process as well as identifying potential care management discrepancies.

Funding Sources

This research was partially supported by the Kansas City Area Life Sciences Institute (KCALSII). The dataset used for analysis described in this study was obtained from KUMC’s HERON clinical data repository, which was supported by institutional funding and by the KUMC CTSA grant UL1TR002366 from NCRR/NIH.
A Resuscitation Strategy Based on the Optimization of Stroke Volume Is Associated With Significant Clinical and Economic Outcomes

Heath Latham, MD¹; Charles D Bengtson, MD¹; Lewis Satterwhite, MD¹; Mindy Stites, MSN¹; Steven Q Simpson, MD¹

The University of Kansas Medical Center

Introduction:
Targeted volume resuscitation aimed at optimizing stroke volume via non-invasive bioreactance monitoring in ICU patients with severe sepsis and septic shock results in a decreased fluid balance, and decreased ICU length of stay, time on pressors, and less need for mechanical ventilation (MV) and dialysis.¹ The purpose of this study was to analyze study data and economic data associated with these improved outcomes.

Methods:
Cost assumptions were applied to each study variable, and used to calculate total cost avoidance.

Results:
When fluid balance over the entire ICU stay was compared between the two groups, patients in the test group exhibited a significantly decreased fluid balance (1.77 ± 0.60 L) compared to 5.36 ± 1.01 L in the usual care group (p=0.002). Patients requiring vasopressors in the test group received this therapy for significantly less time (32.08 ± 5.22 hours) compared to the usual care group (64.86 ± 8.39 hours; p=0.001). Importantly, patients in the test group exhibited a decreased ICU length of stay (5.98 ± 0.68 days) compared to usual care (8.87 ± 1.18 days; p=0.03) yielding a reduction of 2.89 days and an $8953 savings (2.89 days X $4004 [Direct Cost of ICU Day]²- $906 [Avg Floor Day]³). Additionally, patients in the test group were less likely to require MV (relative risk, 0.51; CI 0.36 to 0.72; p=0.0001). The average duration of MV in septic shock is 5.1 days.³ Assuming an absolute 25% reduction in patients receiving mechanical ventilation results in a cost savings of $1940 (5.1 days X .25 X $1522 [Cost of MV/day]⁴). Patients in the test group also exhibited decreased need for dialysis (6.25%) compared to usual care (19.5%; RR .32; p = 0.01) A reduction in 10 dialysis cases resulted in a savings of $1527 savings per patient ($27,182 [Mean Cost Dialysis]³ X 10 cases avoided/178 total patients).

Conclusions:
Optimization of stroke volume guided by NICOM in patients with severe sepsis and septic shock was associated with a total estimated savings of $12420 per patient.

¹ J Crit Care 2017; 28: 42
² JAMA 2013; 173: 1187
³ Premier Data Set, 2013
⁴ Crit Care Med 2005; 33:1266
Clinician-led In-basket EPIC Training – An Educational Intervention Project

Mohamad Alhoda Mohamad Alahmad, Narwal Kasmani, 1Internal Medicine Department, KUMC, KS, 2Mercy Health St. Vincent Medical Center, Internal Medicine Residency Program, Toledo, OH

Background:
Internal medicine residents struggle to understand and utilize electronic medical record (EMR) in the first few months of residency. They typically receive EMR training from non-clinician instructors. We pilot tested an educational intervention to try to improve interns’ confidence with the EMR by providing a physician-led training course.

Methods:
We chose the in-basket management (where residents get notifications, phone calls, and medication requests) in EPIC as an example. The pilot project was a pre-post educational intervention. Participants included a convenience sample of 8 incoming interns from our institution who previously received standard EMR training. Prior to the education, participants completed an investigator-developed survey. The survey contained 5 questions to describe the participants’ degree of confidence and satisfaction with managing EPIC’s in-basket. Response choices were on a 5-point scale: 1-less confident to 5-more confident. Four hours of EPIC education was provided to the participants by the academic chief resident of our internal medicine residency program. The training includes a step-by-step approach to handle in-basket tasks in a daily practice and ignores options that are rarely or never used in EPIC system. Immediately following the training, the participants completed the survey again. The median change in participant’s scores were described for each survey question.

Results:
The 8 participants reported high levels of confidence with EMR following the education and satisfaction with the course. Signed rank test showed the improvement was statistically significant.

<table>
<thead>
<tr>
<th>Survey questions</th>
<th>Median Scores (25th-75th percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 Rate your understanding of in-basket concept.</td>
<td>2 - 5</td>
</tr>
<tr>
<td>Q2 How confident you are with it?</td>
<td>1.5 - 5</td>
</tr>
<tr>
<td>Q3 Do you know how to apply what you know?</td>
<td>2 - 5</td>
</tr>
<tr>
<td>Q4 Do you know the right way to manage the in-basket?</td>
<td>1.5 - 5</td>
</tr>
<tr>
<td>Q5 Do you know the wrong way to manage the in-basket?</td>
<td>1.5 - 5</td>
</tr>
</tbody>
</table>

Conclusion:
Physician-led EPIC training may be beneficial for incoming interns. It can facilitate skills acquisition by directing interns to high-yield practical points. This may lead to better patient care particularly in the beginning of the academic year.
Validation of RACE vs. VAN Scores to Predict Large Vessel Occlusion in the Prehospital Setting with a Mobile Stroke Unit

Mohamad Alhoda Mohamad Alahmad, Victoria Calderon, MPH, Osama Zaidat, MD, MS

Mercy Health St. Vincent Medical Center, Toledo, OH

Introduction

Stroke is the leading cause of disability and fifth leading cause of death in United States. Early identification of acute ischemic stroke due to large vessel occlusion (LVO) is vital to provide timely thrombectomy treatment, which has been shown to lead to improved clinical outcome. Two prehospital LVO screening tools are commonly used: the Rapid Arterial occlusion Evaluation (RACE) scale and the Vision, Aphasia, and Neglect (VAN) tool.

The purpose of this study is to compare RACE and VAN’s ability to identify LVO in a community, prehospital setting when used by trained personnel on a mobile stroke unit (MSU).

Methods:

The Mercy Life Flight Network MSU is a specialize, neuro-critical care ambulance equipped with a computed tomography (CT) scanner and telemedicine capabilities that are used to identify, manage, treat, and transport patients from the prehospital field. All MSU personnel are formally trained in both RACE and VAN; they performed these tools routinely during the neurological exam, unaware of the current study design.

Patients were prospectively evaluated by the MSU’s team, and VAN and RACE scores were calculated on the scene. LVO was defined as an occlusion in any of the following arteries: MCA M1, M2, PCA, ACA, ICA, or basilar artery, as identified by computed tomography angiography (CTA), magnetic resonance angiogram (MRA), or digital subtraction angiography (DSA), within 24 hrs of RACE or VAN. The MSU team was unaware of the vascular imaging results.

Results:

<table>
<thead>
<tr>
<th>Diagnostic Indicator</th>
<th>RACE &gt; 4 (n=32)</th>
<th>Positive VAN (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>22% (4%-60%)</td>
<td>33% (9%-69%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>61% (39%-80%)</td>
<td>80% (59%-92%)</td>
</tr>
<tr>
<td>Positive Predicted Value</td>
<td>18% (3%-52%)</td>
<td>38% (10%-74%)</td>
</tr>
<tr>
<td>Negative Predicted Value</td>
<td>67% (43%-85%)</td>
<td>77% (56%-90%)</td>
</tr>
</tbody>
</table>

Table 1: RACE and VAN sensitivity, specificity, and predicted values comparison.

A total of 22 male and 25 female patients were identified. 32 evaluable patients were included in the final analysis: 34% of those patients had RACE > 4 and 24% had a positive VAN score. By the gold standard definition, only 26% of patients had LVO.
Conclusions:

In patients with suspected acute ischemic stroke; VAN had more favorable diagnostic test statistics for predicting LVO compared to RACE (Table 1), although statistical significance cannot be determined with the small sample size. Further research is needed.
Article: Acute Respiratory Failure: A Rare Manifestation Of Sweet Hydrothorax

Authors: Mohamad Alhoda Mohamad Alahmad, M.D. 1 Rahil Kasmani, MRCP2
1Internal Medicine Department, KUMC, KS
2 Nephrology Associate of Toledo, Toledo, OH 42608 United States of America

Introduction:
Peritoneal dialysis (PD) is a form of Renal Replacement Therapy (RRT) offered to patients with End Stage Renal Disease (ESRD). Herein, we present a case of acute respiratory failure due to massive hydrothorax related to PD.

Case Presentation:
A 70 year old female with past medical history of well controlled rheumatoid arthritis and hypertensive nephropathy complicated by ESRD, for which she was started on PD 3 months ago, presented to the hospital with deteriorating dyspnea over 2 weeks.

Vitally, the patient was afebrile and stable with BP of 133/84, HR of 96, and RR in 20s. Laboratory tests showed mild leukocytosis and hyperglycemia (230 mg/dL). Chest x-ray revealed a massive right sided pleural effusion that was not present on an x-ray done few weeks before starting PD. A thoracentesis provided significant symptom relief and was consistent with transudative effusion and high glucose level (260 mg/dL) in the pleural fluid. Tc-99m scintigraphy showed right peritoneo-pleural communication (Figure 1).

PD was discontinued and patient was started on hemodialysis. Follow-up showed no recurrence of symptoms nor pleural effusion.
**Conclusion:**

Hydrothorax is a known complication of peritoneal dialysis that occurs in about 1.6% to 6% of patients with this form of dialysis\(^1\). High glucose concentration in pleural fluid is diagnostic, hence the name “sweet hydrothorax”, and difference of more than 50 mg/dL was found to have 100% specificity\(^2\).

We believe that the acute respiratory failure was due to large pleural effusion that is attributed to starting PD. This is supported by pleural fluid analysis and improvement of symptoms following pleurocentesis and hemodialysis. Technetium study confirmed the diagnosis. Thoracic surgery to repair the defect could be considered in patients who failed conservative management\(^3\).

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Downregulation of miRNA506 mediates EGFR-TKI resistance through induction of Sonic Hedgehog Signaling in non-small cell lung cancer cell lines.

Authors: Inamul Haque, Mukut Sharma, Andrew K. Godwin, Chao Huang

Background: Epidermal Growth Factor Receptor (EGFR) mutation predicts response to a tyrosine kinase inhibitor (TKI) of EGFR in approximately 25% of patients and patients with EGFR mutation eventually develop resistance to EGFR-TKI. The mechanism of resistance is not fully elucidated but majority of the cases is related to emergence of clones with T790M mutation in EGFR, and amplification of c-MET. Recently, increasing numbers of miRNAs, non-coding RNAs are correlated with the drug resistance indicating that miRNAs may serve as novel targets and/or promising predictive biomarkers for anti-EGFR therapy. In this study, we investigated the role of miRNA-506 in the regulation of Sonic Hedgehog (SHh) in TKI-resistant lung cancer cell lines. Methods: To generate cell lines resistant to EGFR TKI, HCC4006 cells were exposed to increasing concentrations of erlotinib over 6 months with increasing concentration up to 20 μM. The resultant clones (designated HCC4006 ER1 to HCC4006 ER4), following expansion from single cell. Cell viability was measured by crystal violet staining assay. The expression of miRNA in parental and resistant clones was checked by real-time qRT-PCR. The mRNA and protein expression level of SHh was determined by real-time qRT-PCR and Western blot. Invasive/migratory ability of parental and resistant clones was measured by Boyden chamber assays. Epithelial to mesenchymal transition (EMT) and stemness markers were evaluated by Western blot. Single-cell suspensions from pre-treated cells were re-suspended at a density of 500 cells/ml mammocult media in ultralow attachment dishes. Number as well as the size of the tumorosphere/spheroids in specified experimental set-up was monitored and recorded alternate day for 8-10 days. Results: The studies demonstrated that miR-506 was downregulated in resistant clone as compared to parental cell lines which promotes significantly the invasive/migratory ability and EMT phenotypes of lung cancer cells through induction of SHh. Interestingly, ectopic expression of miRNA-506 in these resistant cells inhibits SHh signaling and thus reprograms EMT, EGFR-TKI resistance and stemness.

Conclusions: Our data suggest that miR-506 downregulation and induction of SHh are associated with resistance to EGFR-TKI. miR-506 interference and inhibition of SHh pathway are potential therapeutic strategy to reverse resistance to EGFR-TKI in NSCLC with EGFR mutation.
Acute Myeloid Leukemia after Treatment for Pancreatic Neuroendocrine Tumor with Temozolomide and Thalidomide

Nicole Balmaceda, Sunil Abhyankar, M.D., Joaquina Baranda, M.D. KU School of Medicine-Kansas City

Introduction With the acceleration in new drug developments, patients have more treatment options for improved survival and quality of life. However, adverse effects that manifest later in life, including secondary malignancies caused by chemotherapy and radiation, may limit drug use. Temozolomide is an alkylating agent that is FDA-approved for the treatment of glioblastoma multiforme and refractory anaplastic astrocytoma. Unfortunately, a number of cases have reported the development of hematologic malignancy after temozolomide therapy in patients with gliomas. Though not FDA-approved, the National Comprehensive Cancer Network (NCCN) includes temozolomide as an option for treating metastatic neuroendocrine tumors (NET). Unlike gliomas, there are no published reports of leukemogenic potential in the treatment of NET. This is the first case presentation showing the development of Acute Myeloid Leukemia (AML) after temozolomide treatment in a patient with metastatic pancreatic NET.

Case Presentation A 29-year-old female presented to endocrinology for diabetes and hypercalcemia in April 2005. Past medical history included episodic palpitations, hypertension, hypothyroidism, anxiety, and obesity. Abdominal imaging revealed a 10.7 x 8.8 x 9.5 cm lobulated mass within the pancreatic tail and multiple liver masses. Pancreatectomy and debulking of the liver masses confirmed the diagnosis of moderately differentiated NET in the pancreas with liver metastasis. Workup for Multiple Endocrine Neoplasia 1 and 2 was negative. In addition to octreotide therapy, she underwent a number of transhepatic arterial chemoembolizations to control extensive liver-dominant disease. Despite these measures, CT showed progressive disease. Systemic therapy with bevacizumab was started in April 2007 which improved her hypercalcemia, flushing, and diarrhea.

A few months later, she experienced upper GI bleeding from a friable, gastric mass. Bevacizumab was discontinued. Radiation therapy resulted in good palliation of the bleed. However, she continued to show clinical, biochemical, and radiographic evidence of rapidly progressive disease. In March 2008, she started a treatment of 150 mg/m2 temozolomide daily for 7 days, every 14 days and daily thalidomide with intermittent treatment breaks. This provided tumor shrinkage and symptomatic relief.

In March 2011, she complained of worsening fatigue. Labs revealed macrocytic anemia and thrombocytosis. Bone marrow evaluation and cytogenetics showed presence of infiltrating monomorphic myeloid blasts and presence of inversion 3q with breakpoint at q21 and q26, consistent with an aggressive type of AML. All treatment for NET was stopped and AML therapy with daunorubicin and Ara-C in a 3 and 7 combination was started. A year later, she passed away from immunosuppression complications.

Conclusions Patients like this young woman have the potential to live longer and may live long enough to develop secondary malignancy. Leukemogenic potential of temozolomide should be further evaluated as its use increases. This is the first report showing possible development of AML in patients with metastatic NET treated with temozolomide.
A Rare Cause of Anemia: 
74-year-old Male with High-Grade Neuroendocrine Tumor of the Colon

Nicole Balmaceda, Mohammad Telfah, M.D., Mazin Al-Kasspooles, M.D., Hongyan Dai, M.D., Ph.D., Prakash Neupane, M.D., Joaquina Baranda, M.D. KU School of Medicine-Kansas City

Introduction

Colorectal cancer is the third most common cause of malignancies in both men and women, with the overwhelming majority being adenocarcinoma. An exceptionally rare histology type of colon cancer is high-grade large cell neuroendocrine tumors. Highly aggressive, these rare malignancies present challenges in treatment.

Case Presentation

A 74-year-old male presented to his primary care physician with weight loss, poor appetite, fatigue, and diffuse abdominal pain in 2018. Review of systems was negative for nausea, vomiting, change in bowel movement, blood in the stools, shortness of breath, or flushing. Past medical history includes hypertension and chronic kidney disease. On examination, he was pale but had no organomegaly. His hemoglobin was 8 gm/dL and creatinine was elevated. Bone marrow biopsy and urine studies were consistent with monoclonal gammopathy of undetermined significance. Five months later, the patient underwent colonoscopy which showed a large mass within the proximal transverse colon at the hepatic flexure. Biopsy of the colonic mass showed poorly differentiated invasive adenocarcinoma. Because of renal insufficiency, a CT with contrast could not be performed. Therefore, PET/CT imaging was done which demonstrated a hypermetabolic colonic mass with a maximum SUV of 25.9, compatible with primary malignancy, hypermetabolic mesenteric lymphadenopathy consistent with nodal metastatic disease, and multiple hypermetabolic mediastinal, hilar, and periportal lymph nodes of indeterminate significance. The patient underwent laparoscopic extended right hemicolectomy. Intraoperatively, suspicious-appearing enlarged central lymph nodes were noted. Surgical pathology revealed high-grade large cell neuroendocrine tumor with proliferative index of over 90%. He was initially staged as III T3N2aM0. Because of this unexpected pathology associated with rapid progression, a baseline PET/CT was done, and systemic therapy planned. There were lung lesions too small to characterize, but no definite evidence of metastatic disease in the chest. However, this showed abdominal lymphadenopathy consistent with metastatic disease. Liver function tests, serum CEA, and urine 5-HIAA/CP were within normal limits. Chromagranin A was elevated at 315. The patient was started on carboplatin and VP-16 three weeks postoperatively with plans to complete four to six cycles of this regimen.

Conclusions

Neuroendocrine tumors account for only 0.4% of all colorectal neoplasms. Current literature on optimal treatment strategies for large cell neuroendocrine tumors of the colon is sparse. Given the histologic similarities, these colonic malignancies are managed with the same regimens used in small cell lung cancer. However, emerging data suggest that poorly differentiated neuroendocrine tumors are a distinct disease entity from small cell lung cancer. A more thorough investigation of large-cell neuroendocrine tumors of the colon is warranted.
TITLE: E-cig vapors cause CFTR dysfunction and mucosal inflammation in never-smokers in vitro and in vivo.

AUTHORS: Samuel Chung¹, Nathalie Baumlin¹, John S. Dennis¹, Philip L. Whitney², Carolina Aguiar¹, Sheyla Paredes-Aller², Eliana Mendes², Andreas Schmid¹, Michael D. Kim¹ and Matthias Salathe¹.

STUDY LOCATIONS: ¹Department of Internal Medicine, Division of Pulmonary and Critical Care Medicine, University of Kansas Medical Center, Kansas City, KS 66160, USA ²Division of Pulmonary, Critical Care and Sleep Medicine, University of Miami School of Medicine, Miami, FL 33136, USA

BACKGROUND: Widespread adoption of e-cigarette (e-cig) use has been aided by unsubstantiated claims of safety. A common element amongst all e-cig vapors is the liquid vehicles propylene glycol (PG) and vegetable glycerin (VG). To better understand effects of e-cig vapor inhalation (“vaping”), we enrolled human volunteers to vape PG and/or VG for one week and exposed differentiated human bronchial epithelial cells (HBECs) to vape daily for one week.

METHODS: Healthy volunteers with no history of vaping or smoking were recruited for this study with IRB approval. Subjects were randomly assigned to vape e-cig liquids PG/VG (50%/50%, w/v), VG (100%), or PG (100%) using an e-cig device (Joyetech) and instructed to vape at least 100 puffs per day for one week. Collected nasal cells (brushings) and fluids (Leukosorb paper) were assessed for inflammatory markers by qPCR and ELISA. Nasal ion transport was assessed by measuring nasal potential difference (NPD) according to Therapeutic Development Network standards of the Cystic Fibrosis Foundation. All measurements occurred during initial and final visits. HBECs were isolated from consented never-smoker donors whose lungs were found unsuitable for transplantation and cultured at the air-liquid interface. Cells were exposed using a VC-1 smoke robot (Vitrocell). CFTR function was determined by measuring short-circuit currents in Ussing chambers, defined as CFTRinh-172 current suppression after forskolin stimulation in the presence of amiloride.

RESULTS: TGF-β1 and MMP9 mRNA as well as MUC5AC protein levels were increased in volunteers after one week of vaping. NPD changes in response to isoproterenol decreased (consistent with CFTR dysfunction) and to ATP increased (consistent with BK dysfunction). In vitro, HBECs exposed to 100 puffs PG/VG per day exhibited increased TGF-β1 and MMP9 mRNA. Both CFTR and BK channel functions were also reduced. A lower dose (40 puffs/day) reduced CFTR function but did not affect BK channel function nor expression of inflammatory markers.

CONCLUSIONS: Nicotine-free e-cig vapors increase airway inflammation and impair airway CFTR and BK channel function in vitro and in never-smoking/vaping individuals in vivo. A lower dose of vape was insufficient to induce inflammatory changes but still reduced CFTR function, highlighting detrimental effects of e-cig use.

FUNDING SOURCES: Flight Attendant Medical Research Institute, CIA #130033 (to M.S.); James and Esther King Florida Biomedical Research Program, Grant #5JK02 (to M.S.); National Institutes of Health (NIH) – F32-HL140729 (to S.C.) and R01-HL139365 (to M.S.)
TITLE: Electronic cigarette vapor with nicotine causes airway mucociliary dysfunction via TRPA1 receptors

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RATIONALE: Electronic cigarette (e-cig) use has been widely adopted under the perception of safety. As a risk reduction approach, this might hold true for former smokers who adopt “vaping” (inhalation of e-cig vapor), but possible adverse effects of vaping in never-smokers are not well understood. Therefore, we investigated effects of nicotine-containing e-cig vapors on airway mucociliary function in differentiated human bronchial epithelial cells (HBECs) isolated from young never-smokers.

METHODS: HBECs were isolated from consented never-smoker donors, whose lungs were found unsuitable for transplantation, and cultured at the air-liquid interface. Cells were exposed to e-cig vapor using a VC-1 smoke robot (Vitrocell) or nebulized with treatments using the CLOUD exposure system (Vitrocell). Various mucociliary parameters were measured. Calcium effects in HBECs were probed with GCaMP6s, a fluorescent calcium sensor, that was transduced by lentivirus.

RESULTS: Exposure to e-cig vapor reduced airway surface liquid hydration and increased mucus viscosity of HBECs in a nicotine-dependent manner. Acute nicotine exposure increased intracellular calcium levels, an effect primarily dependent on transient receptor potential ankyrin 1 (TRPA1) and not nicotinic acetylcholine receptors. TRPA1 inhibition with A967079 protected against nicotine-dependent impairment of airway hydration, increased mucus viscosity, and increased percent mucus solids. Mucus transport, an in vitro measure for mucociliary clearance, was also significantly reduced after nicotine exposure. However, pre-treatment with nebulized A967079 protected against this effect.

CONCLUSIONS: Our findings demonstrate that the nicotine component of e-cig vapor causes acute airway mucociliary dysfunction in vitro. The main nicotine effect on airway mucociliary functions is mediated by the novel nicotine receptor TRPA1.

FUNDING SOURCES: Flight Attendant Medical Research Institute, CIA #130033 (to M.S.); James and Esther King Florida Biomedical Research Program, Grant #5JK02 (to M.S.); National Institutes of Health (NIH) – F32-HL140729 (to S.C.) and R01-HL139365 (to M.S.)
Examsining the Impact of Interdisciplinary Provider Factors on Patient Outcomes: Case Studies Using Sepsis and Spine Surgery Cohorts

Dammika L. Walpitage
Maren L. Wennberg
Sravani Chandaka
Ellen Harpaer
Amy L. Garcia
Lemuel R. Waitman

Abstract

Background: A considerable portion of the variance in patient outcomes may be attributed to provider factors, both at individual level and at institutional level. Modeling outcome variances using medical claims and other forms of aggregated administrative data may underrepresent any significant contributions associated with individual providers who do not directly involved with billing. However, there are few studies that utilized comprehensive data in Electronic Health Records (EHRs) to model provider impact on patient outcomes. The purpose of this preliminary case study was to examine the effect of provider factors on the length of stay (LOS) using two different patient care processes.

Methods: This study is based on retrospective review of medical records of two patient cohorts, who had treatment for Sepsis at emergency department, and who had undergone Lumbar Spine Surgery (LSS), at the university of Kansas hospital. Sepsis cohort consisted of 2141 patients having septicemia diagnosis, and Spine surgery cohort had 919 patients who underwent LSS. The dependent variable of interest in this study was LOS, and several sets of variables to represent, provider factors, clinical factors, and socio-demographic factors were considered as explanatory variables. The provider set was created with variables to represent number of distinct providers associated with medication orders, medication administrations, flowsheet documentations, and procedure orders. Also, multiple proxy variables were included in the provider set to represent the degree to specialty providers involvement within care process. In addition, Medical Severity Diagnosis Related Grouper (MSDRG) and Charlson comorbidity index were used to represent clinical factors. Patient’s socio-demographic variables (age at visit, gender, race) were considered as other potential predictors. Sequential regression models were used to test the impact of provider related factors above and beyond the effect of clinical and socio-demographic factors.

Results: Provider factors, above and beyond the socio-demographic and clinical factors, explained 59.9% and 60.1% variance in LOS in Sepsis and Spin surgery cohorts, respectively.

Conclusion: This preliminary study showed the promise in decomposing the unexplained variance in outcomes attributed to the variance in provider factors.

Funding Source: This work was supported by a CTSA grant from NCATS awarded to the University of Kansas for Frontiers: University of Kansas Clinical and Translational Science Institute. (#UL1TR002366) The contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH or NCATS.
Polyendocrinopathy, Candidiasis, Ectodermal Dystrophy, Keratoconjunctivitis, Autoimmune Hepatitis, Adrenal Insufficiency and Hypoparathyroidism In An Adult Female.

Authors: Aba Al-Kaabi, MD, Eric T Rush, MD, Selina Gierer, DO

Introduction:
Autoimmune Polyendocrine Syndrome (APS), or Autoimmune Polyendocrinopathy–Candidiasis–Ectodermal Dystrophy (APECED), is a rare autosomal recessive disease caused by mutations in the autoimmune regulator gene (AIRE). Given the wide variation in clinical presentation, the diagnosis of APS can be challenging and delayed.

Methods/Results:
We present a 46-year-old female with a history of tetralogy of Fallot, hypoparathyroidism, autoimmune hepatitis status-post liver transplantation, large granular lymphocytic leukemia, recurrent HSV keratitis status-post four corneal transplants, CMV viremia and disseminated histoplasmosis.

Genetic testing revealed a normal Microarray with biallelic pathogenic variants in the AIRE gene. The homozygous frameshift variant designated c.967_979del13 (p.Leu323SerfsX51) results in an unstable gene product and appears to be one of the most common mutations in APS. This result was diagnostic for APS-1 and provided a cohesive explanation for her keratoconjunctivitis, history of autoimmune hepatitis, adrenal insufficiency and hypoparathyroidism, but not for the congenital heart disease. Genetic testing for known variants of DiGeorge syndrome was negative.

Conclusion/Discussion:
The estimated prevalence of APS-1 is 1:100,000. It is characterized by the development of at least two of three cardinal components: chronic mucocutaneous candidiasis, hypoparathyroidism, and primary adrenal insufficiency. The syndrome can manifest from early infancy to adulthood, and new components can appear throughout life. Patients have an increased risk of cancer and mortality compared to the general population, which makes early diagnosis key. Because of the clinical variability, our patient's diagnosis was quite delayed. Patients need appropriate multidisciplinary care to help prevent and monitor for end-organ damage with early introduction of appropriate immunomodulatory therapy.

References:

Clinical Outcome of Ampullary Carcinoma: Single Cancer Center Experience

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Disclosure
The authors declare that there is no conflict of interest regarding the publication of this paper.

Abstract

Introduction: Ampullary cancers represent a small subset of periampullary cancers and comprise of only 0.2% of all gastrointestinal malignancies. The management of the locoregional disease is primarily a surgical intervention by a pancreaticoduodenectomy (PD) followed by the administration of adjuvant chemotherapy. There is no clear guidance in regards to adjuvant therapy, but patients with resected Ampullary carcinomas often receive concurrent chemoradiation with radiation.

Methods: We retrospectively reviewed the charts of 54 patients at KUMC, who had undergone endoscopic resection or PD for Ampullary cancer from June 2006 to July 2016. Clinical presentation, pathology, treatment modality, recurrence, and survival factors were obtained. Kaplan-Meier method was used to compare the time-to-events.

Results: The median age of the 54 patients [38(72%) males and 15(27%) females] was 67 (37-90). Most of patient are white 40(75%) with 5(3%) African American. 52%(28) have history of smoking, alcohol abuse 20%(11) and history of pancreatitis 13%. Among the 54 patients with localized cancers, 9 (16%) were treated definitively with nonoperative therapies, typically secondary to a prohibitive comorbidity profile, performance status, or unresectable tumor. Adjuvant treatment was administered because of concerns for advanced disease in 18(40%)[CT 13(30%), CRT 5(10%)]. The remaining 27(55%) patients underwent surgery alone. The median OS for the study cohort is 30 months. Recurrence was noted in 40% of patients who underwent surgery. When compared to surgery alone, adjuvant CT or CRT had no statistically significant difference in terms of PFS (P=0.56) or overall survival (OS) (P=0.80). On multivariate Cox proportional hazards regression, high risk features like Peri-pancreatic extension (16%) and Perineural invasion (26%) found to have a predictive value for poor OS. LN metastases was (29%), but did not significantly affect OS (HR 1.42, 95% CI (0.73-1.86); P=0.84). Current data did not suggest lympho-vascular invasion (29%) predict OS (HR 1.22, 95% CI (0.52, 2.96); P=0.76. These results could be due to low sample size.

Conclusions: Despite numerous advances in cancer care and research, efforts in rare malignancies such as Ampullary cancer remain very challenging with a clear lack of an evidence-based standard of care treatment paradigm. Although adding adjuvant chemoradiation likely improves survival in patients with high-risk disease, No standardized regimen exists for Ampullary cancer. In the future, stratification by histological subtype, staging, prognostic factors and/or other molecular profiling in large studies may enable targeted decision making.
Analysis of circulating tumor DNA in peripheral blood as noninvasive surveillance tool for peritoneal carcinomatosis of Appendiceal origin in a patient treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: A paradigm shift towards personalized cancer medicine

Authors: Mohammed AL-Jumayli, MD, John Ashcroft, MD, Anup Kasi, MD

Introduction
Colvera is a blood-based qualitative DNA test to detect colorectal cancer recurrence by indicating the presence of two altered genes, BCAT1 and IKZF1, in Circulating tumor DNA (ctDNA) associated with colorectal tumor growth. The role of Colvera in appendiceal cancers is unknown.

Case Report
A 63 year old female with appendiceal adenocarcinoma, poorly differentiated, mucinous subtype, with peritoneal carcinomatosis underwent CRS+HIPEC. Following this, she received adjuvant chemotherapy for 6 months. Surveillance CT scans revealed nonspecific thickening in the pelvis. Tumor markers were normal. Standard management approach would be to repeat scans in 3 months as she was asymptomatic. However, because of inconclusive evidence of residual disease, Colvera test was obtained which came back positive for malignancy. This indicated residual disease and the decision was changed to pursue maintenance chemotherapy.

Discussion
CRS+HIPEC for invasive appendiceal cancer yields 5-year survival of ~70%. The next challenge, however, is to define appropriate post-treatment follow-up strategy. Surveillance CT has traditionally been considered unsatisfactory in the detection of peritoneal disease. Furthermore, Tumor marker alone is insufficiently sensitive to detect residual disease or recurrence. Colvera maybe more sensitive to detect residual disease or recurrence. This case has led to a clinical trial exploring Colvera in appendiceal cancers at KUCC.

Conclusion
This is the first pilot study investigating utility of ctDNA as a sensitive and noninvasive surveillance tool to detect residual or recurrence of appendiceal cancers. In this modern era of precision medicine, Colvera provides an actionable information in select patients that lead to improved outcomes.
Secondary malignancies in temozolomide-treated metastatic pancreatic neuroendocrine tumors

Nicole Balmaceda, Sunil Abhyankar, Tyler Mouw and Joaquina Baranda

**Purpose:** To determine the incidence of secondary malignancies in patients treated with temozolomide (TMZ) for metastatic pancreatic neuroendocrine tumors (PNET).

**Background:**
TMZ is an oral alkylating agent used to treat glioblastoma multiforme (GBM), refractory anaplastic astrocytoma (AA), and metastatic PNET. This imidazotetrazine analog of dacarbazine lacks the ability to directly crosslink DNA and is thought to be less leukemogenic than other alkylators. Given either alone, or in combination with other therapies, TMZ is associated with improved clinical outcomes. However, serious hematologic adverse events (HAEs) like agranulocytosis, lymphopenia and aplastic anemia are not uncommon. Until recently, metastatic PNET was primarily managed with somatostatin-analogs, but with more reports demonstrating therapeutic activity of TMZ-based regimens, it is anticipated that more patients with metastatic PNET will be exposed to TMZ.

**Methods:**
To determine the incidence of secondary malignancy in TMZ-treated PNET, a systematic review of all known clinical trials, case reports, and other relevant literature regarding PNET and TMZ published before September 2017 was conducted using PubMed, Embase, Cochrane Library, and the FDA database.

**Results:**
Twenty-one publications, including clinical trials, meta-analysis, case reports, and cohort studies were analyzed. HAEs ranged from agranulocytosis to myelodysplastic syndrome. No publications reported any secondary malignancies. Incidentally, at the University of Kansas Medical Center, 3 patients with TMZ-treated PNET developed hematologic malignancies. A 29-year-old female with metastatic PNET was treated with TMZ and subsequently developed acute myeloid leukemia (AML) with cytogenetics consistent with therapy-related leukemia. The second patient with TMZ-treated metastatic PNET developed diffuse large B-cell lymphoma. These two patients both had aggressive disease that was not responsive to multiple rounds of treatment. They succumbed to their hematologic malignancy, and not from metastatic PNET. The third patient is a 29-year-old who was recently diagnosed with high-grade T-cell lymphoblastic lymphoma and is currently undergoing treatment for his lymphoma.

**Conclusion:**
This review did not find any cases of secondary malignancy in TMZ-treated metastatic PNET. Yet, at our own institution, we have identified 3 cases of secondary hematologic malignancies in patients treated with TMZ for PNET. We believe that the leukemogenic potential of TMZ is underreported and anticipate increased reports of secondary malignancy as the use of TMZ increases. It is important for treatment guidelines to address this risk in the decision to pursue TMZ treatment. Appropriate dosing, proper follow up and surveillance, especially in patients who are able to live long enough to develop these hematologic cancers, is crucial.
Comparison of outcomes for AJCC 8th Anatomic and Prognostic staging in contemporary triple negative breast cancer (TNBC) multisite registry.

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University of Kansas Medical Center, Kansas City KS

Background: Eighth edition of the AJCC TNM staging system incorporates biological prognostic factors along with the traditional anatomical factors and currently Prognostic (P) stage must be used for reporting of all cancer patients in the US. Comparison of patient distribution between P and Anatomic staging and outcomes associated with the P stages in a contemporary TNBC population are not known.

Methods: 574 patients with stage I-III TNBC were enrolled in an IRB approved multisite prospective registry between 2011 and 2017. Patients were followed for recurrence and survival. AJCC 8th edition Anatomic (A) Stage and clinical Prognostic (P) stage groups were applied to all patients. Recurrence free survival (RFS) (STEEP criterion) was estimated according to the Kaplan-Meier method and compared among groups by log-rank test.

Results: Median age was 53 years (23-85). 96% of patients received neo/adjuvant chemotherapy. 82% (468/574) of patients were upstaged on P compared to A staging. Significantly lower numbers of patients were categorized within P stage II (36%) compared to A stage II (51%) (p=0.001). Conversely, higher number of patients were categorized within P stage III (29%) compared to A stage III (14%) (p=0.0001), with largest relative increase in stage IIIC (3% to 13%). Table 1 provides 5 years RFS for all A and P stages. Compared to A stage IIIA/B, P stage IIIAB was associated with better RFS (HR=0.42 [0.21-0.86]; p=0.013), whereas P and A stages IIIC had similar RFS. This suggests appropriate upstaging of TNBC patients to IIIC on P staging.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Anatomic</th>
<th>Prognostic</th>
<th>P value</th>
<th>5 year RFS (Est.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>200 (35%)</td>
<td>199 (35%)</td>
<td>NS</td>
<td>86% 87%</td>
</tr>
<tr>
<td>IA</td>
<td>197 (34%)</td>
<td>31 (1%)</td>
<td>0.001</td>
<td>86% 100%</td>
</tr>
<tr>
<td>IB</td>
<td>3 (1%)</td>
<td>196 (34%)</td>
<td></td>
<td>67% 87%</td>
</tr>
<tr>
<td>II</td>
<td>293 (51%)</td>
<td>207 (36%)</td>
<td>0.001</td>
<td>85% 86%</td>
</tr>
<tr>
<td>IIA</td>
<td>205 (35%)</td>
<td>80 (14%)</td>
<td>0.0001</td>
<td>87% 93%</td>
</tr>
<tr>
<td>IIB</td>
<td>88 (15%)</td>
<td>127 (22%)</td>
<td>0.0001</td>
<td>80% 83%</td>
</tr>
<tr>
<td>III</td>
<td>81 (14%)</td>
<td>168 (29%)</td>
<td></td>
<td>57% 70%</td>
</tr>
<tr>
<td>IIIA</td>
<td>66 (12%)</td>
<td>94 (16%)</td>
<td>0.0001</td>
<td>59% 83%</td>
</tr>
<tr>
<td>IIIC</td>
<td>15 (3%)</td>
<td>74 (13%)</td>
<td>0.0001</td>
<td>55% 54%</td>
</tr>
</tbody>
</table>

Conclusion: 82% of TNBC patients are upstaged on P staging compared to A staging. Knowledge of outcomes associated with various P stages can guide prognostic counselling for TNBC patients who plan to undergo standard local and systemic treatment.

Funding Sources: This work was supported by the University of Kansas Research Career Award and the KU Cancer Center’s CCSG (P30 CA168524) Biospecimen Repository
Docetaxel-induced Stevens-Johnson Syndrome in a Patient with Metastatic Prostate Adenocarcinoma

Diab, Osama; McEntire, Dan ; Kerfeld, Mitchell; Campbell, Jonathan; Alsuwaidan, Abdullah; Gbadamosi-Akindele, Maryam

Abstract
Docetaxel is a commonly used chemotherapeutic agent used in a variety of cancer treatment plans. We present a case of apparent docetaxel-induced Stevens-Johnson syndrome (SJS) in a patient recently treated with docetaxel for metastatic prostate cancer. This medication is not classically associated with the development of SJS. We encourage clinicians who employ the use of this medication to be aware of this relationship.

A 63-year-old gentleman with a past medical history of hypertension, hyperlipidemia, and metastatic prostate adenocarcinoma to retroperitoneal lymph nodes, lung, and bone presented to the emergency room with a one-week history of a rash. The rash affected hands, feet, back, and chest. It developed into blisters that later ruptured. The rash was especially painful in the hands and feet. He also reported red eyes and difficulty eating for the past week.

Vital signs upon presentation were: temperature 36.4°C, pulse 83/min, respiratory rate 12/min, blood pressure 121/60mmHg. Physical examination of the patient revealed a severe rash covering less than thirty-percent of the body, oral ulcers, and conjunctival redness.

The patient's current cancer treatment regimen included active hormonal therapy with leuprolide and active chemotherapy with docetaxel. He had received two cycles of docetaxel therapy (75mg/m²), with the last dose of docetaxel received 2 weeks prior to presentation. He was not on other medications at the time of admission.

Treatment of the patient included intravenous fluid replacement, prednisone, piperacillin/tazobactam, ondansetron, and morphine. The skin lesions were kept clean with regular dressing changes.

Because our searches for an established association between SJS and docetaxel were in vain, we elected to obtain a punch biopsy of the lesions to establish pathological evidence of our diagnosis. The punch biopsies were obtained from the edges of lesions on the left forearm and left medial foot. Light microscopy of the hematoxylin and eosin stained specimens were confirmatory for SJS.

Discussion: Docetaxel is a widely used chemotherapeutic agent in the treatment of breast, lung, prostate and other cancers. The classically known side effects of docetaxel therapy include alopecia, pancytopenia, hepatotoxicity, nausea, vomiting, and diarrhea. A number of popular clinical pharmacology resources do not include Stevens-Johnson syndrome (SJS) as a known complication of docetaxel chemotherapy. However, the current case and the cases written by a handful of other clinicians may provide clinical evidence that docetaxel therapy is associated with the development of this potentially life-threatening dermatologic condition.
An Unmet Need: Assessing Financial Education in Medical Residents

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1. University of Kansas, Internal Medicine
2. Mayo Clinic Arizona, Internal Medicine

**Introduction:** Medical education debt is a growing concern for many new physicians. The AAMC reported in 2016 average indebtedness of $189,000. There remains a lack of current research examining resident physician’s current financial education needs and if they are being met. In this multicenter cross-sectional study we analyze these evolving needs.

**Methods:** An IRB-approved anonymous survey was disseminated to Internal Medicine Program Directors. This instrument assessed resident personal loan burden, financial knowledge, formal financial education, perceived importance of financial education, and retirement savings. Data was obtained from 13 participating programs, with a response rate of 69.6%.

**Results:** Of 403 unique respondents, 80.2% reported medical education debt, with 64.5% of those reporting greater than $200,000. Mean and median indebtedness for respondents were $193,623 and $225,000, respectively. 42.9% reported education debt to be a significant source of stress, with more residents in the top quartile of debt reporting high stress levels (67.2% vs 27%, p <0.0001).

While 59.1% of residents reported saving for retirement. 60.1% of respondents stated that their level of indebtedness strongly influenced their decision to save for retirement in residency.

71.4% of residents said they would use debt counseling if provided, with higher utilization by residents with high loans (89.2%, p = 0.0009). In a concerning trend, residents with high debt (>75%ile) were nearly three times as likely to carry revolving consumer debt as those with low debt. (58% vs 20.3%, p=0.0001). Additionally residents with debt were more likely to have a budget with little flexible discretionary funds (47.8% vs 26%, p = 0.0002).

Finally almost all (95.1%) of residents replied they received little to no finance education in residency (<4 hours) and the majority (91.6%) of residents thought personal finance education should be included in resident curriculum.

**Conclusion:** Education debt is a significant stressor for medical residents. Not only are residents with high debt loads more stressed by their loans, they are more likely to carry other kinds of debt. Residency training currently offers little education in financial matters and almost all residents feel that more should be included. Financial stress is an area not currently addressed in a systematic manner by graduate medical education.

*The authors declares no conflicts of interest.*
The association of 5FU-based chemotherapy with pathological response or survival compared to carbo/taxol with locally resectable esophageal cancer.

Mohammed AL-Jumayli, MD, Saqib Abbasi, MD, Anup Kasi, MD, Anwaar Saeed, MD

Background:
Neoadjuvant chemoradiation followed by esophagectomy is the standard of care in advanced EC. While 5FU based chemoradiation has been a common regimen in the past, its utilization has declined in recent years as the CROSS trial study regimen of carboplatin/paclitaxel has become widely adopted. A prospective evaluation of the CROSS regimen compared to the 5FU based regimen was never performed. The aim of this study is to report our institutional experience with these two chemotherapy regimens. To the best of our knowledge, this is the largest retrospective study comparing the two types of chemotherapy regimens.

Methods:
We performed an IRB-approved retrospective review of a prospectively maintained institutional cancer registry. EC patients who completed trimodality therapy with either carboplatin/paclitaxel or 5FU/platinum were identified and divided into groups based on their chemotherapy regimens. Multivariable logistic regression was used to analyze pathologic complete response (pCR) rates, while the Kaplan–Meier and Cox proportional hazards models were utilized to evaluate DFS and OS. Analytical models were adjusted for age, stage, radiation dose, histology sub-type, and time interval from completion of neoadjuvant therapy to surgery.

Results:
224 patients treated between January of 2007 and July of 2017 were identified. Of this group, 139 (62%) had received Carbo/Taxol, while 85 (37%) had received 5FU/platinum. There was no increase in the odds of pCR with 5FU based chemo compared to CROSS regimen (OR = 2.68, P = 0.671). Furthermore, the OS and DFS of 159 patients (80 5FU/platinum, 77 carbo/taxol) with median follow up of ~ 5 yrs were not statistically different with HR 1.08 (0.6-1.7) and P value 0.71.

Conclusions:
Neoadjuvant chemoradiation with 5FU/platinum in resectable EC is not associated with higher rates of pCR, DFS and OS compared to the CROSS regimen of carbo/taxol. Those findings will need to be validated in a larger cohort.
Hypoxic preconditioning suppresses renal inflammation in ischemic and septic AKI

Rafael Torosyan, Ganeshkumar Rajendran, Michael P. Schonfeld, Pinelopi P. Kapitsinou

Background: Prolyl-hydroxylases (PHDs) have emerged as safeguards of cellular metabolism through their oxygen sensing function, which enables them to regulate the activity of hypoxia-inducible factors (HIF). We previously reported that activation of HIF signaling via pharmacologic inhibition of PHDs (PHI) protects against kidney ischemia reperfusion injury (IRI). Here, we investigated whether HIF activation through exposure to normobaric hypoxia mimics the renoprotection induced by PHI. Using an unbiased metabolomic approach, we identified conserved metabolic responses between these interventions.

Methods: C57BL/6 male mice aged 8-10 weeks were subjected to normobaric hypoxia (8% O_2) for 48 hours prior to induction of AKI via unilateral renal artery clamping (IRI) or LPS administration. Untargeted metabolomic screening by a GC/MS and LC/MS based platform was performed in sera from mice treated with PHI or exposed to acute hypoxia.

Results: Pre-ischemic exposure to normobaric hypoxia attenuated kidney injury at day 3 post IRI as indicated by improved kidney histological scores and a 2.3-fold reduction of Kim1 mRNA levels in kidney homogenates compared to normoxic controls (n=7-8, P=0.0002). Furthermore, hypoxic preconditioning suppressed the expression of proinflammatory genes Vcam1 and Tnfa by 2.6-fold (n=7-8, P<0.0001) and diminished the infiltration of Ly6B.2+ve cells in injured kidneys by 47% (P<0.0001) compared to controls. In a septic model of AKI induced by LPS, hypoxic preconditioning suppressed the transcripts of Tnfa and Il-6 by 2.3- and 5-fold respectively (Day 1 post LPS, n= 11-14; p < 0.009). Comparative untargeted metabolomic analysis revealed that exposure to hypoxia and pharmacologic PHD inhibition led to significantly overlapping alterations in serum metabolome. For instance, serum levels of α-ketoglutarate, a TCA cycle metabolite, were reduced by 60% in the setting of hypoxic preconditioning (n=8, P<0.0001) and by 36% with PHD inhibition (n=8, P = 0.004) compared to their corresponding controls.

Conclusion: Our data demonstrate that exposure to normobaric hypoxia attenuates kidney inflammation in both IRI- and sepsis-induced AKI. Furthermore, PHD inhibition induced by exposure to hypoxia or pharmacologic means lead to metabolic reprogramming, which may play a critical role in regulating inflammatory responses in the context of AKI.
Initial False Positive Episodes and Outcomes of Programming Changes with a Novel Implantable Loop Recorder

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Introduction:
Management of voluminous data from implantable cardiac devices is resource intensive. False positive events can be especially problematic with implantable loop recorders (ILRs). We sought to describe our early experience with a novel ILR.

Hypothesis:
Sensitivity adjustment to <=0.10 mV may reduce false positive ILR detection of bradycardia/pauses.

Methods:
A single center retrospective study was performed in patients with the Abbott Confirm RX ILR. Tachycardia, atrial fibrillation (AF), bradycardia, and pause events were reviewed to determine whether they were true or false positives.

Results:
The study included 13 patients (age 67 ±15.8 years, 62% men). The reasons for implant included: AF (n=7, 54%), syncope(n=3, 23%), palpitations (n=2, 15%), and stroke (n=1, 8%). The median follow-up duration was 3.1 months (IQR 1.3-4.4 months). There was no change in serial R waves during mean follow-up of 0.58 months (pre 0.62±0.22 mV, post 0.63±0.22 mV, p=0.52). Tachycardia detection occurred in 6 patients (46%), with only 1 patient having a false positive episode. AF detection occurred in 8 patients (62%), with only 2 patients having true AF episodes. Pause/bradycardia episodes were detected in 5 patients (39%), with false positive episodes in 4 patients. There was no difference in R waves at implant among patients with and without false positive bradycardia/pauses episodes (0.66 ±0.27 vs. 0.44 ± 0.28 mV, p=0.21). The max sensitivity was higher among patients with than without false positive bradycardia/pause episodes (0.14 ±0.01, 0.07 ±0.02 mV, p<0.0001). No patients programmed to sensitivity <=0.10 mV had false positive bradycardia/pause episodes. The sensitivity was adjusted to <=0.10 mV in 3 of 4 patients with false positive bradycardia/pause episodes which eliminated future false positive episodes and did not result in false positive tachycardia/AF episodes. The overall mean monthly rate of false positive bradycardia/pause events was reduced from 387 events/month to zero in these patients.

Conclusion:
Programming the novel ILR to a sensitivity of <=0.10 mV resulted in a marked reduction in false positive bradycardia/pause episodes without an increase in false positive tachycardia/AF episodes.
Clinical and biomarker results from Phase I/II study of PI3K inhibitor BYL719 (Alpelisib) plus Nab-paclitaxel in HER2 negative metastatic breast cancer

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Introduction

Activation of Phosphatidylinositol-3-kinase (PI3K) pathway may confer resistance to taxanes and in preclinical models concomitant inhibition of the PI3K pathway enhances efficacy of taxanes. Alpelisib is a potent oral, class I inhibitor of PI3K alpha isoforms with antitumor activity in tumors that harbor PI3KCA mutations.

Methods

Eligible patients had HER-2 negative MBC with any number of prior chemotherapy. Phase I was 3+3 dose-escalation design with three dose levels of alpelisib (250mg, 300mg, 350mg) PO daily (D1-28) and nab-Paclitaxel (nP) 100 mg/m²D 1, 8, 15 every 28 days. Phase II was designed according to Simon’s Minimax design. Aims were to determine 1) Recommended Phase II Dose (RPTD), 2) Objective Response Rate (ORR), 3) Progression-free survival (PFS). PIK3CA activating mutations in tumor and circulating tumor DNA (ctDNA) were assessed using next-generation sequencing.

Results

There were no DLTs in the three dose levels of phase I (n=10). 33 patients were treated in phase II on the RPTD (Alpelisib 350mg PO daily plus nP 100mg/m² D1,8,15 every 28 days). Median age was 55 years; 30% had TNBC. 84% had visceral disease, 74% had received prior chemotherapy for MBC, 84% had received prior taxane. Hyperglycemia (G3:29%, G4:0%), neutropenia (G3:24%, G4:7%), anemia (G3:12%, G4:0%), diarrhea (G3:7%, G4:0%) were the most common grade 3/4 adverse events. In 42 patients evaluable for response, ORR was 57% (24/42) (CR=2, PR=22) and an additional 21% demonstrated SD ≥16wks. ORR for patients treated at RPTD was 55% (18/33). Median PFS is 9 months (95% CI: 6-12). Mean duration of treatment is 8 months(2-26 months). 40%(17/42) demonstrated tissue and/or ctDNA PIK3CA mutation (ctDNA/tissue concordance=70%). Compared to patients without PIK3CA mutation, those with PIK3CA mutation demonstrated significantly better PFS (7 vs 13 months HR=0.39, p=0.03).

Conclusion:

Alpelisib and nP combination shows encouraging efficacy with manageable toxicity in HER2 negative MBC. Efficacy was especially robust in patients with PIK3CA mutation (ORR=65%, PFS=13months). Randomized trial of this combination in PIK3CA mutation selected patients is warranted.

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Impact of germline \textit{BRCA} mutation status on survival in women with metastatic triple negative breast cancer

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\textbf{Background:} 15-20\% of patients with triple negative breast cancer (TNBC) harbor deleterious germline (g) \textit{BRCA}1/2 mutations. Recent data suggests that in metastatic TNBC (mTNBC) g\textit{BRCA}1/2 mutations are associated with response to PARP inhibitors (PARPi) and platinum chemotherapy. However, diagnosis of mTNBC is associated with short overall survival (OS) with no biomarkers that can identify mTNBC patients with better prognosis.

\textbf{Methods:} 643 patients with TNBC were enrolled in an IRB approved multisite prospective registry between 2011-2018. Clinical, demographic, and treatment information was collected as well as recurrence and survival. 100/643 patients had metastatic breast cancer (de-novo stage IV disease or metastatic recurrence). OS (time of diagnosis of mTNBC to death) was estimated according to the Kaplan-Meier method and compared among groups by log-rank test.

\textbf{Results:} For the 100 mTNBC patients, the median age at diagnosis of metastatic disease was 55 years, 17\% were African American, 20\% were de-novo and 80\% had relapsed. 84\% had visceral disease, 12\% with bone-only, and 4\% with lymph node only. Metastatic treatment: 87\% received chemotherapy, 7\% received radiation only and 6\% didn’t receive treatment. Among de-novo, 35\% (7/20) had breast surgery to remove primary tumor during their metastatic treatment. For all 100 patients, 12\% had g\textit{BRCA} mutation; 72\% had no mutation; and 16\% had unknown status. When compared with non-carriers, carriers were younger at metastatic diagnosis (median age 49 vs. 57 years, \(p=0.02\)). Median follow-up is 31 months, median OS for all patients is 21 months (95\% CI 13-23 months). Median OS is 18 months (95\% CI 15-27 months) for non-carriers and has not yet been reached for g\textit{BRCA} mutation carriers (\(p=0.023\)). On Cox-regression analysis, g\textit{BRCA} carrier status was associated with reduced risk of death (HR=0.33; 95\%CI [0.12-0.91], \(p=0.033\)).

\textbf{Conclusions:} mTNBC patients with g\textit{BRCA} have a clinically significant improved OS at 3 years compared to patients without g\textit{BRCA} (3-year OS of 63\% vs 28\%). Outcomes of g\textit{BRCA} mutation associated mTNBC are likely to be improved with availability of PARPi. Patients with g\textit{BRCA} are at risk for second breast/ovarian cancers, so there is need for further research regarding the role of prophylactic surgeries mTNBC with g\textit{BRCA} mutation.

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Influence of older age on triple negative breast cancer (TNBC) clinical-pathological characteristics and outcomes

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**Background:** The impact of age at diagnosis on clinical presentation and treatment delivery for triple negative breast cancer (TNBC) is unclear. Utilizing data from a prospective registry, the aim of this study was to further elucidate the age-dependent correlation between TNBC clinical-pathological features, and the implications of age-bias on treatment delivery and prognosis.

**Methods:** 480 subjects with stage I-III TNBC were enrolled in an IRB approved multisite prospective registry between 2011 and 2016. Clinical, demographic, treatment information was collected and patients were followed for recurrence and survival. Patients were categorized as older (>60 years) or younger groups (<60 years). Recurrence free survival (RFS) and overall survival (OS) were estimated according to the Kaplan-Meier method and compared among groups by log-rank test.

**Results:** 145 (30%) of 480 TNBC patients were older (> 60 years) at time of diagnosis. Compared to younger patients, older patients were more likely to present with screen detected vs symptomatic cancer (47% vs 25% p=<0.001), more likely to have node negative cancer (71% vs 61% p=0.030), stage I disease (42% vs 28% p=0.003), and low level (1-10%) ER or PR positivity (19% vs 12% p=0.046). Compared to the younger patients, older patients were less likely to have a BRCA1/2 mutation (6% vs 23% p=0.0002) but more likely to have a prior history of hormone positive breast cancer (7% vs 1% p=0.0002). Compared to younger counterparts, older patients were less likely to receive neo/adjuvant chemotherapy (93% vs 99% p=0.0006), and less likely to receive > 4 cycles of neo/adjuvant chemotherapy (61% vs 78%, p=0.0003). Three year RFS for the entire cohort was 80% and was identical for older and younger patients at 80%. Three year OS for the entire cohort was 87% and was similar for older and younger patients. On multivariable analysis only tumor size and nodal status significantly impacted RFS.

**Conclusions:** A significant fraction (30%) of TNBC patients are older (> 60 years) at time of diagnosis. Despite presenting a with more favorable disease stage, older TNBC patients did not demonstrate better outcomes compared to the higher risk younger patients. The underlying reasons for this observation may be tumor biology differences between older and younger TNBC patients or perhaps could be related to underutilization of appropriate systemic chemotherapy (39% of older patients received < 4 cycles of chemotherapy). Further studies are warranted on this subject.

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