Lister Introduces Antisepsis, c. 1952

By Robert A. Thom

Joseph Lister (1827-1912) was a British surgeon who revolutionized the practice of surgery and medicine by introducing the use of carbolic acid (phenol) as an antiseptic. In this painting, Dr. Lister is revealing a boy's well-healed, non-infected wound, which had been treated with carbolic acid for six weeks following surgery on a compound leg fracture. Dr. Lister’s contributions led to reductions in post-operative infection and mortality and he is now referred to as the “father of modern surgery.”
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A 61 year-old female with a history of advanced HIV disease and chronic hepatitis B presented with painful oral ulcers. She denied fevers, chills, or rashes, and the review of systems was otherwise unremarkable. On admission, she was afebrile (temperature 36.8°C) with blood pressure 160/86 mmHg and heart rate 93 per minute. Examination of the oropharynx revealed oral thrush and multiple clean-based ulcers on the tongue and hard palate (Fig. 1). Pulmonary, cardiac, abdominal, neurological, skin, and musculoskeletal exams were unremarkable.

Figure 1: Multiple deep, well-demarcated clean-based ulcers with rolled borders on lateral and dorsal tongue. Similar ulcers were also present on the hard palate.

Laboratory analysis revealed a normal white blood cell count of 4.7 x10⁹/L (normal 4-11 x10⁹/L) with low CD4 T-cell count 88 cells/mL³ (normal 365 - 1437 cells/mL³). Hepatic enzymes were mildly elevated (aspartate transaminase 130 U/L [normal range 10-50 U/L], alanine transaminase 78 U/L [normal 10-50 U/L], alkaline phosphatase 152 U/L [normal 40-129 U/L];) total bilirubin and renal function were normal. Plasma HIV RNA was 216 copies/mL, and a hepatitis B PCR was >17 million IU/mL. An admission chest x-ray was
unremarkable. Fungal blood and bacterial blood cultures were negative at 48 hours’ growth. A biopsy of the tongue lesions was obtained (Fig. 2).

**Figure 2**: Hematoxylin and eosin high power stain of biopsy tissue.

**What is your diagnosis?**
A. HIV-associated aphthous ulcers
B. Secondary syphilis
C. Histoplasmosis
D. Herpes simplex virus
E. Oral Kaposi’s sarcoma

**What is the appropriate management?**
A. No treatment, just monitor
B. Single dose IM penicillin G
C. IV Amphotericin
D. IV acyclovir
E. Chemotherapy
**Diagnosis**
Histoplasmosis

**Management**
Initiate 14 days of liposomal amphotericin 3mg/kg daily followed by itraconazole for a year

**Discussion**
This clinical vignette describes an HIV-infected patient with disseminated histoplasmosis presenting as oral ulcers. The biopsy obtained demonstrates histiocytes containing intracellular yeast forms with an artifactual “halo” (due to retraction of the fungal cell cytoplasm from the poorly stained cell wall). Oral histoplasmosis is a non-characteristic presentation for which the diagnosis should be made on biopsy. HIV-associated aphthous ulcers are common in primary HIV-1 infection and are classically shallow ulcers with well-demarcated borders. These may be found on the oral mucosa, esophagus, genitalia or anus. They improve with control of HIV (with antiretroviral therapy), but may recur at subsequent stages particularly in patients with CD4 cell counts <100/mm³. Secondary syphilis, “the great imitator”, may rarely present with painful oral lesions; these are typically superficial ulcerations but occasionally may have a leukoplakia plaque appearance. Biopsy findings are relatively nonspecific and do not show the causative organism. HSV, particularly HSV type 1, is a common cause of oral ulcers in both immunocompetent and immunocompromised individuals. The diagnosis of HSV can be confirmed with the identification of multinucleated giant cells on a Tzanck smear. Treatment with systemic antiviral therapy (e.g. acyclovir) is appropriate. Oral ulceration can be a manifestation of Kaposi’s sarcoma, occurring in up to two-thirds of patients with the malignancy. Lesions mostly occur on the hard palate but can also involve non-keratinized oral mucosal sites. Biopsy reveals neovascularization, whorls of spindle-shaped cells, and leukocyte-predominant inflammation.

Infection with *H. capsulatum* can manifest in a myriad of ways, ranging from asymptomatic self-limited disease to disseminated life-threatening infection. *Histoplasma capsulatum* is a dimorphic fungus endemic in the Mississippi and Ohio River Valleys of the United States, as well as parts of Central America, South America, Asia and Australia. Soil contaminated by bird or bat guano supports dense growth of *H. capsulatum* that can persist many years after initial inoculation. Symptomatic infection is estimated to occur in less than 1% of exposures, although the incidence in HIV-infected patients is much higher at 5-20%, reflecting the impaired cell-mediated immunity of these individuals.

Histoplasmosis was originally described by Dr. Samuel Darling after several workers building the Panama canal presented with disseminated fungal infections. Symptoms of acute pulmonary histoplasmosis include fever, chest pain, dry cough and malaise over a
course of one to two weeks; approximately 6% of patients may also develop rheumatologic manifestations including pericarditis, arthritis, and erythema nodosum.\textsuperscript{1,8} Pulmonary histoplasmosis can also present in a subacute fashion, with symptoms of several months’ duration, or as a chronic illness with fevers, night sweats, weight loss, dyspnea and pulmonary cavitary lesions.\textsuperscript{1} The presence of extrapulmonary disease implies disseminated infection. Symptoms of progressive disseminated histoplasmosis (PDH) including diarrhea, mucosal ulcers, skin lesions, hepatosplenomegaly and lymphadenopathy may be found on physical examination. Laboratory studies may show transaminitis, pancytopenia, and significant elevations in serum lactate dehydrogenase and ferritin.\textsuperscript{7} Conversion from acute focal to PDH occurs in approximately 0.05% cases, although immunosuppression confers a 10-fold higher risk.\textsuperscript{8}

Although acute pulmonary histoplasmosis is mostly self-limiting and does not require treatment, disseminated histoplasmosis should always be treated.\textsuperscript{9} The recommended therapy involves liposomal amphotericin B (3 mg/kg daily) for one to two weeks, followed by oral itraconazole (200 mg three times daily for three days, then 200 mg twice daily). Patients should receive at least one year of itraconazole and have proven biochemical and clinical symptom resolution prior to discontinuation of suppressive therapy. Additionally, HIV-infected individuals should have a CD4 T-cell count >150 cells/mm\textsuperscript{3} and be receiving suppressive antiretroviral therapy prior to discontinuation.\textsuperscript{9}

\textbf{References}

A 19 year old Hispanic male who moved from rural Mexico with his family 6 months ago presents to the ED with right-sided chest pain, cough, and subjective fevers for the past three days. As per his parents, he has an undiagnosed progressive muscular weakness since early childhood and has been wheelchair dependent since the age of 12 years. When you go down to see him in the ED, you notice flaccid paralysis of all four limbs and the ED attending hands you this peculiar looking EKG:

**Describe the EKG**

Borderline sinus tachycardia, the R waves in leads V1 and V2 are tall with an R/S ratio greater than 1, deep and narrow Q waves are seen in leads I, aVL, V5, and V6

**What is the diagnosis?**

A. Myotonic muscular dystrophy
B. Right ventricular hypertrophy
C. Hypertrophic Cardiomyopathy with septal hypertrophy
D. Duchenne’s Muscular Dystrophy
E. Pulmonary embolism
ANSWER

D. Duchenne’s Muscular Dystrophy

DISCUSSION

An EKG with tall R waves in leads V1, V2 and deep Q waves in I, aVL, and V5, V6 in a young male with progressive muscular weakness is a classic finding for Duchenne’s muscular dystrophy (DMD). DMD is an X-linked recessive disorder that leads to progressive and severe weakness of voluntary muscles. It is caused by a mutation in the dystrophin gene that is responsible for creating the dystrophin protein – a key component of the cytoskeleton of muscle fibers. Dilated cardiomyopathy is very commonly seen among patients that survive to adulthood. It is a significant cause of morbidity and mortality in this group.

The tall R waves in leads V1/V2 and the deep Q waves in the lateral leads are thought to reflect myocardial fibrosis in the posterobasal and lateral myocardium of DMD patients. These changes represent disease progression in the myocardium, but they have not been shown to be age-related. Also, the classic ECG changes do not correlate with echocardiographic findings (such as reduced ejection fraction or increased left ventricular size), or with the presence or absence of dilated cardiomyopathy.

The other options are incorrect because: myotonic dystrophy does not cause flaccid paralysis and does not have this characteristic EKG finding (however, it is associated with heart rhythm abnormalities); right ventricular hypertrophy is usually associated with a right axis deviation and right atrial abnormalities; hypertrophic cardiomyopathy with septal hypertrophy has much higher voltages in leads V1/V2; and lastly, the commonest EKG pattern seen with pulmonary embolism is sinus tachycardia with non-specific ST-T changes.

REFERENCES

Inhibiting Plasma Kallikrein for Hereditary Angioedema Prophylaxis


SUMMARY

Hereditary angioedema is a relatively rare genetic disorder of C1 inhibitor deficiency characterized by high baseline levels of complement activation (low serum C3 and C4) and recurrent episodes of the submucosal and subcutaneous tissues. While the resultant inflammation can occur throughout the body, the classical and most acutely concerning episodes present as acute edema of the face, oropharynx, and larynx with possible airway compromise. Most commonly hereditary angioedema is attributable to decreased circulating levels of C1-esterase inhibitor (Type I), however, a minority of cases are attributable to non-functional circulating inhibitor. To date prevention of angioedema flares as well as their acute management has been limited to laborious injection regimens and non-specific anti-inflammatory therapy of limited efficacy. In the present phase Ib study Banerji and colleagues investigated the use of lanadelumab, human monoclonal antibody inhibitor of kallikrein, with a primary efficacy end-point of angioedema episodes over the 6-week study and secondary end-points of safety and high-molecular weight kininogen activation. For this small pilot study, 37 patients were recruited with confirmed biochemical evidence of C1 inhibitor deficiency by C4 level and C1 inhibitor level and randomized to either placebo or 30 mg, 100 mg, 300 mg, or 400 mg subcutaneous injections of lanadelumab on days 1 and 15 of study with regular periodic repeat measurement throughout 90-days of follow-up. Therapeutic levels of complement activation (i.e. comparable to healthy controls) were obtained in the 300 mg and 400 mg populations by day 8 of study and maintained through day 50 of follow-up. During therapeutic levels of lanadelumab, all patients receiving 300 mg were attack free while only 2 of 9 suffered an attack of angioedema in the 400 mg injection cohort as compared compared to 8 of 11 flares in the placebo control. Notably, no severe adverse events were attributed to lanadelumab over the course of follow-up with the majority of side-effects limited to localized injection-site reaction or head-ache with comparable incidences to placebo control.

COMMENTARY

The present phase 1b study provides evidence for the safety and efficacy of the monoclonal antibody lanadelumab in the treatment of hereditary angioedema. Though the limited study population and follow-up period demands concerns towards generalizability, these
should be addressed with the ongoing phase 3 trial DX-2930. Given the current unduly burdensome nature of all current available therapies, the impact of the possible approval of an intermittent subcutaneous therapy on the field of hereditary angioedema therapy and the lives of this patient population cannot be overstated.

[UTSW Link]
Assessing the Risks Associated with MRI in Patients with a Pacemaker or Defibrillator


SUMMARY

The MagnaSafe Registry was a prospective, multi-center study that sought to better characterize the risks of clinical events and device setting changes that occurred in patients with pacemakers or implantable cardioverter-defibrillators (ICDs) who underwent clinically-indicated, non-thoracic MRIs at 1.5 tesla. Patients included in the registry were ≥18 years old and had “non-MRI-conditional” devices (not previously shown to be non-hazardous under specified conditions) from any manufacturer, implanted after 2001. Exclusion criteria included abandoned/inactive leads unable to be interrogated, “MRI-conditional” devices, devices implanted in non-thoracic locations, devices near the end of battery life, and pacing. Devices were interrogated prior to MRI and reprogrammed per protocol. Pacing-dependent patients with ICDs were excluded since not all models allowed for independent inactivation of tachycardia/bradycardia therapies. Devices were then restored to baseline settings and interrogated. In total, 1000 pacemaker and 500 ICD cases were evaluated. Regarding the primary endpoints, there were no deaths, lead failures requiring immediate replacement, or losses of capture among appropriately screened and reprogrammed devices. One ICD that violated protocol could not be interrogated after MRI and had to be immediately replaced. Six cases (0.4%) developed atrial fibrillation/flutter during MRI that were self-limited. Six cases (0.4%) had partial generator electrical reset (loss of patient/device/lead identification information). No full resets occurred. Regarding secondary endpoints, battery voltage decreases, lead thresholds and impedance changes, and P- and R-wave amplitude changes occurred in 0.4-16.4% of cases (see Table 4).

COMMENTARY

Given the risks of injury from magnetic field-induced lead heating as well as device failure in patients with pacemakers and ICDs undergoing MRI, the long-standing recommendation has been to avoid this imaging modality despite clinical indications. Though there are newer devices labeled by the FDA as “MRI-conditional,” millions of people still have devices that do not meet these standards. This study reveals that “non-MRI-conditional” devices that were appropriately screened and reprogrammed per protocol did not result in device or lead failure, and no clinically significant adverse events occurred. Some changes in device settings did occur but were relatively infrequent and were also clinically
inconsequential. Based on these findings, we should consider establishing protocols to screen patients if there are clinical indications for MRI rather than ruling them out entirely.

Unfortunately, thoracic MRIs would still be contraindicated since these were excluded from this study after consultation with the FDA due to higher perceived risks. It is unclear whether the FDA would permit the use of thoracic imaging in future studies. Also, few devices in the studied population had left ventricular leads so these results may not be generalizable to patients with CRT devices. Lastly, higher magnetic field strengths may impact these findings as 3 tesla or even 7 tesla MRIs make their way into more standard clinical use in the future.

UTSW Link
Endocrinology

Bariatric Surgery Versus Intensive Medical Therapy for Diabetes – 5-year Outcomes

Dr. Stephanie Chiao reviewing Schauer et al. NEJM. 2017; 641-651.

Summary
In the Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, diabetes outcomes were compared after bariatric surgery and medical management versus medical management alone. The trial was a 3-arm (gastric bypass and medical therapy vs. sleeve-gastrectomy and medical therapy vs. medical therapy alone) randomized, controlled, nonblinded single center study of 150 subjects with a glycated hemoglobin level more than 7% and a BMI of 27 to 43. Results at 5 years showed that patients in the surgical group were significantly more likely to achieve the primary end point of a glycated hemoglobin less than 6% (29% in the gastric-bypass group, 23% in the sleeve-gastrectomy group, and 5% in the medical-therapy group). Compared with the medical-therapy group, subjects in the surgical groups also had significant improvements in BMI, waist circumference, triglycerides, HDL, urinary albumin-to-creatinine ratio quality of life measures, while on significantly fewer diabetes, hyperlipidemia, and hypertension medications. Adverse surgical events included 5 subsequent re-operations, 1 fatal MI in the medical-therapy group, 1 stroke in the sleeve-gastrectomy group, and significantly more mild anemia in the surgical groups.

Commentary
The study showed that the addition of bariatric surgery to medical management was effective in improving a number of different outcomes, including glycemic control, weight reduction, cardiovascular risk factors, renal outcomes, and quality of life. These findings are consistent with a number of prior observational and randomized studies, and further add to the body of literature in a few key ways. First, the study included patients with mild obesity (BMI 27-34) unlike most prior studies, which limited eligibility to those with severe obesity. Therefore, the benefits of bariatric surgery may be extended to those with only mild obesity. Second, the study had a longer follow-up period, providing further evidence of the durability of positive outcomes after bariatric surgery. While the study overall is encouraging for bariatric surgery, it is important to note the small sample size, which made the study unable to detect differences in cardiovascular and other clinical endpoints, such as incidence of MI, stroke or death. Furthermore, the medical therapy alone side also had decreased medication compliance, which may have increased the efficacy gap between treatment arms.
The AGA’s Fecal Microbiota Transplantation National Registry: An Important Step Towards Understanding Risks and Benefits of Microbiota Therapeutics


**Summary**

Fecal microbiota transplantation (FMT) has become one of the most effective therapies for recurrent *Clostridium difficile* infection. However, as this paper outlines, there is a void of clinical trials and data to evaluate in a standardized manner the efficacy and safety of FMT. In order to address this void, the American Gastroenterology Association has created a FMT National Registry that encompass both pediatric and adult data, with the goal of 4000 patients at 75 clinical sites across the US. Registered patients will be followed for shorter (<30 days) or longer (2-10 yrs) periods. In order to determine the significance of adverse events, a retrospective control group of patients with C. diff treated with antibiotics will be included. This will allow for a direct comparison of the incidence of adverse events between traditional C. diff antibiotic therapy and FMT. Patients and physicians have access to the registry to enter adverse events. The overall goal of the FMT National Registry is to provide data on safety, effectiveness and determine the most effective method of delivery of FMT.

**Commentary**

*Clostridium difficile* infection is a common inpatient complication of antibiotic use with high mortality rates. Fecal microbiota transplantation has become a novel and reportedly effective therapy for recurrent C. diff infections. However the practice of FMT is still not widely adopted at all clinical sites partially due to lack of data that standardizes the method of delivery and sets an expectation on the effectiveness and side effects. Thus the FMT national registry will be able to provide data that hopefully addresses all these knowledge gaps concerning use of FMT in C. diff infections. Unfortunately, the registry will not directly address the use of FMT for other diseases such as colitis since FMT is currently only FDA approved for C. diff infections. Despite this limitation of the study, the data provided by the FMT national registry will hopefully empower a greater number of clinical sites with the tools to appropriately integrate FMT as a viable alternative therapy for C. diff.

[UTSW Link](#)
Changes in the Utilization and Health Among Low-Income Adults After Medicaid Expansion or Expanded Private Insurance


Summary
In 2010, the Affordable Care Act was signed into law and provided states with the option to expand Medicaid or expand private insurance with the use of Medicaid funds to increase the number of insured people. This article evaluates the changes in healthcare for adults in two of the states that chose alternative methods of expansion (Kentucky-Medicaid and Arkansas-private insurance), compared to one state that opted out (Texas). Baseline characteristics for each state were similar in terms of age, and included patients with incomes below 138% of the poverty line. The study utilized self-reported survey data from 2013 to 2015 to assess several primary outcomes including access to primary care, specialty care, medications, the affordability of care, utilization of care in various settings, testing for glucose and cholesterol, quality of care, and overall health. Both Arkansas and Kentucky expanded in 2014, so 2013 data was used as the pre-expansion baseline for the above outcomes. The survey was completed by roughly 1000 unique individuals in each state per year. Survey questions were based on previously tested national and governmental surveys as well as the Oregon Health Insurance Experiment, which looked at the health effects of Medicaid expansion in Oregon in 2008. Study results showed a significant drop in uninsured persons in both Arkansas (42% to 14%) and Kentucky (40% to 9%) by 2015, compared to a small decrease in Texas (39% to 32%). There were statistically significant improvements in many of the primary outcomes assessed including increased access to primary care, fewer skipped medications due to cost, reduced out-of-pocket spending, and a reduction in ED visits. Furthermore, there was increased screening for diabetes, testing for patients with known diabetes, and care for chronic conditions. Lastly, patients rated their quality of care higher with more people rating their overall health as excellent and with fewer people rating their care as “fair/poor.”

Commentary
Currently, there is great uncertainty about the future of healthcare and what coverage options will be available. These issues are particularly important to low income individuals with limited resources. Limitations of the study include small state sampling and low consumer response rate, with only 21% of eligible people completing the survey. This analysis shows the expansion of Medicaid was associated with better subjective measures.
of health for persons below the poverty line compared to no expansion of care. Reversing or taking away this extra coverage may result in negative effects for these health measures, and states should be aware of this before deciding whether to expand or not.

UTSW Link

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean in Expansion States, 2013</th>
<th>Net Change After Expansion (Arkansas and Kentucky vs Texas)¹</th>
<th>P Value</th>
<th>2014 Net Change, vs 2013 % (95% CI)</th>
<th>2015 Net Change, vs 2013 % (95% CI)</th>
<th>P Value</th>
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<td>Uninsured</td>
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<td>Medicaid</td>
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<td>98 (3.6 to 15.9)</td>
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<td>12.5 (4.8 to 23.2)</td>
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<td>Private insurance</td>
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<td>8.0 (0.0 to 15.0)</td>
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<td>Access to care and affordability</td>
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<td>Has a personal physician</td>
<td>56.9</td>
<td>7.7 (-0.6 to 16.0)</td>
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<td>12.1 (5.4 to 18.9)</td>
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<td>Usual source of care¹</td>
<td>80.8</td>
<td>4.0 (-3.2 to 11.1)</td>
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<td>10.8 (3.5 to 18.1)</td>
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<td>Cost-related delay in care</td>
<td>39.5</td>
<td>-4.2 (-10.8 to 2.5)</td>
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<td>-18.2 (-25.4 to -11.1)</td>
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<td>Skipped medication due to cost</td>
<td>39.2</td>
<td>-9.7 (-16.2 to -3.2)</td>
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<td>-11.6 (-17.8 to -5.3)</td>
<td>&lt;.001</td>
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<td>Trouble obtaining primary care appointment</td>
<td>15.7</td>
<td>3.6 (-2.6 to 9.7)</td>
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<td>0.1 (-5.5 to 5.7)</td>
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<td>Trouble obtaining specialist appointment</td>
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<td>1.0 (-3.5 to 5.6)</td>
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<td>ED is usual location of care¹</td>
<td>9.6</td>
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<td>-6.1 (-10.1 to 2.2)</td>
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<td>ED visit because office visit unavailable</td>
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<td>4.7 (-1.1 to 10.6)</td>
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<td>Trouble paying medical bills</td>
<td>42.9</td>
<td>-8.8 (-14.6 to -3.0)</td>
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<td>Annual out-of-pocket medical spending²</td>
<td>$434</td>
<td>-24.2 (-49.8 to 1.4)</td>
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<td>-29.5 (-54.2 to -4.8)</td>
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<td>Utilization</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td>Any office visits in past year</td>
<td>55.5</td>
<td>2.5 (-3.4 to 8.4)</td>
<td>.41</td>
<td>3.0 (-3.8 to 9.7)</td>
<td>.38</td>
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<td>Any ED visits in past year</td>
<td>21.0</td>
<td>-1.9 (-7.6 to 3.8)</td>
<td>.51</td>
<td>-6.0 (-11.7 to 0.3)</td>
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<td>No. office visits in past year</td>
<td>2.80</td>
<td>0.54 (-0.31 to 1.40)</td>
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<td>0.69 (0.05 to 1.33)</td>
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<td>No. ED visits in past year</td>
<td>1.16</td>
<td>-0.12 (-0.45 to 0.21)</td>
<td>.48</td>
<td>-0.09 (-0.45 to 0.27)</td>
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<td>Any hospitalization in past year</td>
<td>16.9</td>
<td>-1.5 (-6.8 to 3.7)</td>
<td>.57</td>
<td>2.1 (-3.1 to 7.3)</td>
<td>.43</td>
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<tr>
<td>Prevention and quality</td>
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<td>Checkup in past year</td>
<td>45.8</td>
<td>7.0 (-0.6 to 14.5)</td>
<td>.07</td>
<td>16.1 (9.1 to 23.0)</td>
<td>&lt;.001</td>
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<td>Cholesterol check in past year</td>
<td>42.0</td>
<td>-1.0 (-8.0 to 6.0)</td>
<td>.78</td>
<td>1.5 (-5.1 to 8.1)</td>
<td>.66</td>
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<td>Cholesterol check among high-risk patients¹</td>
<td>63.5</td>
<td>2.5 (-7.8 to 12.8)</td>
<td>.63</td>
<td>1.2 (-7.6 to 10.0)</td>
<td>.79</td>
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<td>Glucose check in past year</td>
<td>43.0</td>
<td>2.3 (-5.2 to 9.8)</td>
<td>.54</td>
<td>6.3 (0.0 to 12.6)</td>
<td>.05</td>
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<td>Glucose check among those with diabetes¹</td>
<td>86.2</td>
<td>4.3 (-7.5 to 16.1)</td>
<td>.47</td>
<td>10.7 (1.2 to 20.2)</td>
<td>.03</td>
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<tr>
<td>Regular care for chronic condition¹</td>
<td>65.7</td>
<td>11.6 (2.0 to 21.2)</td>
<td>.02</td>
<td>12.0 (3.1 to 21.0)</td>
<td>.008</td>
<td></td>
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<td>Excellent quality of care</td>
<td>28.1</td>
<td>-2.7 (-10.8 to 5.5)</td>
<td>.52</td>
<td>2.2 (-5.2 to 9.5)</td>
<td>.56</td>
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<tr>
<td>Fair/poor quality of care</td>
<td>19.9</td>
<td>-2.5 (-8.9 to 3.9)</td>
<td>.45</td>
<td>-7.1 (-13.6 to -0.6)</td>
<td>.03</td>
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</tr>
<tr>
<td>Health status</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Excellent self-reported health</td>
<td>12.2</td>
<td>2.4 (-2.3 to 7.1)</td>
<td>.12</td>
<td>4.8 (0.3 to 9.3)</td>
<td>.04</td>
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<tr>
<td>Fair/poor self-reported health</td>
<td>39.6</td>
<td>0.9 (-6.7 to 8.4)</td>
<td>.82</td>
<td>-3.2 (-11.1 to 4.7)</td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>Positive depression screen, PHQ2 score ≥2</td>
<td>47.5</td>
<td>2.0 (-5.5 to 9.4)</td>
<td>.60</td>
<td>-6.9 (-14.6 to 0.8)</td>
<td>.08</td>
<td></td>
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</tbody>
</table>
Geriatrics

Influence of Competing Risks on Estimating the Expected Benefit of Warfarin in Individuals with Atrial Fibrillation Not Currently Taking Anticoagulants: The Anticoagulation and Risk Factors in Atrial Fibrillation Study


Summary

In this cohort study, the authors evaluate the impact of competing risks (such as death from a co-morbid condition) on the estimated benefit from warfarin anticoagulation in atrial fibrillation (AF) using longitudinal data from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) cohort of 13,559 adult patients with nonvalvular AF in the Kaiser Permanente health system. The primary outcome was thromboembolism, including ischemic stroke and systemic arterial embolism. Competing risk events were defined as deaths from any nonthromboembolic cause. Patients were more likely to be on warfarin if they were between the ages of 65 and 74 and had traditional AF stroke risk factors, corresponding to higher CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>-VASc, and ATRIA scores.

Over a 7 year follow up period, the risk of thromboembolism was lower with warfarin: 1.3 events per 100 person years compared to 2.1 events per 100 person years in the non-warfarin group, with adjusted cause specific hazard ratio (HR) of 0.57 (95% CI = 0.50–0.65). However, during the full follow up period, 32.5% of patients (n=4,414) also experienced competing death events. Using a cause specific model, these patients remained in the analysis and were treated as though they were at risk for thromboembolism, even though the outcome was no longer possible. When the authors used a subdistribution hazards model to account for the fact that patients who suffered a competing risk death could no longer experience the primary outcome of thromboembolism, the benefit of warfarin was decreased (HR = 0.87, 95% CI = 0.77–0.99). When analysis was limited to a 1 year follow up period, there were fewer competing death events, and the hazard ratio for thromboembolism with warfarin was not statistically significantly different when adjusted for competing risk events. The attenuation of the warfarin benefit with adjustment for competing risk of death was greatest in patients over the age of 85 (HR = 0.62 with 95% CI = 0.53-0.72 without adjustment, HR = 0.91 with 95% CI = 0.63 – 1.31 with adjustment).
**COMMENTARY**

Anticoagulation is known to reduce the risk of ischemic stroke in AF, but prior to this study, it was not known how the increasing prevalence of death unrelated to stroke in older adults might affect the potential benefit of anticoagulation. The authors use a multivariate model incorporating the competing risk of death from nonthromboembolic causes and find that there is no difference in the benefit of warfarin in reducing the risk of thromboembolic events at 1 year, but that the benefit is markedly attenuated at 7 years when accounting for competing death events. The reduction in benefit from warfarin over time when accounting for competing death events is most pronounced in adults over the age of 85. These findings highlight the importance of considering not only stroke risk factors but also risk of death unrelated to stroke when weighing the risks and benefits of anticoagulation for AF in older adults.

**UTSW Link**

<table>
<thead>
<tr>
<th></th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
<th>7 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in mortality (rate/100 person-years)</td>
<td>1.3</td>
<td>2.2</td>
<td>2.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Difference in VTE (rate/100 person-years)</td>
<td>1.1</td>
<td>0.8</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>0.55 (0.43-0.71)</td>
<td>0.58 (0.49-0.73)</td>
<td>0.56 (0.49-0.64)</td>
<td>0.57 (0.50-0.65)</td>
</tr>
<tr>
<td>Adjusted HR accounting for competing deaths (95% CI)</td>
<td>0.59 (0.46-0.75)</td>
<td>0.73 (0.62-0.85)</td>
<td>0.81 (0.71-0.93)</td>
<td>0.87 (0.77-0.99)</td>
</tr>
</tbody>
</table>

**Table A:** Differences in mortality & VTE rates = rate in no warfarin group – rate in warfarin group. Hazard ratios reflect the risk of the primary outcome of VTE in the warfarin group. Reference group for hazard ratios is the no warfarin group.

In addition to regular faculty mentor Dr. Tom Dalton, special thanks to Dr. Anil Makam for his assistance with the interpretation of the article and creation of this table.
SUMMARY

This article presents the final analysis of the IRIS trial, providing 10-year follow-up data on the trial that led to imatinib approval for use in chronic myeloid leukemia (CML). IRIS was initially an open-label, multicenter trial that randomly assigned chronic-phase CML patients to imatinib versus interferon alfa plus cytarabine. Owing to success in the imatinib group, the trial closed early, allowing interferon-alfa patients to crossover to imatinib and the imatinib patients were allowed to continue on therapy. However, as a result of high rates of cross-over the treatment-specific survival data is not robust and does not allow for long term survival comparisons to be made. Additionally, about 20% of the patients have unknown survival status at the ten-year analysis. Accounting for this, the authors estimate the ten-year survival is between 64.4% and 84.4% (depending on survival assumptions for the missing data). The high rate of crossover prevents a direct comparison of survival at ten years between imatinib and interferon alfa, however those receiving first-line therapy with imatinib have a hazard ratio of 0.74, indicating a 26% lower risk of death. Importantly, no new toxicities were discovered in the ten-year follow-up that had not been reported in the five-year analysis. The most frequent adverse events were abdominal pain (9.3%). 7.1% of patients receiving imatinib had a cardiac serious event, however this figure also includes events unrelated to therapy.

COMMENTARY

The development and success of imatinib undoubtedly changed the field of cancer therapy at a foundational level. IRIS was one of the first trials to demonstrate enhanced survival using therapy targeted specifically at the product of a driver mutation (BCR-ABL1). Since IRIS, two other agents, nilotinib and dasatanib, have also been approved as first line therapy in chronic phase CML. Nilotinib has since been proven to be superior to imatinib for obtaining a major molecular response, complete cytogenetic response, time to progression to accelerated phase, and time to progression to blast crisis. However, the current article’s value is in demonstrating the extreme safety of long term use of imatinib. Additionally, imatinib is now generic, making it a good and well tolerated treatment option for our Parkland patients with CML.

UTSW Link
Variation in Physician Spending and Association with Patient Outcomes


SUMMARY

The bundling of Medicare payments as well as reporting of 30 day mortality and readmission rates represent a significant national initiative to both reign in health care costs and improve quality. While it is well known that inpatient spending varies widely across the United States, less is known about the variation between physicians within the same hospital. The authors of this study sought the answer to three separate but related questions. How much variation exits between physician spending at the same hospital? Are there certain physician characteristics that are associated with increased inpatient spending? What is the relationship between physician level spending and 30 day mortality and readmissions?

Using Medicare data from 2011-2014, the authors identified over 1,000,000 hospitalizations for Medicare beneficiaries, treated by nearly 75,000 different hospitalists and general internists, at over 5,000 different hospitals. Physician level spending was measured by evaluating Medicare Part B spending per hospitalization (while adjusting for patient characteristics). After adjusting for differences in hospitals, the authors were able to calculate the degree to which individual physicians within the same hospital contributed to the variance in spending.

Wide variations existed in Part B Medicare spending across the United States during the years queried. Approximately 10% of this variance was attributable to differences in physicians within the same hospital while only 7% was attributable to hospital level variation. Physicians in the lowest quartile of adjusted Part B spending spent on average $743 per hospitalization versus $1055 for those in the highest quartile. Those in the highest quartile were slightly older and more likely to be female although these differences were small. There was no association between physician spending within the same hospital and 30 day mortality (adjusted OR of 1.00) or 30 day readmission rate (adjusted OR of 1.00).
COMMENTARY

Much of the effort to date to reduce Medicare costs and improve quality has been directed at the hospital level. The author’s finding that a greater deal in spending variation was attributable to physicians within the same hospital rather than between hospitals emphasizes the need to focus on improving efficient utilization at the physician level. The passage of the Medicare Access and Children’s Health Insurance Program Reauthorization Act (MARCA) in 2015 acknowledges the need to address this. Equally notable was the finding that physicians who spent more than their colleagues within the same hospital did not have any improvement in mortality of 30 day readmission rate.

UTSW Link
Risk of Acute Kidney Injury in Patients on Concomitant Vancomycin and Piperacillin-Tazobactam Compared to Those on Vancomycin and Cefepime

Dr. Carolina De La Flor reviewing Navalkele, B et al. CID. 2017 Jan 17;64:116-23.

SUMMARY

Methods:

- Retrospective, matched, cohort-study that compared the incidence of AKI among patients on vancomycin+piperacillin-tazobactam (VPT) to those on vancomycin+cefepime (VC). Subjects were matched based on intensive care unit status, severity of sepsis, duration of therapy, vancomycin dose, and number of simultaneous nephrotoxins.
- Patients were eligible if they were on combination therapy for ≥48h. Patients were excluded if baseline Cr was >1.2mg/dL or if they were on renal replacement therapy.

Results:

- 558 patients (279 VPT-VC pairs) were included
- 81 patients in the VPT group developed AKI vs 31 in the VC group (29% vs 11.1%; HR=4; 95% CI, 2.6-6.2; p<.001) per RIFLE criteria (Figure 1). Rates of AKI were also higher per AKIN criteria and vancomycin consensus guidelines. Multivariate analysis: VPT was independently associated with RIFLE-defined AKI (HR=4.3; 95% CI, 2.7-6.7; p<.001).
- The onset of AKI was 3 days (IQR, 2-5 days) in the VPT group vs 5 days (IQR, 3-7 days) in the VC group (p<.0001)
- The Kaplan-Meier analysis showed that the daily rate of AKI remained steadily higher in the VPT arm during the first week of therapy (Figure 2)
- There was no difference in mortality between the groups
- When the vancomycin trough was divided into 3 ascending categories, there was no association with AKI in the VPT group. In the VC group, there was a direct relationship between vancomycin trough and AKI (Figure 3)

COMMENTARY

VPT was associated with a 4-fold increased risk of AKI compared to VC. Moreover, in the VPT group, the onset of AKI was more rapid, the daily rate of AKI development remained higher, and the median length of stay was longer. Finally, the lack of association of vancomycin troughs with nephrotoxicity in patients receiving VPT further supports the study hypothesis that the VPT combination has higher nephrotoxicity risks. The results of this study help advance the discussion on this controversial topic beyond prior studies that were less well-matched. Therefore, opportune antibiotic de-escalation remains of the utmost importance and would likely diminish AKI risk.

UTSW Link
Figure 1: Comparison of cumulative rates of AKI in patients receiving VPT vs VC

Figure 2: Kaplan-Meier survival analysis for AKI as a function of treatment group

Figure 3: AKI rates as a function of vancomycin troughs
Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes


Summary

Sodium glucose transporter 2 (SGLT2) inhibitors work by reducing glucose reabsorption in the tubule, leading to increased glucose wasting in the urine and decreased serum glucose levels. This class has received a lot of attention since the publication of the EMPA-REG study which described an impressive cardiovascular benefit in patients with diabetes and high cardiovascular risk who were treated with the SGLT2 inhibitor, empagliflozin, compared to placebo. This article is a follow up which reports the secondary objective of the EMPA-REG trial to elucidate the effects of empagliflozin on renal outcomes. It was hypothesized that by decreasing glycosylation of hemoglobin, the SGLT2 inhibitors may have renal protective effects.

7000 patients with diabetes and at high risk of cardiovascular disease were randomly assigned to receive empagliflozin or placebo and were followed for a median of 3.1 years. Progression to macroalbuminuria occurred in 11.2% of the empagliflozin group and 16.2% of the placebo group [HR 0.62(0.54-0.97)]. Doubling of serum creatinine occurred in 1.5% of the empagliflozin group and 2.6% of the placebo group [HR 0.56(0.39-0.79)]. Initiation of dialysis occurred in 0.3% of the empagliflozin group and 0.6% of the placebo group [HR 0.45(0.21-0.97)]. All confidences were statistically significant with p<0.05

Commentary

This study found that empagliflozin had improved renal outcomes, defined by several different metrics, compared to placebo in patients with diabetes and at high risk of cardiovascular events. The authors hypothesize that increased glucose delivery to the macula densa may lead to renal vascular modulation and to a decrease in hyperfiltration. Previous studies have shown decreased intraglomerular pressures in patients treated with empagliflozin. Interestingly, this study showed a transient decrease in eGFR shortly after initiation of empagliflozin, similar to the transient drop seen after initiation of RAAS blockade, lending some credence to the hypothesis that decreased glomerular pressures are leading to improved renal protection. Our current approach to renal protection in patients with diabetes is improved glycemic control and RAAS blockade. If future studies
are congruent with this one, SGLT2 inhibition may also become a mainstay of treatment for prevention of kidney disease.

**UTSW Link**

### Table A: Renal Outcomes

<table>
<thead>
<tr>
<th>Renal Outcome Measure</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident or worsening nephropathy or cardiovascular death</td>
<td>675/4170 (16.2)</td>
<td>497/2102 (23.6)</td>
<td>0.41 (0.35–0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
<td>325/4124 (11.7)</td>
<td>388/2061 (13.8)</td>
<td>0.30 (0.23–0.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Progression to macroadmubinuria</td>
<td>459/4091 (11.2)</td>
<td>330/2033 (16.2)</td>
<td>0.62 (0.54–0.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m²</td>
<td>70/4645 (1.5)</td>
<td>80/2233 (2.6)</td>
<td>0.56 (0.39–0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initiation of renal-replacement therapy</td>
<td>13/4687 (0.3)</td>
<td>14/2333 (0.6)</td>
<td>0.45 (0.21–0.97)</td>
<td>0.04</td>
</tr>
<tr>
<td>Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m², initiation of renal-replacement therapy, or death from renal disease</td>
<td>81/4645 (1.7)</td>
<td>71/2233 (3.1)</td>
<td>0.54 (0.40–0.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident albuminuria in patients with a normal albumin level at baseline</td>
<td>1430/2779 (51.5)</td>
<td>703/1374 (51.2)</td>
<td>0.95 (0.87–1.04)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Empagliflozin better  Placebo worse
Palliative Care

ICU Deaths in Patients With Advanced Cancer: Reasonable Criteria to Decrease Potentially Inappropriate Admissions and Lack of Benefit of Advance Planning Discussions


Summary

The objective of this study was to develop appropriate and effective criteria for ICU admission in patients with advanced cancer. Their goal was to ensure that patients admitted to the ICU would benefit from the intensive and invasive therapies provided in the ICU setting. This was a retrospective chart review that studied patients with advanced cancer that died in the ICU between 2005 and 2010 at the University of Tennessee Health Science Center-VA Medical Center. Before reviewing the charts, a selected group of oncologists, intensive care specialists, palliative care physicians, and nursing staff developed 4 criteria for appropriate admission to the ICU. The criteria included; 1) a postprocedure complication, 2) a recent cancer diagnosis of < 1 month, 3) ECOG performance status of 0 or 1 prior to admission, and 4) a life expectancy of more than 6 months. The charts were reviewed to identify the number of patients that satisfied the proposed criteria.

Four hundred twenty one patients died in the ICU between 2005 and 2010, of these patients, 52 were patients with advanced, incurable cancer. Of these 52 patients admitted to the ICU, 14 (27%) of patients were diagnosed with cancer 1 month or less prior to admission, 21 (40%) patients had ECOG performance status of 0 or 1, 14 (27%) patients had life expectancy of more than 6 months, and 8 (15%) patients were admitted for postprocedure complications. Overall, only 19 (37%) of patients did not meet the proposed ICU admission criteria.

Commentary

The optimization of end of life care in patients with cancer continues to be a challenge. Far too often, patients with cancer spend their last days in the hospital, particularly in the ICU. In many cases, aggressive care and invasive procedures produce more harm than benefit in this vulnerable group. Identifying which patients would benefit the most from ICU level of care is difficult. This study set out to identify criteria for ICU admission for patients with advanced cancer. Based on the group’s findings, institution of their admission criteria would have prevented 37% of inappropriate ICU admissions, thereby avoiding ineffective, aggressive treatment, and delaying appropriate palliative care interventions. At the same
time, a diagnosis of advanced cancer should not prevent a patient from receiving life-saving treatments that are potentially beneficial. Further studies are needed to prospectively investigate the effectiveness of these ICU admission criteria. Physicians would also have to tackle the challenge of addressing patients who request aggressive ICU level of care who do not meet the admission criteria.

UTSW Link
Implementation of Lung Cancer Screening in the Veterans Health Administration


Summary

The United States Preventative Task Force recommended routine lung cancer screening beginning in 2013 based on data from the National Lung Screening Trial (NLST), which demonstrated a mortality reduction of 3 deaths per 1000 high-risk individuals screened. Kissinger et al. draw on data from eight academic Veterans Health Administration centers in order to describe challenges and procedures for widespread implementation of screening in a primary care setting. In all, 93,000 patients met basic eligibility criteria, of whom 18,000 met smoking history criteria and 2,100 underwent low-dose CT for lung cancer screening. A total of 59.7% were positive for nodules or possible lung cancer, though individual site percentages ranged from 30% to 85%. Lung cancer was confirmed in 31 total patients (1.5%). Of those screened, 857 (40.7%) had at least one incidental finding, the most common of which were emphysema, pulmonary disease, and coronary artery disease.

The authors identified a number of logistical challenges to implementing primary lung cancer screening in a large VA primary care setting. First, in the VA system as a whole, nearly 900,000 veterans would be candidates for annual screening, putting a tremendous burden on primary care and radiology departments to meet this need and manage incidental findings. Patients would be exposed to increased radiation, exams, and potential stress related to false positive results.

Commentary

Despite the small mortality benefit found in the NLST, similar studies conducted in Europe have not demonstrated benefit to routine screening of high-risk populations. The Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) offered low confidence that the benefits of screening outweigh the risks due to the potential harm caused by radiation, high rates of false positives, potential for harm caused by invasive workup of nodules and variability in radiology readings. The analysis presented by Kissinger, et al. provides an insight into the challenges in implementing screening
particularly in an elderly, high-risk population. The low rate of lung-cancer detection, high false-positivity rate and low uptake of screening in the VA population presented here are indicative of the challenges and potential harms of screening implementation and encourages further critical consideration of the appropriateness of similar such programs.

UTSW Link
Risk of Active Tuberculosis in Patients with Cancer: A systematic Review and Meta-Analysis

Dr. Carolina De La Flor reviewing Cheng, MP et al. CID. 2017 March 1;64:635-44.

SUMMARY

Methods:

- Systematic review and meta-analysis to evaluate the incidence and relative risk of active tuberculosis in patients with cancer
- Medline, Medline In-Process, EMBASE, PubMed, the Cochrane Database of Systematic Reviews, Cancerlit, and Web of Science were searched between 1970 to December 1st 2015
- Studies that reported new tuberculosis (TB) (bacteriologically, pathologically or clinically diagnosed) at the time or after detection of cancer (pathologically diagnosed) were included
- Cumulative incidence rate/100 000 population (CIR) of new tuberculosis cases in cancer patients and comparative incidence rate ratios (IRR) from each country to the general population to the country were used

Results:

- 23 studies reporting 593 cases of tuberculosis in 324041 patients were included. Patients from 6 US studies accounted for 98% (n=317243) of all study subjects
- Meta-analysis of the 6 US studies: CIR of active TB decreased by 3-fold and 6-fold in hematologic and solid cancers, respectively, before and after 1980. IRR remained similar in hematologic cancers (21 vs 26) and decreased in solid cancers (19 vs 7). After 1980, risk of TB was highest in hematologic cancers (CIR 219/100 000 population; IRR=26), followed by head and neck (143; 16), lung (83; 9), and was lowest in breast and other solid cancers (40; 4).

COMMENTARY

This study confirms that although the cumulative incidence of active TB has declined since 1980 among patients with cancer, the relative incidence of TB remains increased among patients with cancer compared to those without cancer (and varies by cancer type). The US-born population living with hematologic, head and neck, and lung cancer has a 9-fold
greater rate of developing active TB compared to those without cancer. Targeted LTBI screening and therapy in these patients is of the utmost importance. Other solid tumors such as breast cancer should not be screened for LTBI due to the associated risk of hepatotoxicity of therapy. However foreign-born patients with breast and other cancers should be screened and treated. Since 98% of the patients included in this study were from the US, the results are generalizable only to low tuberculosis-incidence regions.

**UTSW Link**

**Figure 1:** CIR of TB by cancer type in the US population between 1950 and 2004. Symbols represent the CIR for each study, arrows show the beginning and end of the inclusion period, and the dashed lines represent the US TB CIR.
Pulmonary and Critical Care

Reevaluation of Diagnosis in Adults with Physician-Diagnosed Asthma

Dr. Sarah Kiani reviewing Shawn D. Aaron et al. JAMA. January 17, 2017 Volume 317, Number 3, pages 269-279

SUMMARY
Authors of this large prospective multicenter cohort from Canada aimed to demonstrate that adults with recently diagnosed asthma may be reevaluated to rule out the disease and safely stop asthma medications. Of 1026 eligible participants (adults with physician-diagnosed asthma established within the past 5 years) identified by telephone screening, 701 (68.3%) participants enrolled in the study between Jan 2012 to Feb 2015. Participants were evaluated with home peak flow and symptom monitoring, spirometry, and serial bronchial challenge tests. Those using daily asthma medications were gradually tapered off their medications over 4 study visits; if the diagnosis of current asthma was ruled out, participants were followed up clinically with repeated bronchial challenge tests over the course of 1 year. 613 out of 701 participants (mean [SD] age, 51 [16] years; 467 women [67%]) completed the study. Current asthma was ruled out in 203 of 613 study participants (33.1%; 95%CI, 29.4%-36.8%). 12 participants (2.0%) were found to have serious cardiorespiratory conditions that had been previously misdiagnosed as asthma in the community. The 12 month follow-up showed 181 participants (29.5%; 95%CI, 25.9%-33.1%) exhibited no clinical or laboratory evidence of asthma. However, 22 of the 203 participants who had been ruled out for current asthma were found to have asthma during the 1 year follow up. 63 of the 144 participants, in whom the diagnosis of asthma was ruled out, had undergone testing for airflow limitation in the community during the initial diagnosis as compared to 177 of the 317 patients with confirmed current asthma (43.8% vs 55.6% respectively; absolute difference, 11.8%; 95% CI, 2.1%-21.5%).

COMMENTARY
Over-diagnosis of asthma has been suggested in many adult and pediatric studies [1, 2]. Asthma is a relapsing and remitting disease with variable clinical presentations; it is therefore challenging to make a retrospective determination of validity of its diagnosis. In this trial, 24% of the community physicians did not respond to a request for diagnostic records, rendering it impossible to determine the procedural credibility of the diagnostic work up. This subsequently makes the distinction between asthma remission and misdiagnosis impossible. Absence of longitudinal follow up beyond 15 months overlooks the possibility that some patients in remission may have disease flare in the future. Though the authors tried to limit bias by random sampling and blinding of patients to study objectives, it is possible that the sample is not a true representation of the population for two reasons. First, patients on oral corticosteroids were excluded raising the possibility of recruitment of patients with milder form of asthma. Second, demographic information of
the 325 (31.7%) of the eligible 1026 patients qualifying for the study who refused to participate was not compared with the 701 (68.3%) study participants.

In addition to benefit of cost effectiveness and avoidance of unnecessary medications, this study effectively shows that an objective and algorithmic approach towards asthma diagnosis prevents failure of identification of potentially serious underlying disease that may clinically mimic asthma. Spirometry and methacholine challenge testing has been shown to be a cost effective and sensitive modality to help physicians diagnose, treat and monitor response to therapy for patients suffering from asthma, allowing for the potential of de-escalation of therapy as per the Global Initiative for Asthma guidelines after symptomatic control has been achieved [3][4]. This study, along with numerous others, suggests that since many patients are able to tell when their asthma is in remission, self-adjustment or discontinuation of asthma medications may be a potential option [5]. Randomized control trials are needed to help delineate a more regimenmed process of step down of asthma therapy to avoid over treatment.

**UTSW link**

Reference List

Readmission Rates After Passage of the Hospital Readmission Reduction Program


SUMMARY

Medicare began publicly reporting readmission rates for hospitals around the country in 2009. The passage of the Affordable Care Act (ACA) in 2010 created the Hospital Readmissions Reduction Program (HRRP). Hospital performance would be measured using 30 day risk standardized readmission rates (RSRR) for acute myocardial infarction (AMI), congestive heart failure (CHF), and pneumonia. Hospitals with higher relative readmission rates began to be penalized (decreased reimbursement) in the 2013 fiscal year. The analysis was meant first to confirm that RSRR for AMI, CHF, and pneumonia did indeed decline after passage of the ACA and creation of the HRRP. Secondly, the authors then sought to determine whether the reduction in RSRR was greatest in the lowest performing hospitals.

Data from nearly three thousand hospitals were included in this analysis. The authors estimated the RSRR for AMI, CHF, and pneumonia using Medicare data for the fiscal years of 2000-2010 and then compared this to 2010-2013. Hospitals were divided into 4 different quartiles based on the financial penalties levied by the Centers for Medicare & Medicaid Services (CMS) in 2013 (highest-performing 0% penalty, lowest-performing ≥0.99% penalty). As compared to the highest-performing hospitals, those in the lowest-performing category were more likely to be a major teaching hospital, to be in an urban setting, and more likely to serve a higher percentage of black and female patients.

After the passage of the ACA in 2010, the total RSRR decreased by 76.6 per 10,000 discharges per year across all hospitals. Those in the lowest-category saw their RSRR decrease significantly more than hospitals in the highest-performing category (Figure 1). Lowest-performing hospitals averted a greater number of readmissions for all three conditions after passage of the law as compared to the highest-performing hospitals.

COMMENTARY

Nationwide, readmission rates for AMI, CHF, and pneumonia have declined since the passage of the ACA. Those hospitals with the highest readmission rates for these conditions improved the most after the institution of financial penalties by CMS. Whether readmission rates for AMI, CHF, and pneumonia accurately reflect the quality of care and services
provided at any given hospital is certainly debatable. Additionally, it is not clear to what degree the decline in readmission rate may be due to a rise in observation admissions.

**UTSW Link**

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<th>Performance Group</th>
<th>Risk-Standardized Readmission Rate per 10 000 Discharges</th>
<th>Readmissions per 10 000 Discharges per Year (95% CI), n†</th>
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<td>2216.4</td>
</tr>
<tr>
<td>Average</td>
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<tr>
<td>Low</td>
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</table>

<table>
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<tr>
<th>Performance Group Comparison</th>
<th>Difference in Risk-Standardized Readmission Rate per 10 000 Discharges</th>
<th>Difference in Readmissions per 10 000 Discharges per Year (95% CI), n</th>
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<tr>
<td></td>
<td>2001</td>
<td>2010</td>
</tr>
<tr>
<td>Average vs. highest</td>
<td>−16.5</td>
<td>−30.8</td>
</tr>
<tr>
<td>Low vs. highest</td>
<td>−40.9</td>
<td>−68.7</td>
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<td>Lowest vs. highest</td>
<td>−75.2</td>
<td>−105.6</td>
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**Figure 1**
**Rheumatology**

**Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis**


**SUMMARY**

Rheumatoid Arthritis (RA) is an autoimmune disease that involves chronic inflammation of the synovial membranes of joints eventually leading to joint damage, extra-articular findings, and disability.

The RA-BEAM trial was a randomized, double-blinded global trial that lasted 52 weeks studying a new agent Baricitinib, a reversible inhibitor of JAK1 and JAK2 molecules. In a ratio of 3:3:2, 1305 patients were randomized to placebo plus background therapy, 4mg of Baricitinib plus background therapy, or 40mg Adalimumab (anti TNF alpha inhibitor) plus background therapy. The placebo group was switched to Baricitinib at 24 weeks. Patients included in this study were those with moderate to severe active RA who had an incomplete response to methotrexate after at least 12 weeks of treatment. All patients had a combination of joint erosions and positive Rheumatoid Factor or anti-citrullinated peptide antibodies. Patients excluded were those with prior exposure to a biologic disease modifying anti-rheumatic agent (DMARD). The primary end point included a 20% improvement in criteria set forth by the American College of Rheumatology (ACR20). Other endpoints included radiographic evidence of progression of joint damage, improvement in patients’ assessment of their pain and disease and lab values (DAS28-CRP, HAQ-DI).

In regards to the primary outcomes, results showed the ACR20 response at week 12 was 70% for Baricitinib vs. 40% for placebo (p<0.001). Additionally, the ACR20 response rate of Baricitinib vs. Adalimumab was 70% vs. 61% (p=0.01) respectively. There were significant improvements in Baricitinib vs. placebo with HAQ-DI, DAS28-CRP, and daily diary assessments patients had of their disease. There was a significant improvement in Baricitinib vs. Adalimumab in DAS28-CRP at week 12(-2.24 Baricitinib vs. -1.95 Adalimumab, p<0.01). At week 24 and 52, there was significant improvement in radiographic evidence of joint damage progression in the Baricitinib and Adalimumab group vs. placebo.

**COMMENTARY**

Treatment for RA thus far has revolved around anti-inflammatory agents, biologics and non-biologics DMARDs. Baricitinib provides a novel pathway targeting the Janus Kinase
(JAK) pathway. Specifically, targeting Jak1 and Jak2 inhibits intracellular cytokine signaling. Of note, cytokines IL-1, IL-7, and TNF and the respective receptors are not dependent on the JAK pathway.

The results of the study suggest methotrexate and Baricitinib are superior to methotrexate and Adalimumab in terms of a 20% improvement in RA disease activity at 12 weeks as assessed by ACR20. Baricitinib also showed superiority in improvement of the DAS28-CRP as compared to Adalimumab. Additionally as compared to placebo, Baricitinib had a reduction in progressive radiographic joint structure damage. One limitation in this study is that most of the patients received methotrexate as background therapy and only 15-18% in each of the three groups received other DMARDs. Thus the effectiveness of Baricitinib in the setting of other DMARDs cannot be fully assessed.

UTSW Link
Faculty and Fellow Mentors

We would like to acknowledge and thank UTSW’s Internal Medicine Journal Watch faculty and fellow mentors for their time and effort in assisting with this endeavor:

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