Louis Pasteur (1822-1895)

Performing the classic ‘Swan-neck flask’ experiment, disproving the then prevailing theory of spontaneous generation
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EKG Challenge

-by Dr. Jeanney Lew

Mr. A.S is a 79 year-old man brought to the ED via EMS following a syncopal episode.

Per wife: “We were sitting at the table when out of the blue he told me he wasn't feeling well. Shortly afterwards I saw him slump over and fall off his chair. He became very pale and it didn't seem like he was breathing. Then, his face and arms started twitching. I think he was having a seizure. He was out for what seemed like 5-10 minutes.”

In the ED, you examine Mr. S. He has a laceration on his forehead with surrounding ecchymoses. Otherwise, he is resting calmly in bed. He reports pain in his head and face, but has no other complaints.

EKG was obtained below:

QUESTIONS:

1. What abnormal findings are significant on this EKG?
2. What is the name of the diagnosis?
3. What is this patient at risk for developing?
4. What is the definitive treatment?
DISCUSSION

**Q1: What abnormal findings are significant on this EKG?**

- **Rhythm:**
  - 3rd degree heart block
  - Non-conducting p waves at rate of 90 (↓)
- **Rate:**
  - Ventricular rate ~35
  - Escape rhythm likely originating from left Purkinje/His system (given the RBBB pattern)
- **QRST:**
  - Prolonged QTC (~527)
  - Large, wide inverted T waves in leads II, III, aVF, V1-V6

T waves on the electrocardiogram represent ventricular repolarization. Several conditions may result in changes in T wave morphology, making it a sensitive, but non-specific marker for abnormal processes [1]. However in certain clinical situations, abnormal T waves can suggest very specific pathology.

This patient has very large (giant) T wave inversions involving the precordial leads, leading to an interesting differential (next page):
### Giant T Wave Inversions – DDX:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Possible Causes</th>
</tr>
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<tbody>
<tr>
<td>INCREASED VENTRICULAR MASS</td>
<td>• Apical HOCM</td>
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<td></td>
<td>• Severe RVH</td>
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<tr>
<td>MYOCARDIAL ISCHEMIA</td>
<td>• ACS (e.g., Wellen's syndrome) – see <em>April 2015 JW</em>-</td>
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<tr>
<td></td>
<td>• Cocaine</td>
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<tr>
<td>ARRHYTHMIA / CONDUCTION ABNORMALITIES</td>
<td>• Heart block</td>
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<td></td>
<td>• Pacemaker syndrome</td>
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<td>• Wolf-Parkinson-White</td>
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<td>CNS</td>
<td>• CVA / Subarachnoid hemorrhage</td>
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<tr>
<td></td>
<td>• Elevated ICP</td>
</tr>
<tr>
<td>GI / HEPATOBILIARY</td>
<td>• Acute pancreatitis / cholecystitis</td>
</tr>
<tr>
<td></td>
<td>• Acute abdomen</td>
</tr>
</tbody>
</table>

**Q2: What is the name of the diagnosis?**

- Stokes-Adams disease

He demonstrates 3rd degree heart block with giant T wave inversions and a history of syncope with full recovery post-event. This combination points to a condition known as a Stokes-Adams attack (or Stokes-Adams disease), which was first described in the 18th and 19th centuries by multiple individuals. Stokes-Adams disease classically refers to individuals with heart block who experience episodes of syncope secondary to ventricular standstill, ventricular tachycardia, or a combination of these, resulting in a sudden drop in cardiac output [2].

Characteristic history and EKG in Stokes-Adams disease:

- Inverted T waves: deep, broad, or bizarre, involving precordial leads
- Prolonged QTC
- History of syncope associated with sudden loss of consciousness, pallor, absent pulse, +/- seizure activity
- Some individuals experience flushing of the skin upon resolution of syncope
Q3: What is this patient at risk for developing?

- Ventricular arrhythmias (e.g., VF, torsades de pointes)

High-grade heart block, especially with signs/symptoms of hemodynamic instability (syncope, lightheadedness, etc.) is at risk of degenerating into potentially fatal ventricular arrhythmias. Immediate EP evaluation is warranted.

Q4: What is the definitive treatment for this condition?

- Pacemaker

KEY POINTS

- Stokes Adams attacks/disease characterized by:
  - Syncope
  - Heart block
  - Prolonged QTc
  - Large/bizarre inverted T waves, especially precordial
  - Can mimic seizure

- Consult EP!
- Indication for pacemaker

REFERENCES

Dermatology: Image challenge: by Dr. Joshua Owen

A white woman in her 30s with no significant past medical history presented to the Parkland ED with a 4-day history of a diffuse, painful, pruritic eruption involving her neck, back, face, arms, palms, and legs. She reports having fevers, myalgias, fatigue, arthralgias, and axillary lymphadenopathy over this time. She denies cough, nausea, vomiting, headache, or abdominal pain. Only recent travel was camping trips to Nevada and Austin in the last 4 months. She does not recall being bitten by any insects or animals. Her face (Figure, A) and legs (Figure, C) exhibit erythematous papules that coalesce into swollen plaques. Some of the papules look vesicular. Her mouth (Figure, B) contains erythematous ulcerated papules under her tongue and on the posterior oropharynx. She denies tongue swelling, dysphagia, or starting any new medications.

1. What is your diagnosis?
A. Systemic lupus erythematosus
B. Sweet syndrome
C. Erythema multiforme
D. Hand, foot, and mouth disease

2. All of the following are potential etiologies, except:
A. AML
B. Pregnancy
C. Penicillin
D. URI

A: Erythematous and edematous papules and plaques on cheeks, eyelids, chin, neck
B: Ulcerated papules under tongue and on lips
C: Scattered erythematous papules on leg, some of which look vesicular.
Discussion

Sweet syndrome (acute febrile neutrophilic dermatosis) was first described in 1964. It is an uncommon, but not rare, disease that was classically described in middle-aged women associated with a respiratory or GI infection. The average age of onset is 30-60 (less commonly in the young and elderly), with a 4:1 female predominance. About 20% have internal malignancy with no sexual predilection.

**Sweet syndrome is associated with many conditions:**
- Infections: URI (*Streptococcus* spp.) and GI (*Yersinia* spp.)
- Hematologic malignancies (including AML), solid tumors
- Inflammatory bowel disease
- Medications (including G-CSF, furosemide, hydralazine, minocycline, TMP-SMX, and all-trans retinoic acid)
- Pregnancy

The most common signs/symptoms are fever and leukocytosis (neutrophilia). Less common are arthralgias, arthritis, myalgias, and ocular involvement. Uncommonly lung, bone, and renal involvement are seen; rarely hepatitis, myositis, aseptic meningitis, and pancreatitis have been reported. This patient presented with signs and symptoms of a possible viral or bacterial infection (acute onset fevers, arthralgias, myalgias, lymphadenopathy) in the setting of new skin lesions.

The typical primary lesions in Sweet syndrome are urticaria (hives), described as edematous (“juicy”) papules or nodules that are dermal-based. As with this patient, the dermal edema can be robust enough to cause the papule to look pseudo-vesicular or pseudo-pustular. The typical distribution involves the head, neck, trunk, and upper extremities.

The differential diagnosis for urticaria is broad; the presence of systemic symptoms, as with this patient, often leads to hospitalization. Differential categories include medications, vasculitides/autoimmune, hematologic, infectious, and autoinflammatory. Viral URI are the most common cause of acute urticaria; medications are second. A 3-week medication timeline is important if a serum sickness-like reaction is suspected. A CBC with differential
is useful in identifying cytopenias, eosinophilias, or atypical cells present in systemic
diseases. However, an unguided approach with extensive testing has not been shown to
identify the underlying cause of urticaria.

Skin biopsy in this patient demonstrated diffuse dermal edema and dense neutrophilic
infiltrate, consistent with Sweet syndrome. If left untreated, Sweet syndrome will likely
persist for weeks or months, but will resolve spontaneously without scarring. The
recurrence rate with or without treatment is about 30%, and about 50% in patients with
hematologic disorders.

First line treatment for Sweet syndrome is oral prednisone (0.5–1.0 mg/kg/day) for 4–6
weeks, which quickly ameliorates the skin and extracutaneous manifestations. A prolonged
low-dose prednisone taper for a couple months may be necessary to suppress recurrences.
Antibiotics are generally ineffective unless the disease is associated with a recognized
infection. Major non-steroid alternatives include potassium iodide, dapsone, and
colchicine. This patient responded well to treatment with daily prednisone. She was
referred for age-appropriate cancer screening.

1. Micheletti R, Rosenbach M. An Approach to the Hospitalize Patient with Urticaria and

Endocrinology

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes


Summary:

Empagliflozin is a member of the new class of oral anti-hyperglycemic agents for type 2 diabetes mellitus that works via inhibition of the sodium-glucose cotransporter 2 in the kidney causing urinary glucose excretion. In the randomized, double-blind, placebo controlled EMPA-REG OUTCOME trial, this medication lowered the rate of composite cardiovascular outcome (i.e. death from cardiovascular causes, nonfatal MI, or nonfatal stroke) and all-cause death from 12.1% to 10.5% and 8.3 to 5.7%, respectively, when added to standard of care among patients with type 2 DM with established cardiovascular disease. The reduction in all cause death was largely driven by reduction in death from cardiovascular causes. Follow up for this study was 48 months.

Commentary:

Rigorous establishment via prospective, randomized, placebo-controlled trials of the cardiovascular benefits and risk of oral antihyperglycemics has become a gold standard in the introduction of new medications in the care of type 2 diabetes. This was historically driven by several studies, including the infamous meta-analysis by Nissen and Wolski regarding rosiglitazone that highlighted the potential for harm rather than benefit in cardiovascular outcomes. The EMPA-REG OUTCOME trial demonstrated that empagliflozin when added to standard of care among patients with type 2 diabetes who have established cardiovascular disease have reduced cardiovascular risk. This study provided the much needed safety data regarding macrovascular outcomes of a medication from this drug-class.

The 2015 ADA and EASD guidelines currently include SGLT2 inhibitors among the approved agents after failure of lifestyle modification and metformin monotherapy for glycemic control. These agents have been associated with modest weight loss (~2kg) and consistent lowering of systolic and diastolic blood pressure (~2-4/~1-2 mmHg). The major adverse effects include an increase in mycotic urinary tract infections. There is also a concern for a possible diuretic effect so caution must be practiced when prescribed to patients with tenuous volume status or advanced age. Moreover, there are scattered reports of euglycemic diabetic ketoacidosis in patients using this drug class.
Ultimately, this study adds important information regarding macrovascular outcomes when choosing the most appropriate oral antihyperglycemic regimen for your patient. Consistent with ADA guidelines, choice of antihyperglycemic agents should largely be driven by a patient-centered approach with selection of agents that best address a patient’s co-morbid risk factors and balance that drug’s adverse effect profile against your patient’s baseline risks.

UTSW Link
Impact of proton pump inhibitor treatment on gastrointestinal bleeding associated with non-steroidal anti-inflammatory drug use among post-myocardial infarction patients taking antithrombotics: nationwide study


PPI use in post-MI patients taking NSAIDs is associated with fewer episodes of GI bleeding.

Summary:

In this Danish cohort study, investigators sought to determine whether PPIs reduce GI bleeding regardless of GI risk in the post-MI population taking both antiplatelet agents and NSAIDs. The study population included 82,955 patients in the Danish National Patient Registry 30 years of age or older who presented with a first diagnosis of acute MI over a 14-year period who received either aspirin or clopidogrel. Excluding the first 30 days, the periods of exposure to NSAIDs and PPIs were calculated based on pharmacy prescription data, with patients able to move between groups as exposures changed. The primary outcome of hospitalization for or death from GI bleeding was determined from national registries. Of the study patients, 42.5% received NSAIDs, 45.5% received PPIs, and 12.8% received both NSAIDs and PPIs. There were 3,229 episodes of GI bleeding in this population, of which 327 occurred during NSAID exposure. Of these, 267 occurred in patients not taking PPI (2.1 events per 100 person years) and 60 occurred in patients who were taking NSAIDs (1.8 events per 100 person years), a statistically significant difference with a hazard ratio of 0.72 (0.54, 0.95). Subgroup analysis for type of NSAID and specific PPI yielded similar results.

Commentary:

NSAIDs are generally contraindicated post-MI, but the realities of pain control often result in NSAID usage. GI bleeding prophylaxis is therefore an important aspect of the care of these patients who can ill afford the additional stress caused by blood loss anemia. Current ACG and ACC guidelines recommend PPI prophylaxis for patients who are at higher risk of GI bleeding, namely those with a history of prior GI bleeding, age > 65, high dose NSAID therapy, or previous history of uncomplicated ulcer. ACC guidelines recommend against routine use of PPI for patients at lower risk of upper GI bleed. This study, however, shows that patients on antiplatelet agents and NSAIDs benefit from a PPI regardless of the risk of GI bleeding. While only a cohort study, as discussed in the previous issue of Journal Watch, the Danish population is well-suited to studies such as these due to the large patient registries yielding a large study population. Furthermore, aside from short courses of low-
dose ibuprofen or short courses of high-dose aspirin, NSAIDs require prescriptions for insurance coverage, making the population ideal for studying the effects of NSAIDs. Interestingly, during the study period, the rate of PPI and NSAID concurrence rose from <10% to >30%, suggesting that clinicians have already incorporated them into their practice based on their own experience.

UTSW Link
Loss of Infliximab Into Feces Is Associated With Lack of Response to Therapy in Patients With Severe Ulcerative Colitis


Severe UC patients who did not respond to infliximab had higher fecal drug levels than responders, although inference of causality of fecal loss of antibodies as the reason of lack of response is speculative.

Summary:

In this prospective study conducted in the Netherlands, the authors sought to determine whether fecal levels of infliximab were higher in those patients with severe UC who did not respond to the drug initially (i.e. primary nonresponders) compared to those who did. The study population consisted of 30 anti-TNF naïve patients with moderate to severely active UC according to endoscopic Mayo score who had failed corticosteroids and/or immunomodulators. Fecal infliximab concentrations were measured by ELISA after dilution with bovine albumin and homogenization. These were measured prior to beginning therapy and at several times during the initial 2 weeks of treatment. All patients received standard infliximab dosing of 5 mg/kg. Endoscopic response was defined as a drop in endoscopic Mayo score of ≥ 1. Clinical response was assessed using the Simple Clinical Colitis Activity Index, with response defined as a drop of 50% or more from baseline or a total score ≤4. This was assessed before treatment, at 2 weeks, and at 3 months. Furthermore, patients who needed increasing doses or who underwent colectomy were determined to be nonresponders. In the first 2 weeks, 83% of patients had detectable infliximab levels in feces. At week 2, clinical nonresponders had a higher fecal infliximab concentration (5.01 μg/mL vs 0.54 μg/mL) than responders. Endoscopic nonresponders also had higher concentrations (4.66 vs 1.16), though the difference did not reach statistical significance. However, compared to other characteristics (disease duration, baseline...
colitis activity, CRP, albumin, fecal calprotectin), day 1 fecal infliximab concentration most closely predicted response. Those patients with detectable day 1 fecal infliximab levels also had higher disease activity scores (11 vs 7) and higher fecal calprotectin levels. Interestingly, fecal levels of infliximab did not inversely correlate with serum levels.

**Commentary:**

While loss of response to infliximab has been associated with the development of antibodies to the drug and to decreased serum levels, it is unclear why some patients (30% according to the ACT 1 trial) do not respond to the drug initially. While increased loss of the drug in feces from an inflamed and leaky colon may be a reason for lack of response, the more likely explanation is that it may be more a reflection of higher disease activity that is then more resistant to treatment. Increased intestinal permeability to even macromolecules in IBD occurs as a result of impaired tight junctions, apoptosis, and mucosal lesions as reported in several papers and review articles (PMIDs: 26582965, 24574793, 17545772, 19027740, 15542502, and others). Furthermore, one study (PMID: 1525248) found increased stool levels of immunoglobulins such as IgA and IgG in patients with active IBD, and that these levels corresponded to disease activity. The current study is the first one to look at the presence of a therapeutic antibody in stool. Unfortunately, the relatively small sample size limited the study's power to detect differences between the populations. Given the significant loss of other macromolecules in active IBD, loss of therapeutic antibodies seems unlikely to be a mechanism for lack of response. Nevertheless, it is useful to be able to predict non-response, especially if this can be done as early as day 1. Further studies are needed to evaluate whether measurements of levels can indeed predict response and can be used for early identification of nonresponders and thereby guide therapeutic decisions.

**UTSW Link**
General Internal Medicine

Isosorbide Mononitrate in Heart Failure with Preserved Ejection Fraction


Summary:
The search for effective therapy in heart failure with preserved ejection fraction (HFpEF) has so far been disappointing, and a number of established therapies in patients with reduced ejection fracture have failed to show a benefit in HFpEF. The current study attempted to study if long-acting nitrate therapy would improve exercise capacity and other clinical markers in patients with HFpEF.

In this study, 110 patients with HFpEF were randomly assigned to a 6 week regimen of isosorbide mononitrate with dose escalation or placebo, with subsequent crossover to the other group for 6 weeks. The primary endpoint was daily activity level as measured by patient-worn accelerometers. Secondary end points included quality-of-life scores, 6-minute walk distance, and levels of NT-proBNP. Contrary to the group’s hypothesis, the study did not show a benefit in any of the primary or secondary endpoints for patients on isosorbide mononitrate. On the contrary, in the group receiving isosorbide mononitrate including all dose regimens (30, 60, or 120 mg), activity levels were lower (−439 accelerometer units (approximately 4.5% reduction; 95% CI, −792 to −86; P = 0.02). Additionally, in the individuals receiving the highest dose of isosorbide mononitrate, there was a reduction in the number of hours of activity per day (−0.30 hours; 95% CI, −0.55 to −0.05; P = 0.02). Patients on isosorbide mononitrate also had increased rates of adverse events (such as syncope or worsened heart failure). A strength of this study is that it was a cross-over study so each participant could serve as his or her own control.

Commentary:
Although this study was relatively small and may have been underpowered, the lack of benefit at any dose and the evidence of harm clearly indicate that isosorbide mononitrate is ineffective in HFpEF patients for improving heart failure symptoms or exercise tolerance. This study suggests that isosorbide mononitrate should not be used in patients with HFpEF for the purposes of improving activity levels, and should be used with caution in preventing angina symptoms given the possible negative effects on activity levels.

UTSW Link
On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection


Summary:
The study was a double-blind, randomized trial of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) for sexual activity-dependent HIV-1 pre-exposure prophylaxis (PrEP) among men who have unprotected anal sex with men. Participants were randomly assigned to take a combination of TDF and FTC or placebo before and after sexual activity. Four hundred participants were enrolled, and participants were followed for a median of 9.3 months. Two HIV-1 infections occurred in the TDF-FTC group and 14 in the placebo group, resulting in a relative risk reduction in the TDF-FTC group of 86% (95%CI: 40-98%; p=0.002). Participants took a median of 15 pills of TDF-FTC or placebo per month. The rates of serious adverse events were similar in the two study groups; however, the TDF-FTC group had higher rates of gastrointestinal adverse events (14% vs. 5%, P = 0.002) and renal adverse events (18% vs. 10%, P = 0.03).

Commentary:
Previous research used daily rather than intermittent prophylaxis, and participants had variable rates of medication adherence, which correlated with the degree of PrEP efficacy. This study suggests that intermittent prophylaxis is as effective as daily prophylaxis, provided that patients take at least 15 pills a month. The results cannot be extrapolated to persons who take fewer pills. Longer studies would also be needed to see if adequate adherence with intermittent prophylaxis would be sustained for longer periods of time. These findings are consistent with prior animal studies in macaques as well the iPrex study, the only other large RCT study of PrEP in a similar population. Therefore, PrEP use, either daily or intermittent, is an increasingly well-established and important component of the armamentarium for effective HIV prevention efforts. The patient can choose either daily or intermittent dosing depending on which is most likely to lead the highest adherence rates.

UTSW Link
Randomized Trial of Reduced-Nicotine Standards for Cigarettes


**Summary:**

In an attempt to provide another route for patients to quit smoking, this study assessed whether reducing the amount of nicotine in cigarettes would decrease overall consumption. 780 subjects who had no intention of quitting completed the six-week double-blind study, in which participants were randomized to smoke their usual brand of cigarette or any of 6 investigational cigarettes with nicotine content ranging from 0.4 mg/g to 15.8 mg/g. Participants were invited back each week to complete three questionnaires that assessed the number of cigarettes they smoked that week, the frequency with which they had urges, and any adverse events they may have experienced. At the end of the six-week investigation, the study found that nicotine content strongly affected the amount of cigarettes consumed. Whereas participants in the 15.4 mg/g nicotine-content group, i.e. the control group, smoked 22.2 cigarettes per day, those in the investigation group smoked 16.5, 16.3, and 14.9 cigarettes per day when consuming 2.4, 1.3, and 0.4 mg of nicotine per cigarette, respectively. Furthermore, at the end of six weeks those subjects randomized to consume cigarettes containing the least amount of nicotine exhibited the least dependence to tobacco products, as evidenced by their scores on withdrawal questionnaires.

**Conclusions:**

In an age where cigarette alternatives are numerous (e.g. gum, patches, e-cigarettes), this study flirts with the possibility of having the cigarettes lead to their own demise. Several studies in recent years have looked into new modalities for cigarette cessation. While others have attempted to answer the question through behavior modification and financial incentives, this study actively changed the content of cigarettes themselves. Although six months can hardly be enough time to prove that lower nicotine concentrations will help smokers kick their habit, it is certainly interesting to see how even urges for tobacco can significantly decrease with less amounts of nicotine. Many of us in the primary care setting have heard patients say they depend on the action of putting a cigarette in their mouth more than the actual content of the cigarette, and this study proves it. If further studies can expand upon these results over several months, they could pave the way for using cigarettes to stop tobacco addiction much in the same way that methadone is used to stop heroin addiction.

[UTSW Link]
Geriatrics

American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults


Summary:

The American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication (PIM) Use in Older Adults is an evidence-based list of medications that are best avoided in older adults in general, those with certain diseases or syndromes, or that should be prescribed at a reduced dosage or with caution or carefully monitored. The target audience is practicing clinicians. The criteria are applicable to patients aged 65 and older in the United States in all ambulatory, acute, and institutionalized care settings, with the exception of hospice and palliative care. The criteria were last updated in 2012. For the 2015 update, a 13 member interdisciplinary expert panel performed a systematic literature review and evaluation of the evidence available from August 1, 2011 to July 1, 2014, which included systematic reviews, meta-analyses, randomized controlled trials, and observational studies but excluded case reports, case series, editorials, and letters. They followed the Institute of Medicine’s 2011 report on developing practice guidelines and rated the quality of evidence and the strength of recommendation for each criterion using the American College of Physicians’ Guideline Grading System. After consensus was reached within the expert panel, the updated guidelines were circulated for peer review. Notable updates from the 2012 criteria are listed below.

- The recommendation to avoid nitrofurantoin in patients with a creatinine clearance of less than 60 mL/min has been revised. Two retrospective studies demonstrate relative safety and efficacy in patients with a creatinine clearance greater than 30 mL/min.
- The recommendation to avoid antiarrhythmic drugs as first line treatment for atrial fibrillation has been removed, as new evidence suggests that rhythm control strategies can have outcomes as good as or better than rate control strategies. Amiodarone is still to be avoided as first line therapy unless the patient has concomitant heart failure or substantial left ventricular hypertrophy. Dronedarone is to be avoided in patients with permanent atrial fibrillation or severe or recently decompensated heart failure. Disopyramide should be avoided because of its highly anticholinergic properties. Digoxin should be avoided as first line therapy for atrial fibrillation or heart failure because of increased mortality in older patients and
should not be prescribed in daily doses greater than 0.125 mg because of decreased renal clearance and increased risk of toxicity in older adults.

- Nonbenzodiazpine, benzodiazepine receptor agonist hypnotics (eszopiclone, zaleplon, zolpidem) should be avoided regardless of duration of use because of the significant risk of adverse events and minimal efficacy in treating insomnia.
- “Sliding scale insulin” is defined as the sole use of short or rapid-acting insulins in the absence of basal or long-acting insulin, and should be avoided (regardless of care setting) because of the increased risk of hypoglycemia without improvement in hyperglycemia management.
- Proton-pump inhibitors should not be used for longer than eight weeks without justification (such as Barrett’s esophagitis, erosive esophagitis, pathological hypersecretory condition, oral corticosteroid use, chronic NSAID use, or demonstrated need for maintenance treatment) because of the associated risk of Clostridium difficile infection and bone loss and fractures.
- Desmopressin should not be used to treat nocturia or nocturnal polyuria because of the risk of hyponatremia.
- Antipsychotics should be avoided for treatment of behavioral problems of dementia or delirium unless nonpharmacological interventions have failed or are not possible and the older adult is threatening substantial harm to self or others because of the increased risk of CVA and mortality in combination with conflicting evidence on effectiveness.
- A new table has been added highlighting drug-drug interactions that are highly associated with adverse outcomes in older adults.
- A new table has been added with medications that should have their doses adjusted or be avoided based on creatinine clearance in older adults. Particularly notable on this list are the novel oral anticoagulants, low molecular weight heparins, duloxetine, gabapentin and pregabalin, tramadol, and H2 blockers.

Commentary:

The Beers Criteria is an important reminder that older adults metabolize and react to medications differently than younger adults and that we must constantly weigh the risks and benefits of medications to avoid causing harm to our older patients. Medication reconciliation is an important part of every clinical encounter and presents an opportunity for us to assess the appropriateness and safety of the drugs our older patients are taking. We should be mindful of the Beers Criteria recommendations when performing medication reconciliation and take the opportunity to discontinue potentially harmful medications and find alternatives when possible.

UTSW Link
Hyperparathyroidism Associated with Long-Term Proton Pump Inhibitors Independent of Concurrent Bisphosphonate Therapy in Elderly Adults

Dr. Nathalie Kalandjian reviewing Hinson et al, JAGS. 2015 Oct 63 (10): 2070-2073

Summary

This is a retrospective chart review of individuals age 60 and older on chronic proton pump inhibitor (PPI) therapy. Four groups were enrolled in this study for comparison: 20 subjects taking a PPI for at least 6 months, 20 subjects not taking a PPI, 20 taking a PPI with a bisphosphonate (BP) and 20 taking a BP alone. Calcium, PTH, Vitamin D and creatinine was measured in each group using a t test to establish statistical significance. Patients with Cr greater than 1.3 mg/dL or Vit D levels less than 30 ng/mL were excluded. The aim of the study was to monitor the effect of PPIs on PTH, vitamin D and calcium with and without bisphosphonates.

Previous studies have found associations between chronic (>1 year) high dose PPI use and fracture risk, especially in those aged 50 and over. PPIs cause hypochlorhydria which impairs calcium absorption, reduces calcium bioavailability and causes hyperparathyroidism with increased bone turnover. PPIs may also directly inhibit acid dependent osteoclast activity impairing bone resorption. Many elderly patients are exposed to PPIs both for chronic GERD and PUD treatment in the outpatient setting and for shorter periods as inpatients.

Serum calcium and PTH were significantly higher in the PPI v. non-PPI groups. In the patient population taking bisphosphonates, PPI use was also associated with a statistically significant decrease in serum calcium levels (P=.04) and increase in PTH (P=.05). There was no significant difference in calcium or PTH between the –PPI/BP and –PPI groups.

Commentary

This study suggests that that PPI therapy is associated with mild secondary hyperparathyroidism regardless of bisphosphonate therapy. Several mechanisms might explain proton pump inhibitor induced hyperparathyroidism. Hypochlorhydria as stated above causes decreased calcium absorption triggering secondary hyperparathyroidism. Chronic hyperparathyroidism can also cause thyroid hyperplasia resulting in PTH release despite calcium supplementation. PPIs also suppress somatostatin, triggering increased gastrin levels which have been shown to increase PTH gene expression in certain studies. PPIs have also been shown to inhibit effects of bisphosphonates by suppressing hydrogen secretion needed for acid-dependent osteoclasts to function.
Providers should be cautious in prescribing chronic PPI therapy, especially in elderly patients, and those with increased fracture risks to prevent adverse effects. PPIs should only be prescribed when indicated and their need should be reassessed to prevent unnecessary long term use. More research is needed to investigate PPI effects on blood pressure therapy in the management of fracture risk.

**UTSW Link**
**Hematology / Oncology**

**Chimeric antigen receptor T cell therapy: 25 years in the making**

*Dr. Arjun Gupta reviewing Gill et al, Blood Rev. 2015 Nov 6*

**Summary**
Adoptive transfer of engineered T cells expressing chimeric antigen receptors (CAR) is a promising anti-cancer therapy. Patient’s own T cells are collected and T-cell receptor (TCR) specificity is assigned by the in-vitro transfer of genetic material, usually by retroviral vectors; the resulting CAR-modified T cells can thus be engineered to target virtually any tumor associated antigen. After infusing back into the patient, CAR T cells traffic to the cancer and can provide sustained anti-cancer effect.

**Commentary**
CAR T cells have shown efficacy in treating multiple cancers, particularly B-cell malignancies that express CD19, including relapsed leukemia. Multiple trials in multiple cancers are underway at this time. A major issue, especially for solid tumors, is identifying a target tumor associated antigen. Although one can model a CAR T cell on existing targets of known monoclonal antibodies (e.g. against Her2/neu for breast cancer), efficacy and toxicity profiles between these products differ considerably. Healthy tissue may express the same target antigens as the tumor cells, leading to outcomes similar to graft-versus-host disease. Selection of antigens that are suitable for CAR T cell-based therapy must thus be conducted very carefully and modeled using relevant preclinical models. Cytokine release syndrome is also a known toxicity and is characterized by high persistent fevers, nausea, myalgias, arthralgias, and can evolve to capillary leak, shock and death.

**UTSW Link**
Infectious Diseases

Association Between Hospitalization With Community-Acquired Laboratory-Confirmed Influenza Pneumonia and Prior Receipt of Influenza Vaccination


Summary

Influenza infections cause substantial morbidity and mortality every year. Influenza-associated pneumonia is one of the known complications of influenza infections. Studies have shown that the influenza vaccine is effective in decreasing the rates of hospital admissions due to influenza-associated respiratory infections; however, limited evidence exists on the impact of the vaccine on admissions due to influenza-associated pneumonia. In a prospective case-control analysis of the CDC’s Etiology of Pneumonia in the Community (EPIC) study, Grijalva and colleagues were able to examine this association. The researchers recruited 2767 patients admitted to 4 centers in the US during 3 influenza seasons, with diagnosis of pneumonia based on symptoms and radiologic findings. Among all the patients recruited, 162 (5.9%) were influenza positive. Of the 162 patients with influenza-associated pneumonia, 28 (17%) had been vaccinated for influenza compared with 766 (29%) of the 2605 patients with influenza-negative pneumonia who had been vaccinated for influenza. The odds ratio for influenza vaccination in influenza-positive compared with influenza-negative pneumonia was 0.43 (95% CI: 0.28-0.68) after adjustment for demographic and clinical factors, meaning that odds of influenza vaccination among cases hospitalized with influenza-associated pneumonia was 57 percent lower than among non-influenza pneumonia controls. Vaccine effectiveness was estimated to be 57% across the entire study period (table 1).

Commentary

This study shows one more compelling reason for patients to be vaccinated yearly against influenza. Strengths include a large sample size in a diverse population, well adjudicated and radiographically-confirmed cases of influenza pneumonia, and a period covering multiple influenza seasons. However, it took place in only four sites in the US in two metropolitan areas, which makes generalization limited. Furthermore, even though the study was conducted during 3 influenza seasons, a rather small number of influenza-associated pneumonia cases met eligibility criteria, causing poor precision for some subgroup analysis such as older adults. For this reason, no conclusion was achieved on the association between influenza vaccine and pneumonia in this group. Finally, the vaccine effectiveness estimates may be lower in a real world setting if the vaccine match with the circulating strains in a particular influenza season is poor.
|                                | Cases Who Were Vaccinated, No./Total No. (%) | Controls Who Were Vaccinated, No./Total No. (%) | Adjusted Odds Ratio (95% CI) | Estimated Vaccine Effectiveness, % (95% CI)
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<tbody>
<tr>
<td><strong>Overall estimate</strong></td>
<td>28/162 (17)</td>
<td>766/2605 (29)</td>
<td>0.43 (0.28 to 0.68)</td>
<td>56.7 (31.9 to 72.5)</td>
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<td><strong>Included self-reported vaccination</strong></td>
<td>56/190 (29)</td>
<td>1241/3270 (38)</td>
<td>0.52 (0.37 to 0.75)</td>
<td>47.5 (25.3 to 63.2)</td>
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<td><strong>Influenza season definition</strong></td>
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<tr>
<td>≥4% Positive tests per week</td>
<td>28/154 (18)</td>
<td>579/1563 (37)</td>
<td>0.41 (0.26 to 0.65)</td>
<td>59.1 (35.3 to 74.1)</td>
</tr>
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<td>≥5% Positive tests per week</td>
<td>28/153 (18)</td>
<td>523/1458 (36)</td>
<td>0.40 (0.25 to 0.63)</td>
<td>60.1 (36.8 to 74.8)</td>
</tr>
<tr>
<td>2010-2012 Season</td>
<td>28/156 (18)</td>
<td>721/2300 (31)</td>
<td>0.44 (0.28 to 0.69)</td>
<td>56.4 (31.2 to 72.3)</td>
</tr>
<tr>
<td>Hospitalization within 7 d of symptoms onset</td>
<td>23/136 (17)</td>
<td>624/2071 (30)</td>
<td>0.41 (0.25 to 0.68)</td>
<td>58.9 (32.3 to 75.0)</td>
</tr>
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<td>Hospitalization within 14 d of symptoms onset</td>
<td>26/154 (17)</td>
<td>710/2379 (30)</td>
<td>0.43 (0.27 to 0.68)</td>
<td>57.3 (31.7 to 73.2)</td>
</tr>
<tr>
<td>Independent radiographic confirmation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24/139 (17)</td>
<td>700/2389 (29)</td>
<td>0.43 (0.27 to 0.71)</td>
<td>56.6 (29.2 to 73.4)</td>
</tr>
<tr>
<td>Controls positive for other viruses&lt;sup&gt;d&lt;/sup&gt;</td>
<td>28/162 (17)</td>
<td>368/1196 (31)</td>
<td>0.37 (0.23 to 0.61)</td>
<td>62.8 (39.5 to 77.1)</td>
</tr>
<tr>
<td>Controls negative for all viruses&lt;sup&gt;d&lt;/sup&gt;</td>
<td>28/162 (17)</td>
<td>398/1409 (28)</td>
<td>0.46 (0.29 to 0.74)</td>
<td>53.8 (25.5 to 71.4)</td>
</tr>
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<td>Excluded patients with previous antiviral use</td>
<td>27/155 (17)</td>
<td>750/2546 (29)</td>
<td>0.44 (0.28 to 0.70)</td>
<td>56.2 (30.4 to 72.4)</td>
</tr>
<tr>
<td>Propensity score-adjusted analysis&lt;sup&gt;a&lt;/sup&gt;</td>
<td>28/162 (17)</td>
<td>766/2605 (29)</td>
<td>0.45 (0.29 to 0.72)</td>
<td>54.9 (28.5 to 71.5)</td>
</tr>
<tr>
<td>Cases with respiratory syncytial virus pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td>125/396 (32)</td>
<td>641/2209 (29)</td>
<td>1.18 (0.88 to 1.58)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-18.0 (~57.6 to 11.7)</td>
</tr>
</tbody>
</table>

**Table 1:** Sensitivity analysis within study of Influenza Vaccination and Influenza Pneumonia

**UTSW Link**
**Nephrology**

**Prevention of Contrast-Induced Nephropathy by Central Venous Pressure-Guided Fluid Administration in Chronic Kidney Disease and Congestive Heart Failure Patients**

*Dr. Jeanney Lew reviewing Qian, G., et al. JACC Cardiovasc Interv, 2015*

**Summary:**

In patients with concurrent CKD and CHF, the use of central venous pressure (CVP) to guide fluid administration can reduce risks of contrast-induced nephropathy (CIN) while avoiding complications such as acute pulmonary edema.

**Commentary:**

CIN is a complicating factor in up to 25% of those undergoing coronary angiography [1]. It is associated with increased morbidity and mortality and those with CKD or CHF are at higher risk. While IV hydration is the most important factor in preventing CIN, the fear of precipitating acute pulmonary edema in heart failure patients has limited aggressive hydration in this population.

This prospective, randomized controlled, double-blinded trial included Chinese individuals aged 18 years and older with CHF and non-dialysis dependent CKD, scheduled for coronary angiography or non-emergent PCI. Subjects were randomly assigned to either CVP-guided hydration (n=134) or standard hydration (control, n=135) for 6 hrs prior and 12 hrs after LHC. The CVP-guided arm was divided into 3 dynamic groups: group 1 (CVP <6), group 2 (CVP 6-12), and group 3 (CVP >12), with group 1 receiving the most aggressive and group 3 receiving the most conservative hydration rates (table).

The CVP-guided group received higher volumes of fluid (1827 ml vs. 1202 ml; p<0.001) and developed less CIN (primary end-point), defined as peak increase in sCr of either ≥25% or ≥ 0.5 mg/dl over baseline during first 72 h post-cath (15.9% vs. 29.5%; p=0.006). There was no difference in incidence of pulmonary edema between the groups (3.8% vs 3.0%; p=0.500).

This study demonstrates that CVP-monitoring may be an effective means of balancing the benefits of aggressive hydration with the risk of pulmonary edema in CHF patients undergoing coronary angiography. It is important to emphasize that the CVP-guided group received higher volumes of fluid compared to the control group and that this was a main driving force in the observed outcomes. Similar findings were seen in the **POSEIDON study** in which LVEDP monitoring allowed for higher volumes of fluid, which was in turn
associated with reduced rates of CIN. The bottom line seems to be that more volume offers more protection, and methods of hemodynamic monitoring may allow for optimizing hydration.

**UTSW Link**

**Supplementary Materials**

**Inclusion criteria:**

- CHF defined as LVEF <50%, typical attack of left heart failure in the past 1 year, presented with PND or orthopnea with rales or wheezes
- CKD defined as eGFR 15-60 ml/min/1.73 m²
- Patients scheduled to undergo diagnostic cardiac angiography or PCI

**Exclusion criteria:**

- Dialysis dependent
- Age <18
- Pregnancy or lactation
- Emergency cardiac cath
- Exposure to contrast within prior 7 days
- ADHF or cardiogenic shock

**Table:** Rates of IV fluid administration in CVP-guided and control groups

<table>
<thead>
<tr>
<th>CVP-Guided Hydration</th>
<th>Control</th>
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<tbody>
<tr>
<td>Group 1 CVP &lt;6</td>
<td>Group 2 CVP 6-12</td>
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<tr>
<td>3 ml/kg/hour</td>
<td>1.5 ml/kg/hour</td>
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</tbody>
</table>

**References**

Intensive Supportive Care plus Immunosuppression in IgA Nephropathy


Summary:

In patients with high-risk IgA nephropathy with urinary protein between 0.75 and 3.5 grams per day, immunosuppressive therapy in addition to supportive care does not significantly alter outcomes. Despite higher remission of proteinuria at the end of 3 years, there was no difference in annual rate of decline in eGFR.

Commentary:

IgA nephropathy is the most common glomerular disease worldwide and leading primary cause of ESRD in young white adults [1]. Current guidelines emphasize supportive care with ACE-inhibitors or ARBs to control proteinuria and blood pressure. The benefit of adding glucocorticoids has been unclear.

This multicenter, open-label, randomized, controlled trial with two-group, parallel, group-sequential design included adults in Germany aged 18-70 with biopsy-confirmed primary IgA nephropathy and proteinuria with hypertension or impaired renal function. Patients were enrolled in a 6-month run-in phase (n=337) of intensive supportive care: ACE/ARB (targeting BP <125/75 and proteinuria <0.75 g/day), target total cholesterol of <200 mg/dl, and lifestyle modification (diet, smoking cessation, avoidance of NSAIDs and nephrotoxins).

Among the 309 individuals who completed the run-in phase, 97 were excluded from the study phase due to improvement in proteinuria <0.75 g/day with supportive care. Individuals with proteinuria 0.75 and 3.5 g/day were randomly assigned to supportive care alone (n=80) or supportive care plus immunosuppressive therapy (n=82). Of note, the mean urine protein/creatinine ratio prior to randomization was decreased to 1.0 (>1g/d is currently an indication for immunosuppression). Those assigned to immunosuppression received either glucocorticoid monotherapy or cyclophosphamide, followed by azathioprine depending on eGFR.

The primary endpoints after 3 years of follow up included:

1) Full clinical remission:
   a. Protein-to-creatinine ratio <0.2
   b. Stable renal function eGFR did not drop more than 5 ml/min/m2
2) Rapid decline in eGFR of at least 15 ml/min/1.73 m2 of BSA.
While addition of immunosuppressive therapy resulted in greater remission of proteinuria (17% vs. 5%; p=0.01), there was no significant difference in rate of decline or rapid decline in eGFR (26% vs. 28%; p=0.75). Additionally, in the steroid arm, the improvement in proteinuria was transient, perhaps due to abrupt cessation rather than tapering of steroids. Immunosuppressive therapy was associated with increased incidence of adverse effects such as weight gain (p=0.049) and impaired glucose tolerance and diabetes (p=0.02).

An important finding in this study is that approximately 30% of subjects experienced clinically significant improvement in proteinuria with supportive therapies alone (prior to randomization). This highlights the power of simple interventions such as ACE/ARB, lipid-lowering therapy, and avoidance of risk factors such as smoking and nephrotoxic agents in this population, factors that can be implemented and encouraged in the primary care setting.

**UTSW Link**

**Supplementary Materials**

**Inclusion Criteria:**

- Age 18-70
- Primary IgA nephropathy (biopsy)
- Proteinuria >0.75 g/day + either:
  - HTN (≥140/90 or antihypertensive medications)
  - Or impaired renal function (eGFR<90)

**Exclusion Criteria:**

- eGFR<30 ml/min/1.73 m2
- Secondary or rapidly progressive, crescentic IgA nephropathy
- Other chronic renal diseases
- Prior immunosuppressive therapy
- >3.5g/d proteinuria after run-in phase

**References**

Pulmonary and Critical Care

Permissive Underfeeding or Standard Enteral Feeding in Critically Ill Adults


Summary:

There is minimal difference in outcomes of critically ill patient who receive permissive underfeeding versus standard non-protein calories.

Commentary:

The optimal amount of nutritional support for critically ill patients is not clear. Recent evidence has suggested that restricting non-protein calories may be beneficial. The hypothesis of this study was that permissive underfeeding would result in lower mortality rates in critically ill patients.

This study was a multicenter RCT (n = 894) that compared different feeding strategies in critically ill patients. The treatment group received permissive underfeeding (40 to 60% of calculated caloric requirements) and this was compared to a control group receiving standard enteral feeding (70-100%) for up to two weeks while maintaining similar protein intake between the groups. The primary outcome was 90-day mortality. The results showed there was no statistical difference in the primary outcome (27.2% vs. 28.9%) and all secondary outcomes between the two groups. A post-hoc analysis did show that the permissive underfeeding group has a lower incidence of renal-replacement therapy (7.1% vs. 11.4%). This study did not meet the hypothesized end-point, but does add to the literature that permissive underfeeding of non-protein calories is at least equivalent to standard feeding. The decreased incidence of renal-replacement therapy in the treatment group supports the concept that higher caloric intake may be associated with kidney injury. Further research should address whether there are certain subpopulation that may benefit from permissive underfeeding. In conclusion, permissive underfeeding compared to standard feeding had similar outcomes suggesting there may be benefit to starting trickle feeding in the most critically ill patient in the first 48 hours of care.

UTSW Link
Anticholinergic vs. Long-Acting B-Agonist in Combination with Inhaled Corticosteroids in Black Adults with Asthma


Summary:

In African American adults with asthma treated with inhaled corticosteroids (ICS) adding a LABA compared to tiotropium did not improve time to asthma exacerbation.

Commentary:

Asthma treatment guidelines recommend adding a LABA to asthma patients with suboptimal control on low-dose ICS. LABA therapy, however, has questionable safety with possibly increased hospitalizations and death which seem to disproportionately affect African American individuals with increased effects in patients with a specific genetic variation on the beta2 receptor (Arg16Gly locus of the β2-adrenergic receptor - ADRB2 gene).

This study was a multi-center RCT (n = 1,070) that compared LABA vs. tiotropium in African American patient’s with suboptimally controlled asthma on low dose ICS. Patients underwent genotyping to determine if they had the specific genetic variation on beta2 receptor associated with increased adverse events. The primary outcome was time to asthma exacerbation and secondary outcomes included adverse events at 18 months. The results showed there was no statistical difference in the primary outcome (0.42 vs. 0.37 exacerbations/person-years), percentage of people free from exacerbation at 1 year (74% vs. 75%) or adverse events (2% vs. 3%). The presence of the specific genetic variation on the beta2 receptor also did not affect outcomes. This study challenges the recommendations of adding LABA therapy to patients on low dose ICS and provides evidence that tiotropium can be considered as an alternative option, specifically in African Americans. However, adverse effects were not different between the treatment and control group in this study and further studies to compare the adverse effects of these medications is needed.

UTSW Link
Rheumatology

Symptom Assessment in Knee Osteoarthritis Needs to Account for Physical Activity Level

Dr. Wally Omar reviewing Lo, et al Arthritis Rheumatol. 2015 Nov;67(11):2897-904

Summary:

This study re-evaluated the main modality by which osteoarthritis progression is tracked (patient self-reporting) and whether this is actually an appropriate way to determine treatment options. 2,127 patients from a larger, multi-institution cohort known as the Osteoarthritis Initiative (OAI) were enrolled in this investigation, which focused on knee pain. Patients with and without knee osteoarthritis were given an accelerometer to wear, which tracked both the number of steps they had taken in a given day and their activity level overall. After 4-7 days of consistent accelerometer-wear, the patients were asked to complete a WOMAC pain scale as well as a Visual Analog Scale of pain. These results were taken in conjunction with the patients’ activity level and compared against knee plain-films to determine whether there is a correlation between the radiographic evidence of OA and the clinical evidence. The results of the investigation found severe limitations in the traditional WOMAC and VAS scales, with a “floor effect” of pain within each level of radiographic severity. When the pain scale was adjusted for level of activity using a “PAKS” scale, a more even distribution of pain was witnessed within each group, showing that symptomatic OA is actually more prevalent than currently exhibited when patient’s activity levels are assessed appropriately.

Conclusions:

We all know that OA is the most common type of arthritis, and with the population becoming more obese each year, the disease will only become more prevalent. The current methods by which we assess symptoms appear to be severely limited as they rely on the patient's reporting of pain rather than objective data. One of the flaws of the current method is that it does not take into account the fact that patients with longstanding OA tend to avoid activities that worsen their pain. These patients, therefore, will inevitably minimize the degree to which their disease affects them, as the result of their OA is no longer pain but inactivity. Newer technologies enables us to objectively measure daily activity levels in patients without forcing them to present to a gym or physical therapy center, which allows us as physicians to distinguish the patient who gets knee pain after walking three blocks from the patient who gets a similar amount of pain after running 10 miles. We can agree that the latter patient has more severe disease, regardless of what the radiographic evidence shows, but we now have a more objective method to describe this.
Should the PAKS rating system take flight, we may soon see a paradigm shift in OA treatment, as objective data has the capability of replacing subjective pain, especially when the stakes are as controversial as total knee replacement.

Table 2 highlights the fact that, when adjusted for age, sex and BMI, patients were less likely to report high levels of pain using the standard WOMAC score. When a PAKS score was calculated using activity level, however, a newer symptom score is generated, which appears to be reflective of the radiographic evidence of OA Severity (K/L grades)

**UTSW Link**