Dr. Edward Cary (A) first came to Dallas in 1890 as a medical salesman for his brother. He would go on to attend Bellevue Hospital Medical College (now NYU), specializing in ophthalmology. His brother unfortunately died in 1901, prompting a return to Dallas, where he opened an ophthalmology practice. He was recruited to serve on the faculty of The University of Dallas Medical Department later that year and was appointed dean of the University the next year. This school went on to become the Baylor College of Medicine in 1903 after Dr. Cary convinced Baylor University in Waco to form an affiliation with the Department. Dr. Cary was known for his strict academic standards, at one point awarding only 4 diplomas to a 120-person class, and for his fundraising ability. He was instrumental in raising money to establish what is now the Southwestern Medical Foundation and securing support for the original Southwestern Medical College. In his honor, the Basic Science Hall, the first building on campus, was renamed after him in 1960 (B).

(C) Parkland Hospital originally opened its doors on Oak Lawn and Maple Avenue in May 1894. The original hospital had 100 beds and sat on land that was originally designated as a city park. (D) The medical school sat in the famous barracks behind Parkland on Oak Lawn Avenue until 1955, when the Harry Hines campus was developed. Parkland would move to the location on Harry Hines boulevard in 1954. The medical school would then be renamed The University of Texas Southwestern Medical School after Baylor College of Medicine moved to Houston and the Southwestern Medical College formed an affiliation with The University of Texas.

Source: Perspectives Fall 2014 Images courtesy UTSW digital Archive.
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Introduction

Welcome and thank you for reading the inaugural 2017-2018 edition of UTSW Internal Medicine Journal Watch! UTSW IM Journal Watch is a bi-monthly publication produced and edited by the residents of the Internal Medicine Residency at UTSW with the assistance of faculty mentors. The purpose of the publication is to provide quick updates and commentary on recent publications in all the specialties in internal medicine, including general internal medicine, geriatrics, and quality improvement. It is our goal to provide everyone with opportunities to critically read and interpret recent medical literature to improve and advance the care for the patients for whom we serve.

The editors welcome feedback for the publication as well as suggestions for recent articles to review in future editions. The editors can be reached at UTSWIMJournalWatch@gmail.com. In the meantime, you can follow us on twitter @UTSWIMJW and http://www.utswimjournalwatch.wordpress.com/.

We thank the authors of the following reviews, as well as the faculty mentors for dedicating their time to further our education. We hope you enjoy reading!

Timothy Brown, Christina Yek, Emily Bowen, Stephanie Chiao
UTSW IM Journal Watch Editors, 2017-2018
CASE:
A 52-year-old Caucasian male with a past medical history of hypercholesterolemia and type 2 diabetes presents to the ED with new-onset shortness of breath and chest discomfort that began at rest. Troponin T at the time of presentation is negative, and all other labs are pending. The following EKG is performed on presentation to the ED, 90 minutes after the onset of symptoms:

![EKG on presentation, 90 minutes after the onset of symptoms](image)

**Figure 1.** EKG on presentation, 90 minutes after the onset of symptoms

**DESCRIBE THE EKG:**
Borderline sinus bradycardia, J-point depression with upsloping ST-segment continuing into peaked-T waves in the precordial leads, and isolated ST-segment elevation in aVR

**WHAT IS THE DIAGNOSIS?**
A. Acute Coronary Syndrome (ACS)
B. Left Ventricular Hypertrophy (LVH) with Strain
C. Hyperkalemia
D. Early Repolarization Pattern (ERP)
E. Pulmonary Embolism

**WHAT IS THE NEXT BEST STEP IN MANAGEMENT?**
This patient’s EKG pattern, described as “de Winter’s EKG pattern,” is highly indicative of proximal left anterior descending artery occlusion, and—according to the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction (STEMI)—warrants immediate referral for invasive
angiography. These guidelines suggest performing a transthoracic echocardiogram to assist with triage if the EKG is difficult to interpret, but recommend cath lab activation if doubt still remains. As an internal medicine resident, if one is unsure of the diagnosis, the most practical approach would be to manage the patient per the non ST-segment elevation acute coronary syndrome (NSTE-ACS) guidelines, contact the cardiology fellow immediately, inform her/him of your suspected finding, and get the ultrasound to bedside; however, if one feels confident in the diagnosis, immediate cath lab activation is indicated.

**DISCUSSION:**
First described by de Winter, Verouden, Wellens, and Wilde in a correspondence to the editor of NEJM in 2008, de Winter’s EKG pattern is defined as “a 1- to 3-mm upsloping ST-segment depression at the J-point in the precordial leads continued into tall, positive symmetrical T waves...[usually with] a 1- to 2-mm ST-segment elevation in lead aVR” (Figure 1, leads V3-4 and lead aVR). Additionally, an identifying feature of this pattern—which differentiates it from the rare and transient hyperacute T-waves known to be associated with early STEMI—is its static nature (Figure 2). Within their database of 1532 patients with anterior myocardial infarction, de Winter et al. found that 2% of patients did not have the expected anterior ST-segment elevation, but instead had this new characteristic pattern. Further investigation led to the finding that patients with this EKG pattern were more likely to be male, to be younger, and to have hypercholesterolemia than those with traditional STEMI EKG findings. The mechanism for this electrophysiological phenomenon is currently unknown but the suggested explanations include the following: (1) an anatomical variant of the Purkinje fibers with endocardial conduction delay; (2) ischemic ATP depletion leading to lack of activation of the sarcolemmal ATP-activated potassium channels; (3) a large area of transmural ischemia preventing anterior injury currents and presenting only superiorly in aVR; and (4) isolated subendocardial injury secondary to subtotal occlusion of the LAD, total occlusion of the LAD with collateral circulation, or total occlusion of the LAD without collateral circulation in the setting of subepicardial downregulation of myocardial metabolism protecting it from ischemia.

In summary, of the option choices above, ACS is the best answer given the patient’s presentation and the characteristic EKG pattern as described by de Winter et al. LVH with strain is an incorrect answer as this patient’s EKG does not exhibit any of the several QRS-dependent diagnostic criteria for LVH; additionally, in the setting of strain, the ST-segment and T-wave are concordant with each other and discordant with the preceding QRS polarity. Hyperkalemia is an incorrect answer as it classically presents with diffuse peaked T-waves without ST-segment depression or chest discomfort. ERP is an incorrect answer as this pattern exhibits J-point elevation, not depression, and is not associated with chest discomfort. Pulmonary embolism is an incorrect answer as it is not associated with the above-described ACS-related pattern.
Figure 2. EKG performed 71 minutes after the initial EKG with persistence of the aforementioned EKG findings and without evolution to STEMI

REFERENCES:
Dr. Grace Liu

A 36 year old otherwise healthy man presented to the ED with a 2-day history of fever and a diffuse pruritic rash. The lesions began as small red papules that progressed to vesicles, pustules, and crusted papules over his scalp, face, upper extremities, chest, abdomen and back. He endorsed associated malaise and mild headache. Social history was negative for recent travel, drug use, or use of any new foods, detergents, or medications.

**WHAT IS YOUR DIAGNOSIS?**

A) Disseminated herpes simplex virus  
B) Disseminated zoster  
C) Primary varicella  
D) Disseminated bacterial folliculitis

**WHAT LAB TEST WOULD YOU ORDER TO LOOK FOR POTENTIALLY FATAL COMPLICATIONS OF THE DISEASE?**

A) Basic metabolic panel  
B) Liver function tests  
C) Urinalysis  
D) Complete blood count

---

**Figure.** A) Generalized erythematous papules (some crusted) and pustules on the neck, anterior chest, and bilateral upper extremities. B) Similar crops of papules and vesicles on an erythematous base across the upper back.
**DISCUSSION**

Primary infection with varicella zoster virus (VZV), or chickenpox, is a highly contagious infection characterized by an exanthematous vesicular rash accompanied by systemic symptoms. VZV is transmitted through inhalation of infectious droplets or through direct contact with fluid contained within vesicular lesions. The viral incubation period ranges from 10-21 days, and patients are infectious from two days before the rash starts until all the vesicles have crusted over. Most patients seroconvert after primary infection, but VZV can lie dormant in ganglionic neurons and reactivate to cause herpes zoster (shingles) in 10-30 percent of the population. (Gnann)

Symptoms of primary varicella include a flu-like prodrome prior to the onset of a rash. The rash begins as erythematous macules and papules that progress to become vesicles and finally, crusted papules. The lesions develop in a centripetal pattern beginning on the face and trunk and spreading to involve the extremities. The presence of lesions of different stages and ages at presentation is a hallmark physical finding. (Leonid and Evelyn) While generally a benign and self-limiting disease in children, primary varicella can result in serious complications in infected adults including pneumonia, bacterial super-infection of skin and soft tissue, neurologic disease (encephalitis, acute cerebellar ataxia), and hepatitis. Liver involvement with varicella generally affects immunosuppressed patients and, while rare, can lead to fulminant liver failure and death. (Gnann)

In the case described, the diagnosis of primary varicella was made based on history and examination. A swab of vesicular fluid sent for confirmatory VZV PCR returned positive. Other methods of diagnosis include a bedside Tzanck smear of the blister roof (revealing multinucleated giant cells with intranuclear inclusion bodies) or serologic testing for VZV IgG/IgM (of note, IgM is usually negative with zoster reactivation) (Leonid and Evelyn). Antiviral therapy is recommended within the first four days of the cutaneous eruption in adults, pregnant women, and immunocompromised hosts. Our patient was treated with a 5-day course of valacyclovir 1g three times daily, with which his infection resolved.

**REFERENCES**

Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor


SUMMARY

Hereditary angioedema is a rare condition characterized by potentially fatal episodic attacks of localized swelling without urticaria or pruritus. It is caused by deficiency or dysfunction of the C1 inhibitor protein, promoting bradykinin-mediated capillary hyperpermeability. Current standard prophylaxis is replacement with intravenous C1 inhibitor, which is effective at reducing the frequency and severity of attacks, but carries several risks and burdens associated with requiring reliable intravenous access, including infection, thrombosis, and phlebitis.

The Clinical Study for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy (COMPACT) study was a phase 3, international, prospective, double-blind, randomized controlled trial that tested whether subcutaneous CSL830, a human plasma-derived C1 inhibitor preparation, could reduce the frequency of attacks in patients with angioedema when compared with placebo. The trial recruited individuals diagnosed with hereditary angioedema with significant functional impairment not already receiving IV C1 inhibitor. Participants were randomized to receive either 40 IU per kilogram body weight or 60 IU per kilogram body weight of CSL830 twice weekly for 16 weeks followed by placebo for 16 weeks or vice versa in an intention-to-treat analysis. The primary endpoint was the number of angioedema attacks per treatment period, while secondary endpoints included the percentage of participants with >50% reduction in the number of attacks and the number of times rescue medication was used.

The mean difference in attacks compared with placebo was 2.42 fewer attacks per month with 40 IU CSL830 and 3.51 fewer attacks per month with 60 IU CSL830. While the rate of attacks did not differ significantly between the two doses, the percentage who had a response was greater in the 60 IU group (90% vs 76%). The severity of attacks was also lower than in those receiving placebo. The mean frequency of rescue medication use was reduced compared to placebo. Strikingly, nearly 40% of participants in each CSL830 group did not have an attack, compared with up to 9% of participants in the placebo groups. Most adverse events were mild, and only one serious adverse event occurred – urosepsis in a patient receiving the 40-IU dose.

COMMENTARY

Given the rarity of this disease, the present study demonstrates considerable efficacy of subcutaneous C1 inhibitor in reducing attack rate and severity with a high response rate, comparable to that of IV C1 inhibitor. However, the follow up period is too limited to remark on long term adverse events or sustained efficacy. Further, the doses used in the present study are 3-4 times greater than the 1000IU twice weekly dose of IV C1 inhibitor, suggesting costs would be even higher than that of IV C1 inhibitor which already costs over $4000 per dose. While subcutaneous administration offers the potential for increased accessibility, the novelty and associated cost may make it very difficult to offer to patients.
### Table 1: Primary, Secondary, and Exploratory Efficacy End Points in the Intention-to-Treat Population

<table>
<thead>
<tr>
<th>End Point</th>
<th>Treatment Sequences with 40 IU/kg</th>
<th>Treatment Sequences with 60 IU/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSL830 (N=43)</td>
<td>Placbo (N=44)</td>
</tr>
<tr>
<td></td>
<td>Within- Patient Difference</td>
<td>P Value</td>
</tr>
<tr>
<td>No. of time-normalized attacks per mo</td>
<td>1.19 (0.54 to 1.85)</td>
<td>3.6 (2.96 to 4.26)</td>
</tr>
<tr>
<td>— mean (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in attacks vs. placebo — %</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>Median</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Secondary efficacy end points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with a response — % (95% CI)</td>
<td>76 (62 to 87)</td>
<td>90 (77 to 96)</td>
</tr>
<tr>
<td>&gt;50% reduction in attacks vs. placebo</td>
<td>67</td>
<td>83</td>
</tr>
<tr>
<td>&lt;70% reduction in attacks vs. placebo</td>
<td>52 (42 to 79)</td>
<td>64 (44 to 91)</td>
</tr>
<tr>
<td>50% reduction in attacks vs. placebo</td>
<td>43 (29 to 58)</td>
<td>58 (42 to 72)</td>
</tr>
<tr>
<td>Use of rescue medication per mo</td>
<td>1.13 (-1.44 to 3.69)</td>
<td>5.55 (3.10 to 8.00)</td>
</tr>
<tr>
<td>— mean (95% CI)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in use of rescue medication vs. placebo — %</td>
<td>89</td>
<td>100</td>
</tr>
<tr>
<td>Median</td>
<td>70</td>
<td>89</td>
</tr>
<tr>
<td>Exploratory efficacy end points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of days of interstitial angioedema symptoms per mo</td>
<td>1.57±2.64</td>
<td>7.00±5.75</td>
</tr>
<tr>
<td>Average severity score for attacks†</td>
<td>1.71±0.59</td>
<td>2.01±0.49</td>
</tr>
<tr>
<td>Patients with reduction to &lt;1 attack per 4 wk period — no./total no.(95%)‡‡‡</td>
<td>34/49 (53)</td>
<td>32/45 (71)</td>
</tr>
</tbody>
</table>

* Listed are values for the patients in the intention-to-treat population for whom data were available. CI denotes confidence interval.
† Values in this category are least-squares means as estimated from a mixed model.
‡ In this category, the estimated difference between the patients who received 40 IU of CSL830 per kilogram and those who received 60 IU of CSL830 per kilogram was -0.64; 95% CI, -1.43 to 0.16; P=0.11.
§ The reduction in attacks was evaluated in 58 patients in the 40-IU group and in 40 patients in the 60-IU group.
¶ In this category, the estimated difference between the patients who received 40 IU of CSL830 per kilogram and those who received 60 IU of CSL830 per kilogram was -0.76; 95% CI, -2.29 to 0.77; P=0.31.
†† Severity scores were 1 for mild, 2 for moderate, and 3 for severe.
‡‡‡ Values are for patients who had at least one attack during a 4-week period while receiving placebo.
Cardiology

Cardiac Manifestations of Parasitic Diseases


**Summary**

Parasitic infections due to protozoa and helminths are extending outside endemic areas and becoming more common worldwide. These parasitic infections present in a variety of ways, including injury of the myocardium and pericardium. It is essential that healthcare workers globally are aware of these clinical manifestations.

**Protozoa**

Chagas disease or American Trypanosomiasis, caused by Trypanosoma cruzi, is most prevalent in Latin America. Transmitted by infected triatomine bugs, the infection has an acute and chronic phase, with the latter continuing for the duration of the host’s life. Chagas disease is characterized by involvement of the esophagus, colon, nervous system and heart with Chagas cardiomyopathy being the most serious form of disease. The heart disease is considered an “arrhythmogenic cardiomyopathy,” characterized by atrial and ventricular arrhythmias and conduction system defects that manifest as right bundle branch block on ECG. Fibrosis classically involving the posterior and apical regions of the left ventricle differentiates Chagas from other forms of cardiomyopathy. Apical aneurysm associated with mural thrombi and embolic events is a hallmark finding as well. Treatments include nifurtimox or benznidazole.

Sleeping sickness or African Trypanosomiasis, caused by Trypanosoma brucei gambiense and brucei rhodesiense are transmitted by tsetse flies and occur mostly in sub-Saharan Africa. There are two stages with stage 1 (hemolymphatic) being a systemic febrile illness and stage 2 (meningoencephalitic) being a variety of neurologic symptoms. Cardiac manifestations such as myocarditis, pancarditis, arrhythmias and heart failure occur mostly during the hemolymphatic stage. ECG findings may show low voltage, PR depression, nonspecific ST-T wave changes and prolonged QT. Treatments include Suramin, pentamidine, eflornithine and organic arsenicals.

Leishmaniasis is mostly transmitted by the phlebotomine sand fly, which is found in the tropics, subtropics and southern Europe. There are some case reports of myocarditis and pericarditis but most commonly, the cardiac complications are caused by treatment side effects. Pentavalent antimonials (SbV) are associated with t-wave inversions, prolonged QT, AVCs, PVCs, torsades de pointes and SCD at higher doses. Amphotericin B can cause a reversible cardiomyopathy.

**Helminths**

Schistosomiasis is caused by Schistosoma mansoni, S. haematobium and S. japonicum, affects people in over 70 countries, and requires direct contact with snail-infested water. In humans, the worms migrate in the blood to the liver to mature and spread to the intestines, bladder or other sites. The disease is characterized by acute and chronic phases, both of which can be asymptomatic or include symptoms such as portal hypertension, urinary reflux and obstruction, and pulmonary arterial hypertension leading to right heart failure. Diagnosis is made by finding schistosome eggs in stool, urine or rectal snips. Treatment is recommended regardless of symptoms with Praziquantel.
Tropical Endomyocardial Fibrosis, thought to be the most common form of restrictive cardiomyopathy worldwide, is found mostly in the tropics of Africa, Asia and South America. Etiology and pathogenesis are not understood well but chronic hypereosinophilia from parasitic infections is thought to be a probable principal cause. Separated by active and chronic phases, EMF typically presents initially as a febrile illness associated with pancarditis and hypereosinophilia. The chronic phase is characterized by ventricular thrombosis leading to endocardial fibrosis, eventually involving both ventricles. Patients often present with heart failure (with right ventricular restriction predominating) and ascites. Diagnosis is made with echocardiography exhibiting restrictive filling with apical fibrosis, reduction of ventricular volume, and atrial enlargement and dysfunction. EMF has a poor prognosis with a high occurrence of sudden death from fatal arrhythmias or thromboembolism. Medical management of heart failure, arrhythmias and thromboembolism is standard but surgical intervention improves survival.

**COMMENTARY**

Protozoa and helminths can affect the heart, mostly the myocardium and pericardium. As the number of travelers and those with immunocompromise increases, these illnesses which were previously contained in specific endemic areas are beginning to be seen around the world, including our very own Parkland Hospital! It is essential that clinicians know the risk factors and presentations of these parasitic infections and keep them in their differential.
Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes
Dr. Laurette Femnou Mbuntum reviewing Neal, B, et al. NEJM 2017 Jun 12 [Epub ahead of print].

SUMMARY
Canagliflozin is a sodium glucose cotransporter 2 (SGLT2) inhibitor that is used as a second line oral agent in patients with diabetes and has been shown to reduce hyperglycemia, blood pressure, albuminuria, and body weight. This study includes analysis of data from the original CANVAS (Canagliflozin Cardiovascular Assessment Study) study as well as the renal arm, CANVAS-R. Participants were 10,142 men and women with type 2 diabetes with hemoglobin A1c between 7% and 10.5%. They were either 30 years old or older with known symptomatic atherosclerotic cardiovascular disease or 50 years old or older with two or more cardiovascular risk factors. There was a required eGFR of at least 30 ml per minute per 1.73 m² of body-surface area. Patients in the CANVAS arm were randomized to receive placebo, canagliflozin 300 mg daily, or canagliflozin 100mg daily. In the CANVAS-R arm, patients were randomized to receive canagliflozin 100 mg daily with an optional increase in dose to 300 mg daily after 12 weeks vs placebo. Further diabetes management was in accordance with local best practices. The primary outcome was a composite outcome, which included death from cardiovascular causes, nonfatal myocardial infarction, and stroke. Rates of primary outcome events were lower in the treatment group compared to the placebo, 26.9 vs. 31.5 events per 1000 patient-years (hazard ratio, 0.86; 95% CI, 0.75 to 0.97; P<0.001 for noninferiority; P=0.02 for superiority). There was no difference between the treatment and placebo groups for the secondary outcomes of death from any cause and death from cardiovascular causes. Progression of albuminuria occurred less frequently in the treatment group than the control, and regression of albuminuria occurred more frequently in the treatment group than the control. Regarding the safety profile of canagliflozin, there was a higher risk of limb amputation in treatment group (6.3 vs. 3.4 participants with amputation per 1000 patient-years; hazard ratio of 1.97; 95% CI, 1.41 to 2.75). This trial also demonstrated the known risks of increase in bone fractures, infections of genitalia, and volume depletion.

COMMENTARY
Cardiovascular disease and renal impairment commonly co-exist in patients with long standing type 2 diabetes. SGLT2 inhibitors are receiving a lot of attention because of their favorable effects on cardiovascular outcomes. Similar to the EMPA-REG trial, the CANVAS study showed improvement in the primary composite end point of cardiovascular death, non-fatal MI, and stroke. The number needed to treat in CANVAS is around 220, compared to 63 for EMPA-REG. This higher number needed to treat could be due to the fact that the CANVAS trial included high risk patients without proven CV disease in addition to patients with known CV disease. This second positive study suggests that the cardiovascular benefit is a class effect of SGLT2 inhibitors. In addition, the study shows that canagliflozin slows the progression of albuminuria in patients with baseline albuminuria and can even reverse the process. Currently, ACE inhibitors are the main drugs used in diabetic patients with proteinuria. The CANVAS trial suggests that SGLT2 inhibitors could be considered as an alternative in diabetic patients with proteinuria and contraindications to ACE inhibitors. SGLT2 inhibitors alone are likely not adequate to treat hyperglycemia in diabetes as
monotherapy, given the relatively small reduction in hemoglobin A1C (-0.58%). However, for patients who are experiencing macro and microvascular complications of diabetes including renal dysfunction and cardiovascular disease, they should be considered preferentially as second line agents, particularly for those patients who are already close to A1C goals. However, canagliflozin is very expensive, costing about $486 for a one month supply of the 100 mg dose and $517 for a one month supply of the 300 mg dose. Additionally, one must consider the side effect profile of canagliflozin, including amputations with a number needed to harm of 344.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (N=5795)</th>
<th>Placebo (N=4347)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
<td>26.9</td>
<td>31.5</td>
<td>0.86 (0.75–0.97)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.87 (0.72–1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.85 (0.69–1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>7.1</td>
<td>8.4</td>
<td>0.90 (0.71–1.15)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>11.2</td>
<td>12.6</td>
<td>0.89 (0.73–1.09)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>7.9</td>
<td>9.6</td>
<td>0.87 (0.69–1.09)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>118.7</td>
<td>131.1</td>
<td>0.94 (0.88–1.00)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>5.5</td>
<td>8.7</td>
<td>0.67 (0.52–0.87)</td>
</tr>
<tr>
<td>Death from cardiovascular causes or hospitalization for heart failure</td>
<td>16.3</td>
<td>20.8</td>
<td>0.78 (0.67–0.91)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.5</td>
<td>0.87 (0.74–1.01)</td>
</tr>
<tr>
<td>Progression of albuminuria</td>
<td>89.4</td>
<td>128.7</td>
<td>0.73 (0.67–0.79)</td>
</tr>
<tr>
<td>40% reduction in eGFR, renal-replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.60 (0.47–0.77)</td>
</tr>
</tbody>
</table>
Gastroenterology and Hepatology

Association between time to colonoscopy after positive fecal test results and risk of colorectal cancer and cancer state at diagnosis


SUMMARY

Every PCIM and PRIME resident knows that in a busy clinic, a screening colonoscopy can be a hard sell. Alternative colon cancer screening methods like annual fecal immunohistochemistry testing (e.g. FIT) are becoming increasingly popular due to ease of use, low cost, and effectiveness. But when you’re on a MICU rotation and a positive FIT result lands in your “In Basket,” how quickly must you schedule your patient for colonoscopy? This large retrospective cohort study in the Kaiser Permanente system in California examined over 81,000 positive FIT tests in 1.2 million patients (8.5% positive rate). The primary outcome was diagnosis of colorectal adenocarcinoma at any stage diagnosed within 6 months after colonoscopy. The authors observed patients with positive FIT and separated them into cohorts based on the time to follow up colonoscopy: within 8 to 30 days, 2 months, 3 months, 4 to 6, 7 to 9, 10 to 12, or more than 12 months. Most patients received early follow-up with colonoscopy (63% within 2 months, 75% within 3 months, 83% within 12 months). The overall cancer detection rate within 12 months was 4.9% in patients with a positive FIT test. Compared with patients who received follow up within 1 month, patients who had colonoscopy within 9 months did not have an increased risk of any colorectal cancer or advanced stage cancer. Those who had a colonoscopy more than 10 months later had a higher risk of diagnosis with colon cancer (OR, 1.48 [95% CI, 1.05-2.08]). These differences persisted after controlling for factors such as age, sex, ethnicity, smoking status, and anemia in the year before the FIT.

COMMENTARY

This study provides reassurance to doctors, patients and health systems like Parkland and the VA that there is no urgent need to rush to colonoscopy after a positive FIT test. A recent study at a VA hospital showed the median follow-up time between positive FIT and colonoscopy was 101 days, which is acceptable according Corley et. al; similar median follow-up times are reported in county health systems. Several societies and systems like the VA recommend colonoscopy within 30-60 days. This may be unnecessary. While the authors report that a 10-month delay was associated with an increase in the risk of cancer diagnosis, some caution is needed even in this interpretation. Two limitations of the study include the facts that the study was observational, and the reason for colonoscopy was not recorded. A possible explanation is that patients who underwent colonoscopy in the late follow-up period disproportionately did so due to symptoms of cancer; in fact, 14% of patients with a positive FIT never had a colonoscopy. A randomized trial would be needed to tease out this association (but this may be unlikely to occur). On a more basic level, these results are compatible with our mechanistic understanding of colon cancer as a slow step-wise process resulting from accumulating genetic mutations and/or epigenetic alterations over decades.

Mortality rates from colon cancer have decreased significantly over the past several decade (see figure) driven by multiple factors including improved screening and early detection. But improved treatments such as better surgical practices, highly effective neoadjuvant chemotherapy regimens, and better diets also have contributed significantly.
**Figure**: Colorectal-Cancer Mortality (Top) and Stage-Specific Incidence (Bottom) among People 50 Years of Age or Older in the United States, 1975–2012. From Welch et al (2)

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**REFERENCES**

Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults: The ALLHAT-LLT Randomized Clinical Trial.

Dr. Jake Hutto reviewing Han, Benjamin H., et al. JAMA Intern Med 2017 Jul 1;177(7):955-65.

SUMMARY

Statins for primary atherosclerotic cardiovascular prevention reduce cardiovascular events and morbidity, but there is not a clear consensus of data supporting the use of statins for primary cardiovascular prevention in adults over the age of 75. This article is a post-hoc secondary analysis of participants in the Lipid Lowering Trial (LLT) component of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) that took place from 1994-2002. The authors evaluated statin treatment in 2867 adults aged 65 years and older with hypertension and without known atherosclerotic cardiovascular disease. 1467 individuals were randomized to treatment with pravastatin sodium 40mg daily, and 1400 individuals were randomized to usual care (UC). Treatment in the UC group was at the discretion of the patient’s primary care physician. The primary outcome was all-cause mortality, and secondary outcomes included cause-specific mortality and nonfatal myocardial infarction or fatal coronary heart disease combined. Hazard ratios for all-cause mortality in the pravastatin group vs. the UC group were 1.18 (95% CI 0.97 - 1.42, P = 0.09) for all adults 65 years and older, 1.08 (95% CI 0.85 - 1.37, P = 0.55) for adults aged 65 - 74 years, and 1.34 (95% CI 0.98 - 1.84, P = 0.07) for adults aged 75 years or older. Hazard ratios for coronary heart disease events, stroke, heart failure, and cancer rates were also not significantly different among treatment groups. Overall, there was no significant benefit with pravastatin treatment for primary cardiovascular prevention in adults over 65 with hypertension, as well as a statistically non-significant trend towards increased all-cause-mortality with pravastatin treatment in individuals over the age of 75.

COMMENTARY

We see numerous older adults in clinic that are on many medications, and this article highlights an opportunity to discuss with our patients the risks and benefits of starting statin therapy beyond the age of 75 years. Studies have shown that elevated lipid levels are less predictive of overall cardiovascular risk as patients age, and have also shown an increased mortality rate associated with low lipid levels in the oldest age groups. Though evidence is unclear, there are also studies that show adults over the age of 65 are at higher risk for statin-induced myopathy and musculoskeletal problems. They also have a five times higher risk of hospitalization for rhabdomyolysis compared to adults under the age of 65. Furthermore, there is questionable evidence regarding the use of statins in elderly individuals and negative effects on cognition. Some studies showed that statin treatment did not lead to cognitive decline or incidental dementia, but these studies acknowledge that they included only a very small number of patients over the age of 80. The HOPE (Heart Outcomes Prevention Evaluation) randomized elderly individuals to rosuvastatin treatment or placebo and showed no statistically significant difference in death from any cause between the two groups (5.3% vs 5.6%, respectively). When individuals were stratified by age to compare all-cause mortality in individuals 65 years or younger with those older than 65 years, no benefits in all-cause mortality were noted between the two groups.
While this analysis of the ALLHAT-LLT trial does not address continued statin therapy in elderly patients with known atherosclerotic coronary artery disease or treatment with a high intensity statin, it does highlight an opportunity for us to avoid adding to polypharmacy by discussing the risks and benefits of starting statins for primary prevention in older adults.
The Testosterone Trials:

- Testosterone Treatment and Cognitive Function in Older Men with Low Testosterone and Age-Associated Memory Impairment
- Testosterone Treatment and Coronary Artery Plaque Volume in Older Men with Low Testosterone

Dr. Jasmine Singh reviewing:


Summary

The Testosterone Trials (TTrials) were a set of 7 trials that studied the efficacy of testosterone replacement in elderly men with low testosterone secondary to aging. The trials consisted of nearly 800 men from multiple US academic medical centers over the age of 65 who had low serum testosterone (<275 ng/dL) and symptomatic hypogonadism, defined by impaired sexual function, physical function or vitality. Patients were assigned to either testosterone gel (n=394), adjusted to keep the serum testosterone within the normal range for young men, or placebo (n=394) for 12 months. Two important sub-trials studied the effect of testosterone replacement on cognitive function as well as on coronary artery non-calcified plaque volume.

The Cognitive Function Trial consisted of a subgroup of 493 men (n=246 for placebo and n=247 for testosterone) who met criteria for age-associated memory impairment (AAMI), which was based on both objective evaluation of memory performance and subjective memory complaints. The primary outcome was mean change from baseline to 6 and 12 months for delayed paragraph recall and did not show a significant difference between either group (adjusted estimated difference, −0.07 [95%CI, −0.92 to 0.79]; P = .88). Secondary outcomes included visual impairment (Benton Visual Retention Test), executive function (Trail-Making Test B minus A), and spatial ability (Card Rotation Test) and also did not show a mean change between treatment and placebo.

The Coronary Plaque Trial consisted of a sub-group of 138 men (n=65 for placebo and n=73 for testosterone). The primary outcome was non-calcified coronary artery plaque volume, measured by Coronary Computed Tomographic Angiography (CCTA), and showed a significantly greater increase in non-calcified plaque volume from baseline to 12 months after therapy (estimated difference, 41mm$^3$; 95%CI, 14 to 67mm$^3$; P = .003). Secondary outcomes included total coronary artery plaque volume and coronary artery calcium score and also showed a mean difference between treatment and placebo group. There were no major adverse cardiovascular events observed in either group.

Commentary

The Cognitive Function Trial showed that despite previous claims, testosterone replacement is not associated with improved cognitive function in hypogonadal men with AAMI. The Coronary Plaque trial found an increased coronary artery non-calcified plaque volume as measured by CCTA, raising concern about the cardiovascular safety of testosterone replacement in older men.
One limitation of these trials is the duration of therapy, as they only examined variables prospectively for the duration of one year. Furthermore, a longer Coronary Plaque Trial could potentially provide insight about the effect of testosterone on major cardiovascular outcomes. One limitation particular to the Coronary Artery Plaque Trial includes its small size, and larger studies are warranted to clarify its findings. Notably, the TTrials only examined the effects of testosterone replacement in elderly men with hypogonadism caused by aging, and these findings may not generalize to other populations such as men of other ages or with androgen deficiency of other etiologies. The TTrials are the largest placebo-controlled study examining the effects of testosterone replacement in elderly males and provide important insight about implications of replacement therapy.
Infectious Diseases

Antibiotic Prescribing for Nonbacterial Acute Upper Respiratory Infections in Elderly Persons

Dr. Adrian Peña reviewing Silverman et al, Ann Int Med. 2017 June 6;166 (11):765-774

Summary

This study was a one-year, retrospective analysis examining the prevalence and predictors of antibiotic prescribing for non-bacterial acute upper respiratory infections (AURIs) among older (≥66 years) Canadian patients in primary care settings. Data was obtained from population-based administrative databases from the Institute for Clinical Evaluation Sciences and included all primary care physician visits for nonbacterial AURIs in Ontario, Canada. The primary outcome was the prescription of antibiotics within 30 days of patient presentation with a nonbacterial AURI.

Data from 185,014 distinct patient episodes were included in the study. The most common infections were the common cold (53.4%), acute bronchitis (31.3%), acute sinusitis (13.6%), and acute laryngitis (1.6%). Overall, antibiotics were prescribed to 46.2% of patients. Regression analysis showed that patients were more likely to receive antibiotic prescriptions from male physicians (43.0% vs 41.8% female physicians, p=.016); late-career physicians (43.0%) as compared to early-career physicians (38.4%, p<.001); physicians without hospital affiliation (43.3% vs 40.8%, p<.001); physicians whose daily patient load exceeded 45 patients per day (44.4%) as compared to physicians who saw <25 patients per day (40.3%, p<.001); and physicians who trained outside of the US and Canada (45.2%) as compared to physicians who were US/Canadian graduates (41.6%, p<.001). Finally, US/Canada-trained physicians were more likely to prescribe broad-spectrum antibiotics for nonbacterial AURIs (66.0%) than physicians who trained outside of the US and Canada (71.6%, p<.001).

Commentary

Antibiotic resistance is recognized as a major public health concern and one of the greatest threats to human health worldwide (CDC). While antibiotic resistance has historically been a clinical problem in hospital settings, recent data show resistant organisms have been detected in primary care settings as well (IDSA). This phenomenon is largely driven by unnecessary antibiotic use. Despite guidelines discouraging this practice, antibiotics continue to be prescribed at high rates for non-bacterial AURIs (CDC). Prior studies have found that rates of inappropriate antibiotic prescribing may be explained in part by facility and regional characteristics (Zhang, Steinman and Kaplan). In this retrospective cohort study, Silverman et al sought to explore physician factors associated with inappropriate antibiotic prescribing.

This study found that physician career stage, daily patient volume, and location of training were predictive of inappropriate antibiotic prescribing. Limitations of the study include an older cohort (in large part due to the eligibility of the Ontario Drug Benefit Program), and a widespread catchment area including both rural and urban settings (patient and practice location were not accounted for), which may limit generalizability of results. Also, the study did not capture a physician’s motivation to prescribe antibiotics, which could reveal medical justification and/or identify additional modifiable factors.

Identifying physician factors contributing to inappropriate antibiotic prescribing may help guide the development of stewardship interventions. For late career physicians, one reasonable approach might include accountable justification for prescription, financial incentives for reducing
antibiotic prescription, and peer-comparison approaches along with electronic medical record-based decision support where available. Another high-impact cohort would be trainees in undergraduate and graduate medical education. Possible interventions in this target group include emphasizing adverse drug events associated with macrolide and quinolone use (i.e. cardiac arrhythmias, drug interactions, neuropathic toxicity), education on morbidity and mortality associated with antibiotic overuse (especially with regards to multi-drug resistant organisms), reinforcement of knowledge on clinical indications for antibiotic usage in the outpatient setting, and promotion of antibiotic stewardship at an earlier stage of clinical training.

Given that clinical practice guidelines alone have had limited effects on antibiotic prescribing practices, alternative strategies are needed. These study findings may aid the development of future educational initiatives if confirmed in other practice settings.

REFERENCES

Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients
Dr. Christopher Scoma reviewing Goldberg et al, NEJM. 2017 Jun 15;376(24):2394-2395.

SUMMARY

The THINKER (Transplanting Hepatitis C Kidneys into Negative Kidney Recipients) trial was an open-label, single-group, pilot trial at the University of Pennsylvania that enrolled hepatitis C virus (HCV)-negative patients with end-stage renal disease on the waiting list for kidney transplantation (n=10). Study participants consented to receive single kidney transplantation from deceased donors with untreated HCV genotype 1 infection. The primary outcome of the study was rate of HCV cure after transplantation; secondary outcome was renal allograft function at 6 months post-transplantation.

Transplant recipients received induction therapy with intravenous glucocorticoids and rabbit anti-thymocyte globulin, followed by oral tacrolimus, mycophenolate mofetil, and prednisone. Three days after transplantation, 100% (10/10) recipients had detectable plasma HCV RNA ranging from 15 IU/mL to 193,000 IU/mL. Elbasvir–grazoprevir was initiated in all recipients once HCV viral load was detected and therapy was maintained for 12 weeks. All recipients were cured of HCV (defined as sustained virologic response 12 weeks after end of treatment).

Recipient serum creatinine at 6 months post-transplantation ranged from 0.8-1.3mg/dL (median 1.1mg/dL); eGFR ranged from 51.8-83.1 mL/min (median 62.8mL/min). One patient experienced delayed graft function, another developed transient class I donor-specific antibodies, another with pre-transplant IgA nephropathy developed post-transplant proteinuria with focal segmental glomerulosclerosis on renal biopsy, and two recipients had transiently elevated aminotransferase levels.

COMMENTARY

The availability of donor kidneys for transplantation is limited, and over 500 deceased donor kidneys go unused every year because donors were infected with Hepatitis C (Reese et al.). The transmission rate of Hepatitis C from HCV-positive kidney donors to HCV-negative recipients is significant at 57-96% (Pereira et al.). However, recent advances in HCV therapy have led to cure rates of >90% using orally-administered, well-tolerated interferon-sparing regimens (Li and De Clercq). These developments have led to postulation that safe transplantation of organs from HCV-infected donors into HCV-uninfected recipients may be feasible.

The THINKER study evaluated the transplantation of kidneys from HCV-infected donor patients into HCV-negative recipients. It found that recipients receiving HCV-infected kidneys can be cured of transplant-associated HCV infection and maintain stable allograft function at 6 months post-transplantation. Drawbacks of this study include small sample size and the relatively short follow-up period. While the long-term implications of HCV-infected kidney transplantation remain to be seen, this is a promising area of research that has the potential to change thousands of lives.
REFERENCES

**Active Surveillance in Younger Men With Prostate Cancer**

*Dr. Chad Guenther reviewing Leapman MS, et al. JCO. 2017 June 10;35(17):1894-1904.*

**Summary**

The objective of this study was to determine the effect of age on surveillance outcomes for men with prostate cancer (PCa) on active surveillance (AS). The UCSF Urologic Oncology Database is a departmental database containing prospectively accrued data for patient with urologic cancers. Consenting individuals on AS with ≥6 months of follow-up were analyzed with data beginning in 1992. Institutional eligibility for AS including Gleason score (GS) ≤ 3+3, prostate specific antigen (PSA) ≤ 10 ng/mL, clinical stage ≤ T2, ≤ 33% of biopsy core specimen involvement, and no single core with > 50% involvement. AS consisted of PSA measurement every 3 months, confirmational biopsy within 12 months of original biopsy, transrectal ultrasound-guided biopsy every 12-24 months, and institutional pathologist review of outside biopsies if diagnosis was made outside of UCSF (74% of cases). Radical prostatectomy (RP) was offered if there was Gleason score upgrade (GSU), increase in tumor volume, increase in PSA, increase in clinical stage, patient anxiety, or patient preference. Date of diagnosis was defined as the date of first biopsy. Primary endpoint was GSU on biopsy to GS > 3+3. Secondary endpoints were biopsy-proven progression by GSU at biopsy or increase in volume > 33% of biopsy core specimens, rates of definitive treatment, PSA > 0.2 on 2 measurements after delayed RP, or salvage treatment with detectable PSA. Younger patients were defined as ≤ 60 years of age.

Data from 1433 men were reviewed with median follow-up of 49 months and median age of 63 (42% ≤ 60). GS was ≤ 3+3 in 89% of men. Overall, younger men had lower PSA and more frequent GS of 3+3. No GSU was detected by biopsy in 73% versus 64% in younger versus older men respectively at 3 years (p < 0.01) and 55% versus 48% at 5 years (p < 0.01). Younger age was independently associated with decreased risk of GSU (HR 0.969 for each decrease in year at diagnosis, 95% CI 0.956-0.983, p < 0.01) and biopsy-proven progression (HR 0.981 for each decrease in year at diagnosis, 95% CI 0.970-0.993, p < 0.01). Younger age compared to older age had decreased risk of biopsy-proven GSU (HR 0.67, 95% CI 0.55-0.83, p < 0.01) and decreased risk of biopsy-proven progression (HR 0.78, 95% CI 0.65-0.92, p < 0.01). Age groups had similar rates of definitive treatment, with 320 (22%) undergoing RP (64% due to progression, 6% with intermediate risk at diagnosis, 3% with PSA doubling in < 36 months). Eighty-four (26%) underwent RP in the absence of progression by PSA or biopsy.

**Commentary**

Screening for, and treatment of PCa has come under increasing scrutiny in recent years with some asserting that the disease is over-treated. AS is a management strategy wherein the patient is observed closely for signs or changes consistent with disease progression warranting definitive therapy. AS has been advocated as a strategy to avoid overtreatment in the setting of low-risk PCa. Given the natural history of cancer, there are some who feel that delaying definitive treatment might result in missing the opportunity for a cure. This would be especially concerning in younger patients who may otherwise have decades to live. However, younger patients may suffer from a greater overall decrease in quality of life if treated prematurely, especially given the morbidities associated with RP and baseline higher functional statuses. This study adds to the increasing body of evidence that delaying definitive treatment in younger patients may not contribute to worsening outcomes.
when adequately monitored. The implications of this are broad. Perhaps most importantly, AS helps reduce over-treatment. Delaying definitive surgery may also preserve QOL in younger patients without an increased risk of progression. Furthermore, a reduction in over-treatment may help relieve some of the concerns associated with PSA screening in younger patients.

Table A:

<table>
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<th>Parameter</th>
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<th>Strict AS Criteria (n = 948)</th>
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<td>0.909 to 1.044</td>
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<td>Clinical T2 v T1</td>
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Bayesian information criterion: 4,884.4 (v null model 4,897.8) 3,163.1 (v null model 3,166.8)

Table 2. Cox Proportional Hazards Regression Model Examining Factors Associated With Risk of Biopsy Upgrade and Biopsy Progression During Prostate Cancer AS

Biopsy progression

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<th>Parameter</th>
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<th>Strict AS Criteria (n = 948)</th>
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<td>Age at diagnosis (per year decrease)</td>
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<tr>
<td>Year of diagnosis</td>
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<td>1.136</td>
<td>1.107 to 1.166</td>
<td>&lt; .01</td>
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<td>White</td>
<td>.41</td>
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<td>1.086</td>
<td>0.796 to 1.542</td>
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<td>Single/ Widowed vs partnered</td>
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<td>PSA at diagnosis, ng/mL</td>
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<td>0.959 to 1.011</td>
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<td>Biopsy core positive, %</td>
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Bayesian information criterion: 6,587.0 (v null model 6,590.5) 4,117.9 (v null model 4,120.3)

Abbreviations: AS, active surveillance; HR, hazard ratio; PSA, prostate-specific antigen; UCSF, University of California, San Francisco.
Timing of Advance Directive Completion and Relationship to Care Preferences


Summary

There is widespread speculation about whether the timing of completion of advance directives (AD) is related to the aggressiveness of care (AC). This article presents the first empiric data on the relationship of timing of AD and AC as well as the relationship of certain patient characteristics with timing of AD or AC. The authors use data from the Health and Retirement Study, a longitudinal survey of U.S. adults age 51 and older queried every 2 years until death followed by an exit interview with a proxy (typically family members). Patients included in this study expired between 1997 and 2013. AD completed within the last 3 months of life were defined as “late.” AC was defined as unconditionally giving all possible care to prolong life. Bivariate analysis was performed comparing health status and sociodemographic data by AC and timing of AD. Multivariate logistic regression analysis was performed comparing factors associated with late AD and AC.

Out of 9164 respondents with an exit interview, 45% completed an AD before death. The median time for AD completion was 41 months before death. Overall, 5.35% of patients with AD preferred AC, mainly younger respondents (age 50-74), ethnic minorities (defined as Hispanic or black), those with less education, and those with greater overall monetary assets. There was no association between specific health condition and preference for AC. Late completion of AD was associated with younger age (age 50-74), ethnic minorities, lowest quartile of monetary assets, and underlying cancer or lung disease. Overall, preference for AC was relatively low with AD completed 4 months to 10+ years before death, but rose to 12% with AD completed 2-3 months before death and then dropped to 3.9% for AD completed in the last month of life. Factors associated with preference for AC were lower education and minority ethnicity. Patients whose death was expected were less likely to choose AC.

Commentary

Prior to this study, there was limited data to help understand trends in patient decision-making regarding end-of-life care and advanced planning. The authors hypothesized that both early and late completion of AD would be associated with preference for AC. While later completion of AD was associated with preference for AC, early completion of AD was not. Given that only 5.35% of all patients who complete AD prefer AC, the sharp increase in preference for AC at the end of life deserves discussion. Since ethnic minorities were more likely to choose AC and also have late AD, it is possible that some of the increase in AC seen later is due to the effect of greater representation of this subpopulation. Also, it is possible that early AD include more respondents who understand that the standard of care is aggressive and want to make their preferences known to limit end-of-life care. Most importantly, there is a possible association with increased AC with late AD in the setting of hurried goals of care discussions prior to emergent procedures. With less time for the patient and their family to consider as well as less time for an in-depth discussion with the care provider, a patient’s decision may be less likely to reflect their true preferences and values. Thus, goals of care discussions may be more likely to represent a patient’s values when performed earlier in their care.
Table 2
Logistic Regression Models of AD Completion Timing 0–3 Months and AD Preference All Care (N = 2903) HRS

<table>
<thead>
<tr>
<th>Variables</th>
<th>DV: AD Completion 0–3 Months Before Death</th>
<th>DV: AD Preference for All Care Possible</th>
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<td></td>
<td>OR</td>
<td>P &gt; z</td>
</tr>
<tr>
<td>Age (ref = 50–74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75–84</td>
<td><strong>0.40</strong></td>
<td>0.00</td>
</tr>
<tr>
<td>85+</td>
<td><strong>0.27</strong></td>
<td>0.00</td>
</tr>
<tr>
<td>Female</td>
<td>1.08</td>
<td>0.00</td>
</tr>
<tr>
<td>Minority</td>
<td>1.89</td>
<td>0.00</td>
</tr>
<tr>
<td>Education &lt; 12 yrs</td>
<td>1.27</td>
<td>0.11</td>
</tr>
<tr>
<td>Asset lowest 25%</td>
<td><strong>0.57</strong></td>
<td>0.00</td>
</tr>
<tr>
<td>Not married</td>
<td>0.85</td>
<td>0.32</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.84</td>
<td>0.00</td>
</tr>
<tr>
<td>Lung disease</td>
<td><strong>1.49</strong></td>
<td>0.01</td>
</tr>
<tr>
<td>Heart disease</td>
<td>0.88</td>
<td>0.33</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.80</td>
<td>0.17</td>
</tr>
<tr>
<td>Memory</td>
<td><strong>0.46</strong></td>
<td>0.00</td>
</tr>
<tr>
<td>Death expected</td>
<td><strong>1.46</strong></td>
<td>0.01</td>
</tr>
<tr>
<td>Timing AD to death, months</td>
<td><strong>1.00</strong></td>
<td><strong>0.03</strong></td>
</tr>
<tr>
<td>Constant</td>
<td>0.23</td>
<td>0.00</td>
</tr>
</tbody>
</table>

AD = advanced directive; HRS = Health and Retirement Study; DV = dependent variable.
Values in bold indicate P<0.05.

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Fig. 2. Percent electing all care possible in AD by timing between AD completion and death. AD = advanced directive.
Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study

Dr. Neil Keshvani reviewing Marik et al. CHEST. 2017 Jun;151(6):1229-1238.

Summary

This retrospective before-after study compared outcomes of standard therapy (n=47) versus treatment with high dose vitamin C, corticosteroids, and thiamine (n=47) in patients with severe sepsis or septic shock and a procalcitonin score ≥ 2 ng/mL. The treatment group received IV vitamin C 1.5 g every 6 hours for 4 days or until ICU discharge, IV hydrocortisone 50 mg every 6 hours for 7 days or until ICU discharge, and IV thiamine 200 mg every 12 hours for 4 days or until ICU discharge, all of which were started within 24 hours of ICU admission. None of the control patients received vitamin C or thiamine, and only a subset (n=28, 59.6%) received hydrocortisone (50mg every 6 hours) at the discretion of the attending physician. The primary outcome was in-hospital mortality. Secondary outcomes included duration of vasopressor therapy, requirement for renal replacement therapy, ICU length of stay, and change in SOFA score over the first 72 hours.

Baseline characteristics were similar in treatment and control groups. In-hospital mortality was 8.5% (4/47 patients) in the treatment group compared to 40.4% (19/47 patients) in the control group (p<.001). The mean duration of vasopressors was 18.3 ± 9.8 hours in the treatment group, compared to 54.9 ± 28.4 hours in the control group (p<.001). Renal replacement therapy was needed in 310% (3/47 patients) in the treatment group and 37% (11/47 patients) in the control group (p=.02). ICU length of stay was not significantly different in either group. Finally, the change in 72-hour SOFA score was 4.8 ± 2.4 in the treatment group compared to 0.9 ± 2.7 in the control group (p<.001).

Commentary

In this study, Marik et al report mortality reduction and prevention of progressive organ dysfunction in patients with severe sepsis or septic shock treated with vitamin C, thiamine and hydrocortisone. The authors postulate a mechanistic basis for this cocktail: the antioxidant effects of vitamin C and its inhibition of proinflammatory mediators may help preserve endothelial function and microcirculatory flow, and increase vasopressor sensitivity. Hydrocortisone is proposed to act synergistically by increasing the transport of vitamin C into cells. Finally, the addition of thiamine may reduce conversion of vitamin C to oxalate that could otherwise crystalize in kidneys, therefore exerting a renal protective benefit to guard against toxicity associated with high doses of intravenous vitamin C.

This trial is notable for the controversy that has surrounded it. In this analysis, it is useful to focus on three core issues: 1) What is the strength of the evidence, 2) How does this trial compare to previous literature, and 3) What is the threshold for early adoption of the ICU cocktail?

Limitations of this trial are obvious: the sample size is small, and the trial utilizes a single-center design. Additionally, the before/after non-blinded design introduces the potential for bias. The Hawthorne effect, where individuals modify aspects of their behavior in response to their awareness of being observed, may have had a profound effect on outcomes in the treatment group. Of note, only 59.6% patients in the control group received hydrocortisone, an intervention that may decrease vasopressor requirements and reduce sepsis-associated mortality independent of vitamin C use. (Annane et al.) Finally, the control group in this study has an APACHE IV predicted mortality of
40%. However, multiple studies have shown that in developed countries, septic shock patients have an average mortality of 25% at 90 days. This study may not be as generalizable because of this difference.

This trial follows up on recent phase 1 trials regarding the safety of IV vitamin C in severe sepsis (Fowler et al.) and the effect of high-dose vitamin C on vasopressor requirements (Zabet et al.), both of which reported that IV vitamin C is safe and effective in sepsis but are again complicated by extremely small sample sizes. The authors also point to the 50+ years of evidence pertaining to the safety of vitamin C and thiamine as proof that there is low risk of adverse effects. However, much of the literature on vitamin C pertains to oral repletion, not high-dose IV repletion. It is still possible that high-dose vitamin C may have adverse effects or unintended consequences that have yet to be described in safety studies.

Will this trial lead to early adoption of the ICU cocktail? Despite the limitations stated above, these preliminary results are promising. However, in order to truly understand if this protocol has a clear benefit to patients, further evidence is needed. This trial should be viewed as a stepping stone to a larger, multicenter randomized control trial; one that produces more generalizable results and thereby leads to a change in practice.

REFERENCES

Quality Improvement & High Value Care

Cost-effectiveness of Common Diagnostic Approaches for Evaluation of Asymptomatic Microscopic Hematuria

Dr. Allexa Hammond reviewing Halpern et al., JAMA Intern Med 2017 Jun 1;177(6):800-807

Summary

Halpern and colleagues compare the relative cost effectiveness of four diagnostic strategies for work-up in patients with asymptomatic hematuria for possible genitourinary malignancies: CT with cystoscopy (the current guideline recommendation of the American Urological Association), renal ultrasound with cystoscopy, cystoscopy alone, and CT alone. These four diagnostic approaches were each compared with a reference case of no evaluation using simulation modeling to calculate the expected number of GU cancers found. In comparison to the reference case, CT with cystoscopy was expected to detect 246 cancers per 10,000 individuals with asymptomatic microscopic hematuria at a cost of $11.5 million, renal ultrasound with cystoscopy to detect 245 at a cost of $3.5 million, cystoscopy alone to detect 222 at a cost of $2.3 million, and CT alone to detect 221 at a cost of $9.3 million (refer to Table 3).

Since cystoscopy alone or with ultrasound was expected to detect more cancers at a lower cost than CT alone, CT alone was said to be “dominated”. Adding renal ultrasound to cystoscopy was expected to detect 23 additional cancers at a cost of $1.2 million, a net increase of approximately $54,000 per additional cancer detected. Adding CT to cystoscopy was expected to detect 24 additional cancers at a cost of $9.2 million, or approximately $380,000 per additional cancer detected. Replacing ultrasound and cystoscopy with CT and cystoscopy was expected to diagnose 1 additional cancer at a cost of $6.5 million.

Based on their estimate that $100,000 to diagnose a cancer was a reasonable standard, the authors conclude that renal ultrasound combined with cystoscopy was the most cost-effective diagnostic approach for detecting GU malignancy, particularly in high-risk populations. Further discussion is warranted regarding whether renal ultrasound with cystoscopy should replace CT with cystoscopy in national guidelines.

Commentary

Asymptomatic microscopic hematuria is a common finding in internal medicine practice. Although there are many different causes of asymptomatic microscopic hematuria, one of the most concerning is genitourinary malignancy. This holds particularly true for high-risk populations, such as male smokers over 50 years of age.

Clinicians can influence health care costs in a clinically rational way by finding diagnostic strategies that are clinically acceptable and more cost-effective. In the present study, the authors suggest forgoing CT and instead using ultrasound, which offers substantial cost savings with similar effectiveness. The ultimate purpose of this study was not only to offer an alternative diagnostic approach to the evaluation of possible GU malignancy in the setting of asymptomatic microscopic hematuria, but also to provide a message to the reader to continue to question current medical practice with the hopes of preventing wasteful healthcare spending and needless complications arising from tests that may not have been necessary.
### Table:
Incremental Cost per Cancer Detected (ICCD) for Diagnostic Strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cancers Detected</th>
<th>Cost, $</th>
<th>Δ Cancers</th>
<th>Δ Cost, $</th>
<th>ICCD, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evaluation</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CT only</td>
<td>221</td>
<td>9300000</td>
<td>221</td>
<td>9300000</td>
<td>Dominated</td>
</tr>
<tr>
<td>Cystoscopy only</td>
<td>222</td>
<td>2284000</td>
<td>222</td>
<td>2284000</td>
<td>10287</td>
</tr>
<tr>
<td>Renal Ultrasound + cystoscopy</td>
<td>245</td>
<td>3504400</td>
<td>23</td>
<td>1220400</td>
<td>53810</td>
</tr>
<tr>
<td>CT + cystoscopy</td>
<td>246</td>
<td>11540200</td>
<td>1</td>
<td>8035800</td>
<td>6480484</td>
</tr>
</tbody>
</table>
Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial


SUMMARY

Symptomatic knee osteoarthritis is common and disabling. Intra-articular steroid injections are often given for pain control by suppressing inflammation. However, steroids also exhibit anti-anabolic effects on cartilage, with potential to damage joints. The objective of this 2-year double blind, placebo controlled trial was to evaluate whether steroid injections affected pain, function, or cartilage loss. Participants (n=140) were randomized to receive either 1 ml (40 mg) triamcinolone injection or 1 ml saline injection (neither mixed with local anesthetic) every three months for two years. Pain/function questionnaires and knee exams were performed every three months. MRI of the knee was done at baseline then yearly to assess cartilage thickness and damage. The study resulted with a greater rate of cartilage loss with triamcinolone vs placebo (p=0.01). Other MRI structural outcomes were no different between groups, including effusion volume. At two years, there was no significant difference in pain reduction between the groups. There were no significant differences in adverse events either. This study concluded that intra-articular triamcinolone injections resulted in greater cartilage volume loss and no greater improvement in pain as compared to saline.

COMMENTARY

While triamcinolone knee injections did not improve pain more than saline in this trial, they resulted in cartilage volume loss. We lack treatment options for these patients, and a temporary improvement in pain and function may be worthwhile. Especially as it is unknown whether the amount of cartilage loss seen is clinically significant, as there was no increased progression of the disease based on other MR imaging or clinical findings. Although the cartilage loss in this two-year study did not affect symptoms, it has been shown that increased cartilage loss leads to higher rates of arthroplasty over time. It is unclear what effects the frequency and duration of steroid injections would have. Limitations of the study include evaluation of pain every three months, so immediate, temporary benefits may be missed. Second, patients continued their own pain medications, only stopping NSAIDs for 48 hours before pain evaluations. Finally, participants experienced a large placebo effect, narrowing outcome differences. In summary, this article suggests that the commonly used knee injections are no more effective than saline injections and may contribute to greater cartilage volume loss in symptomatic knee osteoarthritis.