(A). St. Paul Sanitarium was originally founded in a building on Hall street in 1896, serving as a hospital dedicated to the care of the general public, as well as a home for the Daughters of Charity nursing sisters. (B) The hospital moved to a new building on Bryan street in 1898, and was complete with electric lights, radiators, elevators, and electric call bells. (C) During the 1918 influenza epidemic, tents were built in front of the hospital to expand the capacity. (D) The hospital was renamed St. Paul Hospital in 1927 and was relocated to its final location in 1964. UT Southwestern purchased the buildings and land in 2000 and assumed operation of the hospital in 2005, adding the “University Hospital” name. Construction on Clements University Hospital began in 2011 and was opened in 2014. St. Paul University Hospital was subsequently demolished in November of 2015.

Source: Images courtesy UTSW digital Archive.
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Welcome and thank you for reading the second issue 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
Dr. Nimish Shah

Case:
A 53-year-old woman with a history of hypertension presents with atypical chest pain, mild headache, and nausea. Other than a blood pressure of 190/100, her vital signs and physical exam are unremarkable. Laboratory tests are pending. An EKG is obtained and is shown below (Fig. 1).

Figure 1. EKG showing sinus tachycardia, prolonged QTc, and broad, deeply-inverted T waves in the inferolateral leads.¹

What is the diagnosis?
A. Brugada syndrome
B. Critical LAD stenosis
C. Intracranial pathology
D. Hypokalemia

What is the next best step in management?
A. Urgent EP study
B. Cath lab activation
C. Non-contrast CT brain
D. Replete potassium
Diagnosis
C. Cerebral T waves due to intracranial pathology (bleed or stroke)

Management
C. CT brain to rule out hemorrhage

Within 1 hour of the above EKG, this patient developed left hemiplegia, facial droop, gaze deviation, and hemineglect. CT revealed a hyperdense MCA sign suggestive of thrombus and hypodensity of the right insular cortex suggestive of ischemia. It was believed that the insular lesion preceded her neurologic deficits and thus contributed to her presenting EKG changes, while the right MCA thrombus occurred at the onset of her neurologic symptoms.¹

DISCUSSION

Deep T wave inversions in the setting of chest pain and predisposing risk factors often suggest cardiac ischemia, however this pattern in conjunction with a severely prolonged QTc may also be reflective of “cerebral T waves.”²,³ These repolarization ECG changes are thought to be neurologically mediated in the setting of acute intracerebral insults, most notably subarachnoid hemorrhage (SAH) and ischemic stroke. While there is a growing body of evidence that neurologic injury is associated with sympathetic overstimulation promoting myocardial contraction-band necrosis, it is unclear whether the ECG changes seen during an acute neurologic event suggest an acute coronary process. In fact, while some early studies demonstrated an association of ischemic stroke with circulating cardiac enzymes,³ other studies have demonstrated normal coronary anatomy in patients with SAH with marked ECG changes as well as in patients with acute ischemic stroke with troponin elevation.²,⁴ Therefore, a high degree of suspicion for an acute neurologic injury is necessary when a “cerebral T wave” pattern is observed (especially in the setting of acute neurologic deficits), as initiating ACS-directed therapy, namely dual antiplatelet therapy and heparin, may increase mortality by promoting intracerebral hemorrhage.

In addition to repolarization abnormalities, the ECG changes seen with acute neurologic insults also include potentially lethal arrhythmias like ventricular tachycardia and torsades de pointes in the setting of prolonged QTc.² Evidence is limited on the duration of repolarization changes and arrhythmias, however it is suggested that they resolve within 1-2 weeks, though may resolve more quickly with treatment of the neurologic insult.²,⁵ Overall, there remains limited evidence on the prevalence of specific ECG changes associated with acute neurologic insults, and as such the sensitivity and specificity of such findings remains limited as well. Further, the brain-heart connection continues to be an active area of investigation.

Brugada syndrome is incorrect, as that is diagnosed by clinical criteria plus the Brugada sign on ECG, a covered ST segment elevation in V1-V3 followed by a negative T wave. Brugada syndrome would require an electrophysiologic study and ICD placement. Critical stenosis of the LAD can produce Wellen’s syndrome (see JW July 2017 issue at https://utswimjournalwatch.wordpress.com/category/ekg/), which is associated with either biphasic T waves or deeply and symmetrically inverted T waves in V2-3, as well as recent angina. While the T wave inversions of Wellen’s can look like cerebral T waves, cerebral T waves are more pronounced and diffuse, and are associated with QT prolongation. The T wave inversions seen with hypokalemia are more flat than cerebral T wave inversions, and
while repleting potassium may reduce the risk for arrhythmia in the setting of an acute neurologic insult, management should be directed at treating the neurologic insult predisposing to arrhythmia.

REFERENCES


Case:
A 59 year-old male presented to the ED with a 3-day history of fevers, generalized weakness, and a rash. The patient denied any history of allergies to medications, illicit drug use, recent procedures or hospitalizations. Physical exam findings were remarkable for fever (T 40.1°C), tachycardia (130/min), and blood pressure 132/82 mm Hg. Cardiac and respiratory exam components were unremarkable. Neurologic exam was notable for generalized weakness but no neck stiffness, photophobia or discrete neurologic deficits. A mottled rash was noted involving the chest, trunk and extremities (Figures A & B). Laboratory tests were notable for thrombocytopenia (platelet count 53 x10⁶/mm³), leukocytosis (white cell count 12,000 /mm³, 81% neutrophils), normal hemoglobin 13.5 g/dL, acute kidney injury (creatinine 3.4 mg/dL from baseline 0.8 mg/dL), mild transaminitis (AST 128 U/L, ALT 72 U/L) with normal bilirubin, creatine kinase 1409 U/L, and troponin elevation to 0.16 ng/mL. Urinalysis showed “large” hematuria with 20-30 red cells/hpf. A peripheral blood smear showed no evidence of hemolysis. Two sets of blood cultures drawn on admission grew gram positive cocci within 24 hours.

What is the diagnosis?
A. Meningococcal septicemia
B. Systemic Lupus Erythematosus
C. Infective Endocarditis
D. TTP-HUS

What is the next best step in management?
A. Transthoracic ECHO
B. ANA with ENA panel
C. Lumbar puncture
D. Plasma exchange
Discussion:

Infective endocarditis is arguably one of the most elusive diseases to diagnose, as well as one of the hardest to treat. In this case, the patient presented with a host of non-specific clinical signs and symptoms. Several features were clues to the ultimate diagnosis: the lacy truncal rash consistent with livedo reticularis and the purpuric palmar rash were suggestive of small- and medium-size-vessel disease. These include primary vasculitides (ANCA-associated vasculitides, IgA vasculitis, cryoglobulinemia), embolic/thrombotic phenomena (e.g. TTP-HUS, DIC, catastrophic antiphospholipid syndrome, cholesterol emboli, septic emboli), and septic vasculopathy (immune-mediated small-vessel vasculitis such as that in meningococcal septicemia). The presence of acute kidney injury with significant hematuria pointed towards glomerulonephritis, suggesting an immune-mediated process. Finally, positive blood cultures and fever were suggestive of a systemic infection of occult origin. Ultimately, the patient met modified Duke criteria for “definite” infective endocarditis: 1 major clinical criteria (2 separate positive blood cultures) and 3 minor clinical criteria (fever, vascular phenomena, immunologic phenomena). Despite a normal cardiac exam, a transthoracic echocardiogram would be a reasonable next step in management as up to 30% of patients with infective endocarditis may not have a new or worsened murmur at presentation.

The differential of the above case is broad. Meningococcal septicemia was considered in light of the patient’s sepsis, rash and thrombocytopenia; however the lack of neck stiffness and neurologic deficits were less suggestive of meningococcal meningitis. Connective tissue disorders such as systemic lupus erythematosus can certainly manifest with livedo reticularis, fevers, thrombocytopenia, and glomerulonephritis; however the patient did not fit the typical demographic profile of this disease, and positive blood cultures pointed towards systemic infection as a more likely cause. Finally, thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS) can present with thrombocytopenia, kidney injury, and fever. Altered mentation is usually seen in these conditions but was missing in this case, and there were no signs of hemolysis (no schistocytes on peripheral blood smear, lack of indirect hyperbilirubinemia), making the diagnosis of TTP or HUS less likely.

In this case, the patient’s blood cultures speciated with S. aureus. Transthoracic echocardiogram showed a large echogenic mass (1.8cm by 1.1 cm) attached to the aortic valve, a large aortic root abscess, as well as moderate-to-severe aortic regurgitation. The patient underwent aortic valve replacement and received a prolonged course of antibiotic therapy, with ultimate cure. However, the nidus of the infection remained unknown, and no risk factors for acquiring infective endocarditis were ever identified.

REFERENCES

Cardiovascular Testing and Clinical Outcomes in Emergency Department Patients with Chest Pain


SUMMARY

This study sought to determine whether noninvasive cardiac testing (exercise ECG, stress echocardiography, nuclear stress test, CT angiography) in patients presenting with atypical chest pain (“without evidence of ischemia”) leads to improved cardiovascular outcomes. The authors used national claims data to perform a retrospective cohort analysis of 926,633 privately insured patients between ages 18 to 64 who presented to the ED with chest pain between 2011 and 2012. All patients had initial findings that excluded the diagnosis of myocardial ischemia. The analysis used an instrumental-variables approach to adjust for potential selection bias and confounders. The primary endpoints were coronary revascularization (PCI or CABG) and acute myocardial infarction (AMI) admission at 7, 30, 180, and 365 days.

Noninvasive cardiac testing was performed within 30 days of presentation in 224,973 patients (24%). In multivariate analyses, patients undergoing noninvasive cardiac testing within 30 days had significantly higher rates of coronary angiography (36.5 per 1,000 patients tested; 95% CI, 21.0 - 52.0) and revascularization (22.8 per 1,000 patients tested; 95% CI, 10.6 - 35.0) at 1 year as compared to those who did not receive testing; however, there was no significant change in AMI admissions (7.8 per 1,000 patients tested; 95% CI, -1.4 to 17.0) at 1 year. Subgroup analysis of high-risk patients similarly showed higher rates of revascularization, with lower risk of CABG surgery, but no change in AMI admissions in patients who received noninvasive cardiac testing as compared to those who did not receive testing (data in supplementary material).

COMMENTARY

As physicians, we are often faced with the question of what to do next in a patient with chest pain once AMI has been ruled out with serial biomarker testing and ECG. The current ACC/AHA guidelines recommend noninvasive testing or coronary angiography prior to discharge or within 72 hours in such patients (moderate strength recommendation).¹ This study, as well as previous observational studies, challenge these recommendations by showing that although noninvasive testing increases revascularization, it is not associated with reduction in AMI admissions.²,³ We should always weigh the risks and benefits of cardiac testing and strive to avoid testing in low-risk patients, but the management of moderate- to high-risk patients is less clear. This study reported that testing those with greater baseline risk did not decrease AMI admission. However, we should also be cautious against viewing AMI as the sole important outcome. Notably, this study did not provide mortality data. There were also potential benefits that were not analyzed - negative test results may be reassuring to patients, and positive test results leading to coronary revascularization may provide relief of anginal symptoms and improvement in exercise tolerance.
In the absence of better risk assessment tools for identification of patients most likely to benefit from cardiac testing, the best course may be to strive for patient-physician shared decision-making to balance resource utilization and improve care.

References


**Endocrinology**

**Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism**


**SUMMARY**

Subclinical hypothyroidism is defined as an elevated thyroid stimulating hormone (TSH) with a normal free thyroxine (T4) level. There is little evidence to support thyroid hormone replacement versus monitoring especially when patients have non-specific symptoms that might be attributed to hypothyroidism. This study is a randomized, double-blind, parallel-group trial analyzing the effect of normalizing the TSH level. Participants were 65 years of age or older with persistent subclinical hypothyroidism on at least two measurements, at least three months apart. Participants in the intervention group received levothyroxine starting at 50 mcg daily, and the dose was increased until TSH was within normal range. Control patients received a placebo with mock adjustment of the dose throughout the study. The primary end point was change in thyroid symptom related quality of life measured using ThyPRO and Tiredness scale scores. Secondary outcomes included several quality of life measurements as well as changes in weight, waist circumference, blood pressure, and body mass index. Patients were followed for one to three years. There were 737 total participants, 368 in the levothyroxine group and 369 in the control group. There was no significant difference in baseline characteristics or drop-out rate between the two groups. There was a statistically significant difference (p < 0.001) between the groups in average TSH level at both one and three year follow up: 3.63 mIU/L and 3.47 mIU/L in the treatment group, at one and three year follow up respectively, versus 5.48 mIU/L and 5.28 mIU/L in the placebo group (normal range 0.4-4.59 mIU/L). There was no significant difference in the primary outcome of hypothyroid symptoms and tiredness scores at one year. At three years, there was a clinically small magnitude 3.5-point decrease in tiredness score (p 0.05) in the levothyroxine group compared to the placebo group, but no difference in hypothyroid symptoms between the groups. One secondary outcome scale showed a small deterioration in quality of life with levothyroxine at one year (p 0.05) but a small improvement with levothyroxine at three years (p 0.03). Otherwise, there was no significant difference in secondary endpoints between the groups. There were 78 serious adverse events in the levothyroxine group compared to 103 adverse events in the placebo group (p 0.049).

**COMMENTARY**

Subclinical hypothyroidism is frequently encountered in older adults in both the hospital and clinic, and the clinical significance is unclear, as symptoms of hypothyroidism may be non-specific and can often be attributed to other chronic conditions. This study is one of the largest randomized controlled trials to evaluate the clinical effects of treating subclinical hypothyroidism and showed no appreciable difference in symptoms or the secondary outcomes of muscle strength, body mass index, blood pressure, and waist circumference. This reinforces the current recommendation of not treating subclinical hypothyroidism with TSH <10 mIU/L in older patients, despite nonspecific symptoms. One
limitation of the study is that the average TSH was only 6.4 mIU/L, and it has been previously noted that older adults may have a slightly higher normal TSH than younger adults, the clinical significance of which is unknown. There were few patients with TSH higher than 10 mIU/L, which is the level at which treatment would be considered. In addition, thyroid antibody levels were not measured. Patients with positive antibodies are more likely to progress to overt hypothyroidism than those without antibodies. More studies are needed to determine the effect of thyroid replacement in subclinical hypothyroidism with TSH level higher than 10 mIU/L in older adults.
Gastroenterology and Liver Diseases

Adiposity amplifies the genetic risk of fatty liver disease conferred by multiple loci.


SUMMARY
The rising prevalence of obesity has led to an increased prevalence of diabetes mellitus, hypertension, hyperlipidemia, and non-alcoholic fatty liver disease (NAFLD), which belongs on a spectrum of disorders ranging from excess liver fat (steatosis), inflammation (steatohepatitis), fibrosis (cirrhosis), and malignancy formation (hepatocellular carcinoma). Susceptibility to NAFLD is highly variable, as not all obese individuals develop NAFLD, and not all cases of steatosis progress further along the spectrum. As early as the mid-2000s, genome-wide association studies performed by UT Southwestern scientists have revealed insight into genetic variants that contribute to differences in hepatic triglyceride content (HTGC). It is now known that a single nucleotide polymorphism in the PNPLA3 gene that encodes the enzyme I148M (rs738409, called the “M variant”) is strongly associated with increased hepatic fat levels, increased serum ALT levels, and liver inflammation. This enzyme normally undergoes nutritional regulation, ensuring almost no amount of the enzyme exists in the fasted state, and increased levels in the carb-fed state. PNPLA3 normally has lipid acyl hydrolase activity and is catabolized through a process involving ubiquitination and proteasome degradation, and the M variant of this protein has been found to be catalytically dead, accumulate on hepatocyte lipid droplets, and avoids ubiquitination (thereby avoiding degradation). In this paper, researchers showed that adiposity amplified the effects of the PNPLA3 I148M variant on HTGC levels, serum ALT levels, and cirrhosis, and 2 new gene sequence variants were seen to have interactions with obesity (TM6SF2 and GCKR). Participants were included from 4 study cohorts, including the Dallas Heart Study (DHS), totaling over 100,000 included participants. Patient’s BMI, HTGC, serum ALT levels were measured, and exome-wide genetic testing for other BMI-associated variants and other associations was performed. After stratifying DHS individuals into four groups based on BMI, the relationship between PNPLA3 genotype (wild-type II, heterozygous IM, or homozygous for mutant MM) and BMI was analyzed. Median HTGC in the leanest BMI group increased in a stepwise manner in the II, IM, and MM groups (1.8%, 2.3%, and 2.8%, respectively, P = 0.0003). This effect was amplified as BMI increased, as median HTGC was 3x higher in MM than II individuals (14.2% vs 4.7%) in the highest BMI group. Serum ALT levels also increased in similar fashion for those with the M variant when stratified for BMI, but only in the 2 highest BMI groups. Two other risk variants associated with HTGC were also found to have similar effects on HTGC and ALT levels with increasing BMI: TM6SF2 rs58542926 (encoding p.3167K) and GCKR rs1260326 (encoding p.P446L). In one cohort, 384 participants had a diagnosis of cirrhosis, and the effect of the PNPLA3 I148M variant on prevalence of cirrhosis increased with increasing BMI as well. The odds ratio of cirrhosis development was 5.8 in MM homozygotes vs. II homozygotes. This study revealed that several genetic variants leading to increased susceptibility to NAFLD and the full spectrum of chronic liver disease have their effects amplified by increasing adiposity.
The results of this paper indicate that gene-adiposity interactions play a major role in the development and progression of NAFLD. The prevalence of hepatic steatosis was only 9% in the lowest BMI individuals with wild-type PNPLA3, and 84% in the highest BMI individuals homozygous for the PNPLA3 I148M variant. As similar gene-adiposity relationships were noted for two other risk genetic variants (TM6SF2 p.E167K and GCKR p.P446L), it appears obesity augments the genetic risk of NAFLD through at least 3 mechanisms, as all 3 of these proteins participate in different metabolic pathways. Due to the PNPLA3 M variant’s effect on cirrhosis development based on BMI, it is presumed that adiposity amplifies the effect of the M variant on the entire spectrum of liver disease, not just NAFLD. What makes the results of this paper important, and previous related papers, is the strength of these single gene – adiposity interactions. Hypertension and hyperglycemia both have common alleles that contribute to their development, but these alleles have much smaller phenotypic effects than the NAFLD susceptibility alleles. These disorders also both undergo homeostatic regulation, while currently there is no evidence that HTGC is subject to feedback regulation of any sort. Overall, these results show that considering adiposity levels in conjunction with genetic studies may improve predicting those at highest risk of progressing from steatosis to end-stage liver disease, that genetic screening for NAFLD risk alleles in high-BMI individuals may be valuable, and that aggressive weight-loss interventions are beneficial in those with steatosis, but particularly in the highest BMI groups.

**Figure 1.** HTGC by BMI and PNPLA3 genotype in the DHS
Continued Statin Prescriptions After Adverse Reactions and Patient Outcomes: A Cohort Study


Summary
This retrospective cohort study evaluated the clinical outcomes of continuing statin medications despite an adverse reaction to the statin. The study evaluated patients (n=28,266) who experienced an adverse reaction to a statin (measured based on either objective EMR data or obtained from notes via a natural-language processing software). It then analyzed the group of patients who were continued on the statin medication against those whose statins were discontinued. Primary outcome was time to cardiovascular event (MI, stroke) or death. Exclusion criteria included previous adverse reaction to a statin medication, incomplete demographic data, or loss to follow-up prior to documentation of adverse reaction. Adverse effects of statins included myalgias, hepatobiliary disorders, drug intolerance, GI disorders and others (n=6934, 2965, 2223, 2517 respectively). The majority of patients (70.7%, n=19,989) continued to receive the statin medication despite an adverse reaction. In this group, the incidence of MI, stroke or death (primary outcome) was 12.2%, compared to 13.9% in the group of patients whose statin medications were discontinued after adverse reaction (difference: 1.7% [95% CI, 0.8% to 2.7%]; P < 0.001).

Commentary
Statin medications have been long known to provide excellent cardiovascular morbidity and mortality benefits, however their side effects pose a common problem for internists and primary care physicians. The most common patient complaint, myalgia, has been reported to occur in 9-20% of statin-users, and can be safely treated through. More significant side effects, including rhabdomyolysis and hepatotoxicity, can be more difficult to work around and are a routine cause of statin discontinuation. This study suggests that, in the absence of truly severe or life-threatening side effects, statin use may be encouraged and continued despite adverse reactions. Strengths of the study include multi-year follow-up and over 28,000 patients enrolled. However, the retrospective study design suggests associational data instead of causal relationships. Additionally, while timing of death was reported, the authors were unable to collect cause-of-death and, which may confound results. Another important weakness of the study is the lack of weight given to discerning a mild side effect from an adverse reaction; this raises the question of whether the same health benefit is seen in patients with mild reactions compared to severe reactions. Regardless, given the prevalence of cardiovascular disease both in the United States and worldwide, ensuring adequate statin use in the correct patient population will ultimately help save lives. It is important for primary care physicians to be vigilant in ensuring that their patients are prescribed statins when medically appropriate.
**Figure 1:** The cumulative incidence for primary outcome. Patients who continued statin medication despite adverse reaction had reduced risk of MI, stroke or death from any cause.

**REFERENCES**

Randomized Clinical Trial of Comprehensive Geriatric Assessment and Optimization in Vascular Surgery

SUMMARY
As the population ages, more geriatric patients are undergoing surgical procedures¹. Elderly patients have unique postoperative complications, and many studies have shown that a comprehensive preoperative assessment provides better outcomes compared with traditional preoperative evaluation²-⁵.

Patients 65 years or older scheduled for either elective aneurysm repair or lower limb arterial surgery were randomized to either standard preoperative assessment or preoperative comprehensive geriatric assessment. The geriatric assessment was delivered by a multidisciplinary team (geriatrician, nurse specialist, social worker, occupational therapist) who assessed patients using peer-reviewed protocols based on current evidence, national and hospital guidelines, and expert opinion. Examples of such protocols include cognition and frailty assessments (Figure 1). The study included 176 patients from an inner-city teaching hospital (control=91, intervention=85). Mean length of hospital stay, the primary outcome, was 5.53 days in the control group and 3.32 days in the intervention group (ratio of geometric means 0.60, 95% CI 0.46-0.79; \( P < 0.001 \)). There was also a statistically significant lower incidence of delirium, cardiac complications, and bladder/bowel incontinence in the intervention group compared with control (secondary outcomes). Furthermore, patients in the intervention group were less likely to require higher level of dependency at discharge (4 of 85 versus 12 of 91; \( P = 0.051 \)).

COMMENTARY
Older adults undergoing major elective vascular surgery had reduced length of hospital stay and perioperative complications and were less likely to decline in functional dependency when a comprehensive geriatric preoperative assessment was performed. Such patients often were diagnosed with previously unrecognized pathology and risk factors that were subsequently intervened upon and led to better outcomes.

This study emphasizes the benefit of comprehensive geriatric assessment prior to elective vascular surgery. Larger scale studies, as well as those across multiple hospital centers, would help further validate these findings. Furthermore, preoperative comprehensive geriatric assessment should be studied with other procedures to understand if such beneficial outcomes are reproducible across surgical disciplines. Positive results would lead to substantial clinical implications for internists performing preoperative risk assessment in the elderly population.

Figure 1. Cognition Protocol
REFERENCES


Evaluating the importance of policy amenable factors in explaining influenza vaccination: a cross-sectional multinational study


SUMMARY

This study is a cross-sectional survey designed to identify policy-amenable factors related to influenza vaccination rates in 3 high-income countries. Adults from the USA, UK, and France were randomly surveyed regarding influenza vaccination between March and April 2014 via online surveys and telephone interviews. Quotas based on gender, age, income, region, ethnicity and settlement type (rural/urban) were used to ensure national representativeness. The online survey was completed by 814 participants in the USA, 791 in the UK, and 787 in France. Via telephone, 80 participants were interviewed in the USA, and 100 in each the UK and France (total N=2412). Data were analyzed using multivariable logistic regression. Generally, the responses of vaccinated and unvaccinated individuals were significantly different. Vaccinated participants were older, insured, wealthier (USA/France), more educated (USA), more concerned about the risks of influenza than the risks of the vaccine and reported a better understanding of the influenza vaccine than unvaccinated individuals. The regression models were able to explain 64-80% of the variation in vaccination rates. Sociopsychological variables (influenza and vaccine risk perceptions, vaccine effectiveness, self-efficacy, perceived knowledge of the vaccine, and trust in key vaccination stakeholders) accounted for more of the variance in past influenza vaccination behavior than demographic, socioeconomic, and health variables (49% vs 22% in the USA, 42% vs 38% in the UK and 45% vs 19% in France).

COMMENTARY

Approximately 49,000 people die every year in the United States from influenza-related illness, but vaccination rates among high risk patients remain sub-optimal. In 2013-2014, only 65% of adults over age 65 and 46% of younger adults at high risk for influenza related complications were vaccinated in the USA. Vaccination decisions are influenced by numerous factors, including demographic, socioeconomic and sociopsychological factors, with the latter being amenable to policy interventions.

This study suggests that sociopsychological factors heavily influence vaccination behaviors, with the most policy amenable factors being social influence and perceptions about influenza. These factors are not consistently assessed but could be used to monitor vaccination sentiment and predict uptake in the population through national immunization surveys. The influence of physician opinion on vaccination rates suggests that improving patient and provider communication should be prioritized. Incentives for providers have been suggested. Efforts should also focus on closing the gap between perceived and actual risks of influenza, with tailored messaging regarding risks to specific groups.

In our PRIME and PCIM clinics, we have a number of individuals who decline the annual influenza vaccine. This study suggests that social influence, specifically from physicians, can increase compliance with vaccination. We have an opportunity each flu season to directly encourage our patients to be vaccinated and to place emphasis on the
risks of influenza in specific age and chronic illness groups, which allows us to be a part of lowering the morbidity and mortality from influenza in the United States.
Emicizumab Prophylaxis in Hemophilia A with Inhibitors
Dr. Nimish Shah reviewing Oldenburg J, et al. NEJM. 2017 July 10; Epub ahead of print

SUMMARY

Hemophilia A is a bleeding disorder caused by deficiency of factor VIII activity. Current prophylaxis for severe bleeding events is IV infusion of factor VIII concentrate two to three times weekly, however this potentiates the development of alloantibodies that render factor VIII replacement ineffective in about a third of patients. In patients with hemophilia A with acquired inhibitors, treatment includes eradication of inhibitor through induction of immune tolerance or prophylaxis with bypassing treatments like recombinant factor VII or activated PCC, which are suboptimally effective. These patients experience high morbidity and decreased quality of life.

Emicizumab is a recently introduced recombinant humanized bispecific monoclonal antibody bridging activated factor IX and factor X to restore the function of factor VIII without inhibition by factor VIII alloantibodies.

The HAVEN 1 trial was a phase 3 open-label, international randomized study that assessed the efficacy, safety, and pharmacokinetics of emicizumab prophylaxis in patients with hemophilia A with inhibitors who had received episodic treatment or prophylaxis with bypassing treatments (n=109). Participants were randomly assigned to receive emicizumab 3.0 mg/kg body weight subcutaneously weekly for 4 weeks, followed by 1.5mg/kg weekly for at least 20 weeks. The control group received no injections. The primary outcome was the difference in the rate of treated bleeding events over at least 24 weeks between patients receiving emicizumab prophylaxis and those receiving no prophylaxis. The secondary endpoint included additional bleeding events as well as quality of life, and validated scales of health status. Patients were also studied in an intraindividual, noninterventional analysis to compare bleeding rates between bypassing treatments/prophylaxis and emicizumab prophylaxis.

The annualized bleeding rate among those receiving emicizumab prophylaxis was significantly lower than among controls (2.9 events [95%CI 1.7-5.0] vs. 23.3 events [95%CI 12.3-43.9]; RR 0.13, p<0.001). Remarkably, while only 1 of 18 controls had 0 bleeding events, 22 of 35 (63%) participants with prior episodic bypassing agent treatment who received emicizumab had 0 bleeding events. Among those who had previously received episodic treatment or prior prophylaxis with bypassing agents, emicizumab treatment also resulted in significantly lower bleeding events with relative risk reductions of 95% and 79%, respectively. Those who received emicizumab prophylaxis also demonstrated significantly better health-related quality of life and health status scores. There were 198 adverse events in 103 treated patients, 15% of which were mild injection-site reactions. Twelve serious adverse reactions including thrombotic microangiopathy, cavernous sinus thrombosis, and skin necrosis-superficial thrombitis were reported in 9 participants who had received high cumulative doses of PCC while receiving emicizumab. One participant who developed TMA after receiving PCC died of rectal hemorrhage. Two participants had evidence of declining exposure to emicizumab, suggestive of antidrug antibodies.
**COMMENTARY**

The magnitude of effect of emicizumab in reducing severe bleeding rates is promising for Hemophilia A patients with inhibitors. However, the potential for serious adverse events including thrombotic microangiopathy is very concerning, especially since these developed with PCC salvage therapy, the use of which would be usual practice for breakthrough bleeding. The authors recognize that scant prior data suggest a synergistic thrombogenic effect when both agents are used, limiting the use of PCC while on emicizumab prophylaxis. The reduced effectiveness of emicizumab in two patients also raises the concern for long-term development of antidrug antibodies, though none were detected in this study. The non-blinded nature of this study may bias the positive effect on quality of life measures, however it is unlikely that the substantial reductions in bleeding rates were biased by this study design. Lastly, while the cost of recombinant and human-derived factors is high, it is likely that the cost of this novel agent will be more prohibitive. Overall, emicizumab may be a promising agent to use in Hemophilia A patients with antibodies to minimize morbidity and improve quality of life, however strict restrictions on salvage therapy for breakthrough bleeding will likely be necessary.

**Figure 1:** Annualized Bleeding Rate in Trial Groups A, B, and C.

![Figure 1](image_url)

Figure 1. Annualized Bleeding Rate in Trial Groups A, B, and C. The annualized bleeding rate was calculated with the use of a negative binomial-regression model. Participants in groups A and B had previously received episodic treatment with bypassing agents; participants in group C had previously received prophylaxis with bypassing agents. Group D was not included in the current analysis owing to the short follow-up at the time of data cutoff.
A Placebo-Controlled Trial of Antibiotics for Smaller Skin Abscesses


**SUMMARY**

This multicenter, double-blind, randomized controlled trial evaluated 786 patients (505 adults and 281 children) with small skin abscesses (≤5cm, smaller size for pediatric patients) that were randomized to undergo incision and drainage plus either clindamycin (300mg every 8 hours), trimethoprim-sulfamethoxazole (TMP-SMX; 160mg/800mg every 12 hours) or placebo for 10 days. The primary outcome was cure at 7-10 days after the end of treatment; secondary outcomes included cure at 1 month, occurrence of new infections, and rate of treatment-associated adverse events.

Cure rates at 7-10 days were significantly higher in the clindamycin group (83%) and in the TMP-SMX group (82%) as compared to placebo (69%; p<0.0001 for both groups). There was no significant difference in the cure rates between the clindamycin and TMP-SMX groups (p=0.73). Subgroup analyses revealed that this beneficial effect was mainly driven by response in patients with culture-proven *S. aureus* infection (cure rates 84% with clindamycin and 83% with TMP-SMX, versus 63% with placebo; p<0.001 for both comparisons), including those with culture-proven MRSA infection (cure rates 82% with clindamycin and 85% with TMP-SMX, versus 63% with placebo; p=0.001 and p<0.001, respectively). Cure rates in patients with pathogens other than *S. aureus* and those in whom cultures were negative were similar among the three treatment groups (p=0.99 for all comparisons).

At 1-month follow-up, cure rates for both clindamycin (79%) and TMP-SMX (73%) groups were significantly higher than placebo (63%; p<0.001 and p=0.01, respectively). New infections were more common after TMP-SMX (14%) and placebo (12%) than after clindamycin therapy (7%; p=0.03 and p=0.06, respectively). Adverse events were more common with clindamycin (22%) than with TMP-SMX (11%) or placebo (13%).

**COMMENTARY**

Uncomplicated skin abscess is commonly seen in the outpatient setting and in the emergency room, with the incidence increasing due to community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA). Current guidelines regarding the treatment of cutaneous abscess do not recommend the routine use of antibiotics following incision and drainage procedure unless signs of systemic infection, significant co-morbidities or recurrent infection are present. This recommendation is driven largely by expert opinion given the lack of high-quality trials in this area.

This study, along with another randomized trial of TMP-SMX versus placebo, suggests that there may be a beneficial role for systemic antibiotics in improving cure rates following incision and drainage. On the other hand, there were no clinically deleterious adverse events in the placebo group, suggesting that low risk patients with small abscesses (<2 cm) may not necessarily need systemic antibiotic therapy following drainage of the abscess, provided they are followed closely. Of note, this study excluded patients at higher risk of complicated infection including those with systemic symptoms, involvement of delicate areas (e.g. perirectal, genital, or hand infection), bites, immunosuppressive
conditions, and surgical site or prosthetic device infection. In such patients, withholding antibiotic therapy may lead to worse clinical outcomes.

REFERENCES
Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy


SUMMARY

This article describes a multi-center, double-blind, randomized control trial to assess the clinical and physiologic effects of steroid use in patients with IgA nephropathy. The study planned to include 750 participants that met the following inclusion criteria: proteinuria >1g/day and estimated glomerular filtration rate (eGFR) between 20-120 mL/min/1.73m², with adequate blood pressure control. However, after about 2 years of follow up, study enrollment was discontinued because of numerous adverse events in the methylprednisolone arm of the trial. A total of 262 participants had been enrolled. The methylprednisolone group was comprised of 136 patients that received a weight-based dose with a maximum dose of 48mg/day. The remaining 126 participants received placebo. Treatment was given at full dose for 2 months and tapered over 4-6 months. The primary outcome was a composite measure defined by the development of end-stage renal disease (ESRD), a decrease in eGFR by 50%, or death due to kidney disease, over a median follow-up duration of 2.1 years. Safety outcomes were also studied including: development of diabetes, gastrointestinal hemorrhage, infection, cardiovascular event, new fracture or development of osteonecrosis.

The primary study outcome was seen in 8 (5.9%) in the methylprednisolone group and 20 (15.9%) participants in the placebo group (p=0.02), driven primarily by an improvement in the risk of 50% eGFR decline in the steroid arm. Four participants (2.9%) in the methylprednisolone arm progressed to ESRD, as compared to 10 (7.9%) in the placebo arm (p=0.10). With regards to proteinuria at 6 months: the rate of complete remission and partial remission were much higher in the methylprednisolone group compared to placebo at 7.8% vs 1.1% (p=0.04) and 45.1% vs 13.7%(p<0.001), respectively. Finally, 20 patients (14.7%) in the methylprednisolone arm experienced adverse events, as compared to 4 patients (3.2%) in the placebo arm (p=0.001). The majority of adverse events in the methylprednisolone group were serious infections, of which two resulted in death. No serious infections occurred in the placebo group.

COMMENTARY

Current guidelines recommend a 6-month course of corticosteroids as treatment of IgA nephropathy in patients with persistent proteinuria after initial supportive care. However, the evidence for this is not definitive. Prior studies hint at clinical improvements in renal function but adverse effects of steroid use are reported inconsistently.

Strengths of this study include multi-center enrollment and larger sample size compared to previous work. However, early enrollment termination and thus decreased study power may have overestimated the risks and benefits of steroid therapy. Another limitation of the generalizability of the study derives from the almost exclusively East Asian ethnicity of the study population. Despite the improvement in proteinuria and modest improvement in eGFR, increased adverse events make it challenging to recommend steroid therapy in IgA nephropathy based on these data.
REFERENCES


Angiotensin II for the Treatment of Vasodilatory Shock (ATHOS-3)


SUMMARY

ATHOS-3, or Angiotensin II for the Treatment of High-Output Shock, is a phase 3 multinational, randomized, double-blind, placebo-controlled trial to determine whether the addition of angiotensin II to conventional vasopressors improves blood pressure in patients with catecholamine-resistant vasodilatory shock. The study population included patients with vasodilatory shock despite treatment with 25 ml/kg of IV volume resuscitation and concurrent administration of norepinephrine > 0.2 μg/kg/min or equivalent dose of another vasopressor for at least 6 hours but not longer than 48 hours. Vasodilatory shock was measured as a cardiac index > 2.3 with a mixed venous O₂ saturation > 70% and a central venous pressure (CVP) > 8. The medication was initially administered over three hours and up titrated to increase the MAP to at least 75 mm Hg (dose 1.25 - 40 ng/kg/min). During this initiation, standard doses of background vasopressors were held constant. If these doses were increased for safety reasons, patients were marked as non-responders. At hour 48, the study infusion was discontinued according to a protocolled tapering process. The primary end point was the change in mean arterial pressure (MAP) at hour 3, with response defined as a MAP of 75 mm Hg or higher or an increase in 10 mm Hg from baseline. Secondary outcomes were change in both cardiovascular and total SOFA scores, and safety outcomes were all-cause mortality at both 7 and 28 days.

The study regimen was initiated on 321 patients - 163 received angiotensin II and 158 received placebo. 69.9% of patients in the angiotensin II group met the primary end point versus only 23.4% of patients in the placebo group (p<0.001, OR 7.95, CI 4.76-13.3). The most common causes of treatment failure included failure to meet blood pressure goals and an increase in the dose of background vasopressors. A MAP increase of 12.5 mm Hg was achieved in the angiotensin II group at 3 hours, versus an increase of 2.9 mm Hg in the placebo arm (p<0.001). This led to a lower dose of background vasopressor use during the first 48 hours in the angiotensin II group versus placebo (article Fig. 2). However, there were no significant differences in the total SOFA score between the two groups (p=0.49). Additionally, death from any cause by day 28 occurred in 46% of patients in the angiotensin II group and in 53.8% of the placebo group (p=0.12). Importantly, safety data were similar between placebo and angiotensin II, with no differences in the rates of atrial fibrillation, digital ischemia, or ventricular tachycardia.

COMMENTARY

This Phase 3 trial is an important stepping stone in the investigation of angiotensin II as a possible vasopressor in vasodilatory shock, of which sepsis is the most common clinical etiology. It showed that angiotensin II had a significant impact on blood pressure compared to placebo, supporting previously published data from phase II trials.1 While administration of angiotensin II did not have a measurable effect on mortality, this study was not powered to measure this outcome. Furthermore, mortality data is lacking with many of the currently used vasopressors, and there are real questions as to whether mortality improvements are necessary before clinical use.

Angiotensin II did not have any detectable patient safety concerns, although the small sample size and relatively short duration of monitoring (28-days) cannot preclude the
possibility of important side effects. However, this study excluded patients with a low cardiac output. Vasoconstriction can result in a further reduction in cardiac output, and therefore this vasopressor could potentially cause severe harm in patients with cardiogenic shock. The physiologic effects of angiotensin II on low cardiac output states needs to be investigated. Further trials should also include a larger sample size and a longer duration of follow-up to further evaluate more long-term adverse effects. This trial presents convincing data as a proof of concept, however, before consideration of clinical use, more investigation is required.

REFERENCES:
**Trial of Tocilizumab in Giant-Cell Arteritis**


**SUMMARY**

Giant cell arteritis (GCA) is a large vessel vasculitis resulting in systemic inflammation with potentially severe consequences of vision loss. GCA often requires frequent prolonged steroid tapers, predisposing to the multiple consequences of long term steroid use. There is urgent need to identify and evaluate steroid sparing agents in these systemic inflammatory diseases requiring such high cumulative doses of steroids. This 1-year randomized, double blind, placebo controlled phase 3 trial (Giant-Cell Arteritis Actemra (GiACTA) trial) evaluated tocilizumab, an IL-6 receptor alpha inhibitor, in the treatment of GCA (either newly diagnosed or relapsing) to achieve higher rates of sustained remission versus placebo. Patients >50 years old with proven GCA (through temporal artery biopsy or imaging plus elevated ESR) were assigned to either weekly subcutaneous tocilizumab 162 mg + 26 week prednisone taper (100 patients), every other week tocilizumab + 26 week prednisone taper (50 patients), weekly subcutaneous placebo + 26 week prednisone taper (50 patients), or weekly subcutaneous placebo + 52 week prednisone taper (51 patients). The primary outcome was sustained prednisone-free remission at week 52 in each of the tocilizumab arms vs placebo + 26 week prednisone taper. Patients who experienced a flare or were not in remission by week 12 or had two consecutive increases in CRP levels were considered not to have responded to the therapy.

At the 52-week trial completion, 56% of weekly tocilizumab patients and 53% with every other week tocilizumab had sustained remission versus 14% of the 26 week taper placebo and 18% of the 52 week taper placebo (p<0.001). The percentage of patients with flares were 23% with weekly tocilizumab, 26% biweekly tocilizumab, 68% placebo with 26-week taper and 49% placebo with 52-week taper. Patients with newly diagnosed GCA did not experience significantly different outcomes between the two dosing frequencies of the tocilizumab; however, patients with relapsing disease at baseline had a lower risk of flare with weekly tocilizumab whereas biweekly dosing was not significantly different from placebo. Patients’ global assessment of disease activity using visual analogue scale (VAS) score decreased with tocilizumab therapy (indicating improvement) by -19 with weekly dosing and -25 with biweekly versus -3.4 and -7.2 in the placebo groups (26 week and 52 week taper respectively). Adverse events were similar in all trial groups, with infection being the most frequent. One patient on tocilizumab had an episode of anterior ischemic optic neuropathy that resolved with steroids. Other tocilizumab reactions included injection site reactions and neutropenia.

**COMMENTARY**

Overall, tocilizumab treatment was superior to placebo + prednisone taper in achieving sustained prednisone-free remission in GCA and adverse reactions were similar. Weekly treatment with tocilizumab resulted in greater disease control (as compared with every other week dosing, in relapsing, presumably more severe/recalcitrant, GCA). Tocilizumab groups required essentially half the dose of prednisone, which should reduce long term consequences of steroids, such as loss of bone density and risk for infection. Limitations of trials in GCA include a lack of validated outcome measures, although strict parameters for flare and remission were used. Future research is warranted to assess long
term efficacy and safety of tocilizumab, as well as cost effectiveness. In conclusion, subcutaneous tocilizumab for GCA appears promising in reducing flares and sustaining remission while requiring lower prednisone dosing.