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ABSTRACT & COMMENTARY

Simple Prediction Tool Facilitates Diagnosis of Heart Failure With Preserved Ejection Fraction

By Van Selby, MD

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Dr. Selby reports no financial relationships relevant to this field of study.

SYNOPSIS: In patients with unexplained dyspnea, a score based on six noninvasive criteria can predict the likelihood of heart failure with preserved ejection fraction.

SOURCE: Reddy YNV, Carter RE, Obokata M, et al. A simple, evidence-based approach to help guide diagnosis of heart failure with preserved ejection fraction. *Circulation* 2018 May 23. pii: CIRCULATIONAHA.118.034646. doi: 10.1161/CIRCULATIONAHA.118.034646. [Epub ahead of print].

Exertional dyspnea is a frequent complaint among patients referred to cardiology clinics. Heart failure with preserved ejection fraction (HFpEF) is common among such patients, but the diagnosis can be challenging without invasive testing. Reddy et al sought to develop a simple risk prediction score based on readily available clinical data. They retrospectively analyzed a cohort of 414 consecutive patients with unexplained dyspnea who were referred for right heart catheterization with exercise testing at the Mayo Clinic. A diagnosis of HFpEF was confirmed if the patient demonstrated a pulmonary arterial wedge pressure ≥ 15 mmHg at rest or ≥ 25 mmHg during exercise. Multivariable logistic regression was used to identify clinical variables associated with the presence of HFpEF.

Of the 414 patients studied, 267 were diagnosed with HFpEF, and the rest were diagnosed with noncardiac dyspnea. The clinical predictors in the final model were obesity, atrial fibrillation, age > 60 years, treatment with two or more antihypertensive medications, an

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E/e' ratio > 9 on echocardiography, and a pulmonary artery systolic pressure > 35 mmHg on echocardiography. The authors developed a weighted composite (the H_2FPEF score) using these six predictors, with scores ranging from 0-9. The score was strongly associated with the likelihood of HFpEF, with the odds of HFpEF doubling for every one-unit increase in score (odds ratio, 1.98; $P < 0.0001$). The area under the curve (AUC) for predicting HFpEF was 0.841 ($P < 0.0001$), with a score of 1.0 representing a perfect test. The H_2FPEF score was validated in a separate cohort of 100 patients with similar performance (AUC, 0.886; $P < 0.0001$).

The authors concluded the H_2FPEF score enables discrimination of HFpEF from non-cardiac causes of dyspnea and is useful in the evaluation of patients with unexplained exertional dyspnea.

■ COMMENTARY

HFpEF can be challenging to diagnose when obvious signs and symptoms are absent. Right heart catheterization with exercise is considered the gold standard for diagnosing HFpEF. However, given the invasive nature and required resources, it is not feasible to refer all patients with suspected HFpEF for such testing. Using data from patients referred to the Mayo Clinic catheterization laboratory for evaluation of unexplained dyspnea, Reddy et al developed an easy-to-use score that predicts the likelihood of HFpEF in such patients using data obtained during routine clinical evaluation.

The H_2FPEF score is simple to calculate: 3 points for atrial fibrillation, 2 points for obesity, and 1 point for each of the other criteria. A score of 0-1 was considered sufficient to eliminate HFpEF. High scores (6-9) usually can establish the diagnosis of HFpEF with reasonable confidence. In patients with scores of 2-5, a diagnosis of HFpEF can neither be confirmed nor ruled out, and further testing (such as an invasive exercise study) should be considered. The authors also provided a more sophisticated calculator (available in the supplementary material published with the article) that can be used if even more precise risk estimation is desired. The H_2FPEF score performed markedly better than other available algorithms for determining the likelihood of HFpEF. For example, when compared to criteria proposed in expert guidelines from the European Society of Cardiology (primarily based on natriuretic peptide levels and echocardiographic parameters), the H_2FPEF score performed substantially better in this Mayo cohort (increase in AUC of 0.169; $P < 0.0001$).

Although the test has advantages over other risk prediction tools, there are important considerations to keep in mind when using the test. Even in patients with a score of 1 (low risk), the prevalence of HFpEF was approximately 20%. When suspicion for HFpEF persists and an alternative explanation for a patient's exertional dyspnea cannot be identified, it is reasonable to consider invasive exercise hemodynamic testing. The test performs much better when the score is high; more than 90% of patients with scores > 5 were confirmed to have HFpEF by invasive testing.

The H_2FPEF score was derived only using data from patients treated at the Mayo Clinic, and it is unclear how the same test would perform outside of this highly specialized, tertiary referral setting. The final model contained multiple variables that are well-known predictors of HFpEF (i.e., echocardiographic evidence of diastolic dysfunction), but left out other predictors that previously were shown to predict HFpEF (such as natriuretic peptide levels).

The authors did not find a strong enough association to include NTproBNP level in the final score, but NTproBNP data were missing for 24% of patients. Does this mean we should ignore NTproBNP levels when evaluating a patient for HFpEF? Probably not.

Tools like H_2FPEF cannot replace clinical judgment. In patients with clear signs and symptoms of vascular congestion, a diagnosis of HFpEF can be made regardless of the score. Similarly, in patients with a clear alternative etiology for dyspnea, the score should not distract from the obvious causes. Despite its limitations, the H_2FPEF score provides a useful framework for estimating the likelihood of HFpEF in select patients with exertional dyspnea that remains unexplained despite appropriate initial evaluation. ■

ABSTRACT & COMMENTARY

Does Childhood Adversity Affect the Menopausal Transition?

By Chiara Ghetti, MD

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Dr. Ghetti reports no financial relationships relevant to this field of study.

SYNOPSIS: The number and timing of adverse childhood experiences in relation to puberty affect the risk of incident major depressive disorder in menopausal transition.

SOURCE: Epperson CN, Sammel MD, Bale TL, et al. Adverse childhood experiences and risk for first-episode major depression during the menopause transition. *J Clin Psychiatry* 2017;78:e298-e307.

The objective of this study was to determine the effect of early-life stress on the risk of having a first episode of major depressive disorder (MDD) during the menopause transition (incident depression) among participants in the Penn Ovarian Aging Study (POAS). In addition, the study authors explored whether the timing of adverse childhood experiences (ACEs) in relationship to puberty affects the risk of lifetime MDD and incident MDD at time of the menopausal transition. This was a cohort study of the POAS group, which is a population-based longitudinal set of cycling premenopausal women between the ages of 35 and 47 years. The cohort initially was identified by random-digit dialing in Philadelphia County, PA, in 1996-1997, and was stratified to obtain equal numbers of white and African-American women. Exclusion criteria included hysterectomy, the use of hormonal contraception or psychotropic medication, the presence of a serious health problem, or alcohol or drug abuse in the previous year. The initial cohort consisted of 436 women. The current study is the analysis of 293 women who remained active in the cohort between June 2012 and August 2012. The main outcomes included: menopausal status obtained by menstrual diaries; ACE, measured using the ACE-Q questionnaire; and history of major depression diagnosis and depressive symptoms, as measured by Center for Epidemiologic Studies Depression (CES-D) scale scores.

The ACE-Q focuses on three general categories of childhood adversity (abuse, neglect, and household/family dysfunction), which are divided into subcategories that include physical, sexual, and emotional abuse; emotional and physical neglect; parental separation; household violence; parental substance abuse or psychiatric disorders; and household member in prison. A CES-D score of ≥ 16 corresponds to a clinically meaningful level of depressive symptoms, while a score of ≥ 25 is suggestive of a clinical diagnosis of MDD. Of the women active in the POAS in the cohort, 243 had completed ACE-Q data. The mean age of these women was 41.6 years, and 47% were African American, with the remainder Caucasian. Forty percent of women had not experienced an ACE, 22% had experienced one ACE, and 38% had experienced two or more ACEs. Most ACEs occurred in the prepubertal window. Groups with high vs. low ACEs differed by race, with African-American women more likely to be in the high ACE group. Women with two or more postpubertal ACEs were significantly more likely to exhibit baseline CES-D scores ≥ 16 or ≥ 25 and body mass index (BMI) ≥ 30 kg/m^2. Of the women at risk for incident menopause MDD, 22.4% were diagnosed with MDD during premenopause, while 20.7% had incident menopause MDD. In logistic regression models adjusted for race, smoking, BMI ≥ 30 kg/m^2, and employment status, subjects with two or more ACEs, compared to subjects with no ACE, were two times more likely to experience a lifetime MDD and incident menopause MDD. Women with two or more postpubertal ACEs were at greater risk of incident menopause MDD but not lifetime MDD when compared to those with no postpubertal ACEs. Women who reported one ACE had significantly reduced MDD risk compared to women who reported two or more ACEs.

■ COMMENTARY

Major depression is very prevalent and is a leading cause for disability. The World Health Organization has ranked depression the fourth leading cause of disability worldwide, estimating that it will be the second leading cause by 2020.[1,2] Lifetime prevalence estimates vary worldwide and are estimated to be 16.9% but are as high as 21% in the United States.[1,2,3] Women are at higher risk for MDD and are more susceptible during certain reproductive milestones. Obstetricians may be most familiar with postpartum depression. However, depression also is common in young women and in women during the menopausal transition. Women with no prior history of depression are two to three times more likely to experience a first episode of depression during perimenopause and early menopause.[4,5] Although a role of childhood adversity has

been established in mood disorders, this is the first study of the role of childhood adversity and the onset of MDD during the menopausal transition.

Chapman et al found that exposure to ACEs was associated with an increased risk of adult depressive disorders and established the role of childhood adversity in major depression.[6] In their study, the most commonly reported adverse experiences were household substance, physical, and sexual abuse, with emotional abuse posing the largest risk for lifetime or recent depression among women. Limitations include the inability to provide more details about specific ACEs. This study includes some data points that may be influenced by recall bias. In addition, Chapman et al were not able to explore the relationships between depression, ACE, and hormone therapy.

Epperson et al built on prior work and established a link between childhood adversity and increased risk of depression in women experiencing the menopausal transition decades after the ACEs. This provides another window into the relationship of depression, stress, and hormonal fluctuations. Although they did not discuss the clinical management of depression, the discussion further underscores the lasting effect of childhood trauma and its role in adult depression, even during the menopausal transition.[7,8,9] As clinicians, awareness of the relationship between trauma and depression may aid us to better care for women with depression throughout the lifespan. ■

REFERENCES

1. Kessler RC, Bromet EJ. The epidemiology of depression across cultures. *Ann Rev Public Health* 2013;34:119-138.
2. Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *Lancet* 2013;382:1575-1586.
3. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994;51:8-19.
4. Bromberger JT, Kravitz HM, Chang YF, et al. Major depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). *Psychol Med* 2011;41:1879-1888.
5. Cohen LS, Soares CN, Vitonis AF, et al. Risk for new onset of depression during the menopausal transition: The Harvard study of moods and cycles. *Arch Gen Psychiatry* 2006;63:385-390.
6. Chapman DP, Whitfield CL, Felitti VJ, et al. Adverse childhood experiences and the risk of depressive disorders in adulthood. *J Affect Disord* 2004;82:217-225.
7. Schüssler-Fiorenza Rose SM, Xie D, Stineman M. Adverse childhood experiences and disability in U.S. adults. *PM R* 2014;6:670-680.
8. Cheong EV, Sinnott C, Dahly D, Kearney PM. Adverse childhood experiences (ACEs) and later-life depression: Perceived social support as a potential protective factor. *BMJ Open* 2017;7:e013228.
9. Brinker J, Cheruvu VK. Social and emotional support as a protective factor against current depression among individuals with adverse childhood experiences. *Prev Med Rep* 2016;5:127-133.

ABSTRACT & COMMENTARY

Oral Antibiotics May Increase the Risk for Nephrolithiasis

By Richard R. Watkins, MD, MS, FACP, FIDSA

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Dr. Watkins reports that he has received research support from Allergan.

SYNOPSIS: A case-control study found that receipt of an oral antibiotic in the preceding three to 12 months was associated with nephrolithiasis. The risk persisted up to five years, and younger patients were at increased risk.

SOURCE: Tasian GE, Jemielita T, Goldfarb DS, et al. Oral antibiotic exposure and kidney stone disease. *J Am Soc Nephrol* 2018;29:1731-1740.

Despite the miraculous benefits of antibiotics, they carry risks and can produce side effects, some of which can be quite detrimental. It is well established that antibiotics disrupt the human microbiome. There also is evidence that patients with nephrolithiasis have an altered gut microbiome compared to those without nephrolithiasis. Therefore, Tasian et al sought to determine whether receiving oral antibiotics increases a patient's risk for developing nephrolithiasis.

The investigators conducted a case-control study that used The Health Improvement Network (THIN), a database from more than 13 million patients who received care from general practitioners in the United Kingdom between 1994 and 2015. Individuals < 90 years of age with a diagnosis code for nephrolithiasis were included. Those with codes for infectious calculi, such as calculous pyelonephritis, were excluded. The primary exposure was receiving

an oral antibiotic as an outpatient within three to 12 months of the index date (i.e., the date of nephrolithiasis diagnosis). Any antibiotic prescription of any dosage and duration within the exposure window was included.

The most common reasons for antibiotic use were chest infection, cough, upper respiratory infection, tonsillitis, and urinary tract infection (UTI). Prescriptions for all classes of oral antibiotics except lincosamides (e.g., clindamycin) were greater among patients with nephrolithiasis compared to controls. The oral antibiotics with the highest association for nephrolithiasis with no adjustment for other antibiotic use were sulfa drugs (odds ratio [OR], 2.37; 95% confidence interval [CI], 2.23-2.52), cephalosporins (OR, 1.93; 95% CI, 1.81-2.07), fluoroquinolones (OR, 1.84; 95% CI, 1.7-1.99), nitrofurantoin (OR, 1.84; 95% CI, 1.67-2.02), and broad-spectrum penicillins (OR, 1.37; 95% CI, 1.28-1.47). Treatment with antibiotics for *H. pylori* was not significantly associated with nephrolithiasis risk. The risk was greatest within three to six months from the index date for antibiotics in all five classes and remained significant for three to five years for all classes except broad-spectrum penicillins.

Furthermore, the odds ratios were greatest for antibiotic exposures at younger ages, which were seen with all five antibiotic classes. When investigators conducted a sensitivity analysis, they found that when patients with a prior UTI were excluded, the magnitude of the association increased for sulfa and nitrofurantoin, decreased for broad-spectrum penicillins, and stayed the same for the other antibiotic classes.

■ COMMENTARY

During the past 30 years, the prevalence of nephrolithiasis in the United States has risen by 70%. The reasons for this spike are uncertain. One hypothesis is that it might be caused by antibiotic use. Because correlation does not always equal causality, the study by Tasian et al is important because it elucidates the association between oral antibiotics and nephrolithiasis. Exposure to five common classes of oral antibiotics increased the risk for nephrolithiasis, even after adjustment for multiple confounding factors, the rate of healthcare encounters, and exclusion of patients with prior UTI. Moreover, the magnitude of the associations was strongest in younger patients. This is an important finding because children receive more antibiotics than any other age group and the incidence of nephrolithiasis has been rising fastest among children and young women. Thus, the results of this study are another reason to promote judicious antibiotic use in the outpatient setting.

How could antibiotics increase the risk for developing nephrolithiasis? One proposed mechanism is that changes in the gut microbiota alter macronutrient metabolism, leading to increased calcium stone formation. Indeed, children might be more susceptible because antibiotic exposure at a younger age produces more profound effects on their microbiome than exposure later in life. Another potential mechanism is that antibiotics select for multidrug-resistant (MDR) pathogens that promote kidney stone formation. Prior studies have shown that up to 70% of bacteria cultured from calcium stones are MDR, and their role in stone formation needs further investigation.

There are a few limitations to the study that should be mentioned. First, the results could have been influenced by unmeasured confounding variables, such as unreported comorbid illnesses. Second, some patients may have had unrecognized, asymptomatic kidney stones before receiving their course of antibiotics. Third, only outpatient data on oral antibiotics were available, so no conclusions about the association of parenteral antibiotics and nephrolithiasis can be reached. Finally, it was presumed that patients prescribed antibiotics took them and no attempt was made to verify medication compliance.

The report by Tasian et al suggests that oral antibiotics from five common classes are a novel risk factor for the development of nephrolithiasis. These findings carry important implications for both the pathogenesis of nephrolithiasis and for promoting better antibiotic stewardship in the outpatient setting. ■

BRIEF REPORT

'The World Is Covered by a Thin Layer of Feces'

By Carol A. Kemper, MD, FACP

Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Santa Clara Valley Medical Center

Dr. Kemper reports no financial relationships relevant to this field of study.

SOURCE: Janezic S, Mlakar S, Rupnik M. Dissemination of *Clostridium difficile* spores between environment and households: Dog paws and shoes. *Zoonoses Public Health* 2018, April 23: doi:10.1111/zph.12475. [Epub ahead of print].

This quote is the best line I've ever heard — by Lucy Tompkins, MD, Stanford (my infectious disease attending many years ago).

Janezic et al examined the risk of acquiring *Clostridium difficile* when walking the dog (literally). The researchers examined 20 households in Eastern Slovenia with a pet dog. Five were urban households and 15 were rural. Samples from the shoes, household slippers, and dog paws were collected within 30 minutes of walking the dog or the owner returning from a walk. Duplicate samples were permitted in households with two dogs. All samples were submitted for PCR ribotyping and toxinotyping, as well as culture.

Ninety samples were collected from 20 households, including 25 from dog paws, 44 from shoes (both the right and the left), and 21 from household slippers. Of these, remarkably, *C. difficile* was detected on 31 of 90 specimens from 14 households. *C. difficile* was isolated from 43% of shoes, 28% of slippers, and 24% of dog paws. Altogether, 465 *C. difficile* isolates were obtained and sequenced, revealing 13 different ribotypes. Half were PCR ribotype 014/020, which was found in 18 different samples collected in eight homes. Five of these 13 ribotypes were toxigenic.

This study fits nicely with earlier work in New York City, which found that sand boxes and dog play areas often are contaminated with *C. difficile*. Basically, *C. difficile* is all around us. But it does make me wonder about the risk of spreading *C. difficile* in the hospital on my shoes. We don't allow dogs in isolation rooms for this reason, but could my feet be a vector while I perform my daily rounds? ■

PHARMACOLOGY UPDATE

Avatrombopag Tablets (Doptelet)

By William Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

The FDA has approved the first drug to treat low blood platelet counts in adults with chronic liver disease who are scheduled to undergo a medical or dental procedure. The FDA issued a fast-track designation and priority review for avatrombopag, a thrombopoietin receptor agonist. It is marketed as Doptelet.

INDICATIONS

Doptelet is prescribed for adults with thrombocytopenia and chronic liver disease who are scheduled to undergo a medical procedure.[1]

DOSAGE

Patients take avatrombopag orally with food once daily for five consecutive days starting 10-13 days prior to a scheduled procedure.[1] Patients should undergo the procedure within five to eight days after the last dose. The recommended dose is 60 mg (three tablets) for patients with a baseline platelet count of $< 40 \times 10^9$/L and 40 mg (two tablets) if platelet count is 40×10^9/L to $< 50 \times 10^9$/L. Avatrombopag is available as 20 mg tablets, too.

POTENTIAL ADVANTAGES

Avatrombopag may decrease or eliminate the need for

platelet transfusion or rescue procedures for bleeding in patients who are candidates for platelet transfusion due to low platelet counts. Doptelet is the first drug approved for this indication.

POTENTIAL DISADVANTAGES

There is potential to increase clotting risk in patients with known risk for thromboembolism (e.g., genetic prothrombotic conditions, antithrombin deficiency).[1] The efficacy has not been established in patients ≥ 65 years of age.[1]

COMMENTS

Avatrombopag binds to the thrombopoietin receptor, but does not compete with endogenous thrombopoietin, which leads to an added stimulus on platelet production.[1] The peak effect is observed 10-13 days after the start of the five-day course. Platelet counts gradually return near baseline after 35 days.

Safety and efficacy were evaluated in two randomized, placebo-controlled trials in subjects with chronic liver disease and thrombocytopenia (baseline count, < 50 × 10^9/L) scheduled to undergo a procedure with low, moderate, or high bleeding risk, which would require a platelet transfusion.[1,2] Subjects were stratified by baseline platelet count: low (< 40 × 10^9/L) or high (≥ 40 × 10^9/L to < 50 × 10^9/L). Those with low counts were randomized to 60 mg or placebo for five days. Those with high counts received 40 mg or placebo for five days.

In trial 1, the authors randomized 90 subjects to avatrombopag in the low count group and 59 in the high count group, with corresponding placebo subjects of 48 and 34, respectively. For trial 2, the number of subjects in the avatrombopag groups were 70 in the low platelet count group and 58 in the high platelet count group, with 43 and 33, respectively, in the placebo groups. Mean baseline platelet counts were 31 to 33 × 10^9/L in the low count groups and 44 × 10^9/L to 45 × 10^9/L in the high count groups. The most common liver diseases were chronic viral hepatitis (57%) and hepatocellular carcinoma (27%).[2] Sixty-one percent of subjects underwent low bleeding risk procedures. Twenty-two percent underwent high bleeding risk procedures. The major efficacy endpoint was the proportion of subjects who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to seven days following an elective procedure (defined as responders). The secondary endpoint was achieving a platelet count of > 50 × 10^9/L.

In the low count group, the frequency of responders was 66% in trial 1 and 69% in trial 2, compared to 23% and 35%, respectively, for the placebo groups. For the high count group, response rates were 88% in both trials for avatrombopag, and 38% and 33% for placebo groups, respectively. In the low count group, 67-69% achieved a count > 50 × 10^9/L compared to 3-7% for the placebo groups. The most frequently reported adverse reactions (vs. placebo) were pyrexia (10% vs. 9%) and abdominal pain (7% vs. 6%).[1]

CLINICAL IMPLICATIONS

Thrombocytopenia is a complication of chronic liver disease, with the level of thrombocytopenia corresponding to the severity of liver disease.[3] Severe thrombocytopenia (< 50 × 10^9/L) complicates invasive procedures for diagnosis or therapy in these patients. However, a recent case series study suggested that bleeding after invasive procedures is rare and not predicted by platelet counts in cirrhotic patients.[4] Strategies to boost platelet counts include platelet infusion or use of a thrombopoietin receptor agonist.[5,6] Platelet transfusion is limited by transfusion reactions, short duration of action, and platelet refractoriness.[7] The thrombopoietin receptor agonist eltrombopag has been associated with portal vein thrombosis.[8] Romiplostim has not been approved for this indication, and there are no published comparative studies with avatrombopag. Avatrombopag is the only approved drug that is an alternative to platelet infusion. The wholesale acquisition cost for a five-day course is $9,000 for the 40 mg daily dose and $13,500 for the 60 mg daily dose. ■

REFERENCES

1. Doptelet Prescribing Information. Dova Pharmaceuticals, Inc., May 2018. Available at: https://bit.ly/2NvmkiX. Accessed July 5, 2018.
2. Terrault N, Chen YC, Izumi N, et al. Avatrombopag before procedures reduces need for platelet transfusion in patients with chronic liver disease and thrombocytopenia. *Gastroenterology* 2018 May 17. pii: S0016-5085(18)34545-1. doi: 10.1053/j.gastro.2018.05.025. [Epub ahead of print].
3. Maan R, de Knegt RJ, Veldt BJ. Management of thrombocytopenia in chronic liver disease: Focus on pharmacotherapeutic strategies. *Drugs* 2015;75:1981-1992.
4. Napolitano G, Iacobellis A, Merla A, et al. Bleeding after invasive procedures is rare and unpredicted by platelet counts in cirrhotic patients with thrombocytopenia. *Eur J Intern Med* 2017;38:79-82.
5. Qureshi K, Patel S, Meillier A. The use of thrombopoietin receptor agonists for correction of thrombocytopenia prior to elective procedures in chronic liver diseases: Review of current evidence. *Int J Hepatol* 2016;2016:1802932. Epub 2016 Oct 9.
6. Afdhal N, McHutchison J, Brown R, et al. Thrombocytopenia associated with chronic liver disease. *J Hepatol* 2008;48:1000-1007.
7. Estcourt LJ, Malouf R, Doree C, et al. Prophylactic platelet transfusions prior to surgery for people with a low platelet count. *Cochrane Database Syst Rev* 2017;2017(9). pii: CD012779. doi: 10.1002/14651858.CD012779. Epub 2017 Sep 2.
8. Afdhal NH, Giannini EG, Tayyab G, et al. Eltrombopag before procedures in patients with cirrhosis and thrombocytopenia. *N Engl J Med* 2012;367:716-724.

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CME QUESTIONS

1. **A clinical score for predicting that a patient has heart failure with preserved ejection fraction is most heavily influenced by:**
   a. atrial fibrillation.
   b. hypertension on two medications.
   c. age > 60 years.
   d. an estimated pulmonary arterial wedge pressure on echo of > 35 mmHg.

2. **Based on the study by Epperson et al, which of the following is true about depression during the menopausal transition?**
   a. It is not common.
   b. It is not related to adverse childhood experiences (ACE).
   c. It is more likely in the setting of two or more ACEs.
   d. It is as likely in women with one ACE as in women with two or more ACEs.

3. **Which of the following is correct regarding exposure to orally administered antibiotics and the development of nephrolithiasis?**
   a. The association is greatest when antibiotics are given to the elderly.
   b. The association is present for only four weeks after antibiotic administration.
   c. The highest association risk is with the use of antibiotics to treat *Helicobacter pylori* infection.
   d. The antibiotics associated with the highest risk were sulfas, cephalosporins, fluoroquinolones, and broad-spectrum penicillins.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages, and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Sepsis-related Neurologic Dysfunction Strongly Associated With Long-term Mortality

Management of Pain Associated With Intrauterine Device Placement