Click Here

Does anemia affect sleep? A number of research studies indicate that the answer is yes, there is a strong correlation between iron deficiency and sleep problems. In this blog, we'll break down the links between anemia and insomnia, as well as other sleep problems. Anemia & Trouble Sleeping Go Hand in Hand Anemia and sleep problems share a number of similar symptoms, including fatigue and feeling generally run down, even after a full night of sleep. Some people with anemia will also experience impaired focus and brain fog, as well as mood swings, anxiety, and depressive symptoms. These symptoms are also commonly found in people with sleep disorders. Other symptoms of anemia include: Irregular heartbeat Chest pain Being short of breath Feeling dizzy or lightheaded Headaches Feeling cold in extremities (hands and feet) Very pale and/or yellow skin Cognitive difficulties, including lack of focus and attention The most common form of anemia is caused by iron deficiency—around 50 percent of all cases of anemia worldwide are caused by the lack of iron. This deficiency can be caused by a lack of sufficient iron in the diet or problems with iron absorption, blood loss, and more rarely, infection. Pregnancy also increases the need for iron in women, which can cause anemia. Iron is needed for the body to produce hemoglobin, a major component of red blood cells that binds to the oxygen molecule and helps these blood cells transport oxygen. Anemia is a condition characterized by an insufficient supply of red blood cells, so the muscles, tissues, and cells are receiving less oxygen. In addition to transporting and delivering oxygen throughout the body, red blood cells also pick up carbon dioxide from the cells and tissues and deliver them back to the lungs, where the carbon dioxide is exhaled. Anemia and Insomnia Recent research studies have identified a specific gene associated with insomnia and anemia stemming from iron deficiency, as well as restless leg syndrome (RLS). Women have a higher risk of insomnia than men, so it's not surprising to find that research shows women are at higher risk for iron-deficient anemia than men. Around 3 percent of all adult men in developed countries have iron-deficient anemia. In contrast, an estimated 20 percent of all women and 50 percent of pregnant women in developed countries have anemia due to iron deficiency. A recent genome-wide analysis has revealed that the gene MEIS1 is linked with insomnia, which has also been implicated in restless leg syndrome and iron-deficiency anemia (IDA), the latter caused by a decrease in the oxygen transporter in the blood–hemoglobin (Hb). – Sleep Review Magazine A larger Chinese medical study explored the links between iron-deficient anemia and insomnia over a period of six years. Among the study population, 4.3 percent had anemia and 15.2 percent reported having insomnia. Several important connections between the two conditions were identified: People who had previously had anemia had a higher prevalence of insomnia. Simply having anemia was associated with a 32 percent greater risk of developing insomnia in the future. Severe anemia was strongly linked to an increased risk for insomnia. Mild and moderate anemia also increases the risk of developing insomnia but to a lesser degree. In an interesting twist, the research study showed that men with anemia were at greater risk for insomnia than women with anemia—perhaps due to basic hormonal differences. Women are already twice as likely as men to have insomnia and are also twice as likely to develop RLS. Treating Iron Deficiency and Sleep Problems The new links between iron deficiency and sleep problems mean that doctors must consider the possibility of anemia in sleep disorders such as insomnia. Most treatments for iron-deficient anemia include a combination of iron supplements and dietary and lifestyle changes, which can also be beneficial to better sleep. In fact, many of the recommended iron-rich foods which help maintain healthy iron levels in the body are also healthy choices for achieving better sleep. These include consuming more dark leafy greens, nuts and seeds, legumes, and grass-fed meats in your diet. A variety of fish containing omega-3 fatty acids are also rich in iron. Since these particular fatty acids are important to supporting sleep, eating more fish can benefit both conditions. The bottom line? Sleep disorders and anemia are quite common for women and men, but women suffer from anemia especially so. If you're experiencing insomnia or other symptoms associated with either condition, it's best to see a doctor or sleep specialist to get to the core issue and get treatment. Schedule a consultation with a sleep specialist. The NICE Clinical Knowledge Summaries (CKS) site is only available to users in the UK, Crown Dependencies and British Overseas Territories. CKS content is produced by Clarity Informatics Ltd (trading as Agilio Software | Primary Care). It is available to users outside the UK via subscription from the Agilio | Prodigy website. If you believe you are seeing this page in error please contact us. The NICE Clinical Knowledge Summaries (CKS) site is only available to users in the UK, Crown Dependencies and British Overseas Territories. CKS content is produced by Clarity Informatics Ltd (trading as Agilio Software | Primary Care). It is available to users outside the UK via subscription from the Agilio | Prodigy website. If you believe you are seeing this page in error please contact us. Detecting iron deficiency early during pregnancy and in young children is crucial. Iron deficiency in children under two years of age can have significant and irreversible effects on brain development. This can lead to negative consequences on learning and school performance later in life. Cognitive development of a child can also be affected if a mother is iron deficient during her last trimester of pregnancy. New World Health Organization guidelines on the use of ferritin concentrations to assess iron status in individuals and populations will help health workers to detect iron deficiency early and avoid the most severe impacts. WHO shows how to best measure ferritin, an indicator of iron stores, to help determine iron deficiency or overload. Ferritin is a protein which can be found in small amounts circulating in a person's blood. Ferritin levels are low in iron-deficient individuals and high in iron-loaded individuals. Accurate measurements of this protein, along with clinical and laboratory evaluation, can guide the appropriate interventions in both individual patients and at a population level. "Reducing anemia is one of the components of our efforts to eradicate all forms of malnutrition. However, progress has been limited and we still have 614 million women and 280 million children globally who suffer from it," said Dr Francesco Branca, Director of the Department of Nutrition and Food Safety at WHO. "Iron deficiency is a major determinant of anemia and measuring ferritin, a key biomarker of iron metabolism, will help us better target and evaluate our action to fight anemia" Iron is an essential element with important functions such as oxygen transport, DNA synthesis and muscle metabolism. Iron deficiency is the main cause of anaemia, which is the most prevalent nutritional deficiency worldwide, affecting 33% of non-pregnant women, 40% of pregnant women, and 42% of children worldwide. In adults, iron deficiency can also have negative effects including fatigue, impaired physical performance and decreased work productivity, as well as impacting social activities. Iron deficiency occurs mainly when the requirements of iron increase during rapid periods of growth and development such as in early childhood, adolescence and pregnancy, but it can occur at other stages in life. In pregnant women, iron deficiency can cause anaemia, reduced birth weight and reduced gestation periods. The new guidelines also cover the early detection of iron overload. Iron overload (accumulation of iron in the body) is generally the result of disorders such as hereditary haemochromatosis, thalassaemia, repeated blood transfusions or other conditions that affect iron absorption or regulation and can also lead to deterioration of a person's health if left untreated. Improved knowledge about the prevalence and distribution of iron deficiency and risk of iron overload in the population helps countries to decide on appropriate interventions, and to monitor and evaluate the impact and safety of public health programmes. For example, nutritional iron deficiency can be commonly found in populations that also have infectious diseases. The adequate evaluation of iron status in countries with infectious disorders can help countries to put in place adequate health policies. The WHO guidelines aim to help WHO Member States and their partners to make evidence-informed decisions on appropriate actions in their efforts to lower iron deficiency and improve the health and quality of life of individuals and populations. For interviews with WHO technical experts, please contact: Pippa HAUGHTON – haughtonp@who.int +41794466331 To access a copy of the full guidelines, please visit Iron is an essential mineral necessary for the production of haemoglobin , which carries oxygen in red blood cells throughout the body. Consuming adequate amounts of iron-rich foods is important for maintaining a healthy immune system and preventing iron deficiency diseases. Following are the consequences of iron deficiency: Anaemia caused by iron deficiency is the most common type of anaemia, and it occurs when the body does not have enough iron to produce red blood cells. According to research 30 to 50 percent of anaemia in children is caused due to iron deficiency. Symptoms include tiredness, weakness and pale skin. Iron is important for brain development and cognitive function, and a lack of iron can cause cognitive problems such as poor concentration, difficulty learning, and slowed mental processing. Also read: 6 Iron-Rich Drinks You Can Make At Home To Combat Deficiency Iron is necessary for the body to produce white blood cells, which help the body fight off infections. Without enough iron, the body's ability to fight off infections is compromised. Reduced Physical Performance Iron helps our body produce energy, and a lack of iron can lead to reduced physical performance. A person may feel fatigued, weak, and unable to exercise. Increased Risk of Pregnancy Complications Iron is important for the health of pregnant women and their babies. Iron deficiency can lead to an increased risk of complications, including premature birth and low birth weight. Also read: What Causes Iron Deficiency & Why Should It Matter Hair Loss Iron helps keep the scalp healthy and is necessary for hair growth. A lack of iron in your diet can lead to hair loss. According to the Journal of the American Academy of Dermatology, hair follicle cells are particularly vulnerable to iron deficiency and may be unable to generate new cells effectively when iron supplies are depleted. Increased Risk of Infections Iron helps the body produce antibodies, which help to fight off infections. A lack of iron can make a person more susceptible to infections. How To Combat Iron Deficiency Include some of the best sources of iron include red meat, poultry, seafood, legumes, tofu, nuts, seeds, and dark leafy greens. Iron-fortified breakfast cereals, oatmeal, and enriched grains are also good sources of iron. A single cup of fortified cereal can provide an adequate amount of iron. Additionally, some fruits, such as apricots, raisins, and prunes, are naturally high in iron. It is important to note that consuming foods that are high in vitamin C can help improve the absorption of iron from plant sources. Vitamin C is found in citrus fruits, tomatoes, peppers, and broccoli. Eating iron-rich foods with foods rich in vitamin C can help maximise iron absorption. In addition to eating iron-rich foods, it is important to limit the intake of certain substances that can interfere with iron absorption. These substances include coffee, tea, and calcium-rich foods, such as dairy products.Read NextBeginners Guide To Protein: Benefits, How Much To Consume, Best Time To Consume & MoreDisclaimer All possible measures have been taken to ensure accuracy, reliability, timeliness and authenticity of the information; however Onlymyhealth.com does not take any liability for the same. Using any information provided by the website is solely at the viewers' discretion. In case of any medical exigencies/ persistent health issues, we advise you to seek a qualified medical practitioner before putting to use any advice/tips given by our team or any third party in form of answers/comments on the above mentioned website. • In anemia, iron deficiency is best diagnosed using a ferritin threshold of less than 45 ng per mL. • Patients with IDA should receive noninvasive testing for H. pylori and celiac disease. • Bidirectional endoscopy is recommended in all adults with IDA. • Video capsule endoscopy is not recommended in asymptomatic adults with IDA. Iron deficiency anemia (IDA) is the most common cause of anemia worldwide. It affects 3% of adults and is slightly more common in women younger than 50 years. The American Gastroenterological Association (AGA) developed guidelines for the evaluation of IDA in adults. Diagnosing Iron Deficiency The AGA defines anemia as a hemoglobin level of less than 13 g per dL (130 g per L) in men and less than 12 g per dL (120 g per L) in patients who are not pregnant. Serum ferritin testing is commonly used to diagnose iron deficiency in patients with anemia. Based on a systematic review, the AGA recommends using a ferritin threshold value of less than 45 ng per mL (45 mcg per L) for diagnosing iron deficiency in patients with anemia. This threshold has 85% sensitivity and 92% specificity for iron deficiency. Without anemia, the ferritin threshold for iron deficiency is uncertain. Ferritin testing is less accurate in patients with chronic inflammatory conditions or chronic kidney disease, and additional tests including serum iron, transferrin saturation, soluble transferrin receptor, and C-reactive protein can help diagnose iron deficiency. Several common conditions associated with IDA can be diagnosed noninvasively, before or after endoscopy. Frequent blood donation, nutritional deficiencies, or malabsorption syndromes may be suggested by initial evaluation. Helicobacter pylori infection is associated with iron deficiency caused by atrophic gastritis and hypochlorhydria, which reduce iron absorption. Treating H. pylori infection improves the benefit of iron supplementation in anemia. After negative bidirectional endoscopy results, the AGA suggests noninvasive testing and treatment for H. pylori in IDA by urea breath testing, although stool antigen testing and serology can also be used. Celiac disease is another common cause of iron deficiency. The AGA suggests serologic testing for celiac disease in patients with iron deficiency, especially those with a family history of the disease, a personal history of autoimmune diseases, or gastrointestinal symptoms. Small bowel biopsy during endoscopy is recommended only if celiac serology is positive. Bidirectional endoscopy (esophagogastroduodenoscopy and colonoscopy) is the primary means of evaluation for IDA, although evidence of patient-oriented benefit is lacking. In men and postmenopausal women with IDA, bidirectional endoscopy is recommended based on diagnosis of colonic malignancy in 9% and upper gastrointestinal malignancy in 2% of patients, more than 10 times the rate of colorectal cancer found in routine screening. The AGA also suggests endoscopy in premenopausal women with IDA because malignancy is diagnosed in 1% of this population. In younger patients who might have a plausible nonmalignant cause of anemia, iron replacement can be offered without further exploration. During esophagogastroduodenoscopy, routine gastric biopsies are not recommended. Although autoimmune atrophic gastritis can be diagnosed by gastric biopsy, it has not been shown to improve long-term outcomes. H. pylori can also cause atrophic gastritis, but it can be diagnosed noninvasively. After normal bidirectional endoscopy, small bowel video capsule endoscopy is not recommended without symptoms because evidence of benefit is lacking. Oral iron supplementation should be provided for most patients with iron deficiency. Oral iron formulations appear to be similarly effective and tolerated. Although 150 mg or more of daily elemental iron was previously recommended, studies show improved absorption and tolerability with lower dosing or every-other-day dosing. The hemoglobin level should increase after one month of oral iron supplementation. Lack of hemoglobin change may be because of low adherence, malabsorption, or blood loss. Intravenous iron may be appropriate with malabsorption, inflammatory bowel disease, chronic kidney disease, or ongoing blood loss. Guideline source: American Gastroenterological Association Evidence rating system used? Yes Systematic literature search described? Yes Guideline developed by participants without relevant financial ties to industry? Yes Recommendations based on patient-oriented outcomes? Yes Published source: Gastroenterology. September 2020;159(3):1085–1094 Editor's Note: Dr. Sonoda is the resident representative for AFP. These guidelines from the AGA add specific recommendations for the workup of IDA. The recommendation to diagnose iron deficiency with a ferritin cutoff of 45 ng per mL is consistent with a previous AFP article (. The recommendation for bilateral endoscopy in all people is interesting because the AGA does not appear to consider evaluation of menstrual bleeding before testing premenopausal women. Similarly, they specifically recommend checking for H. pylori noninvasively only after endoscopy without justifying why. From the primary care perspective, noninvasive testing for H. pylori and celiac disease before endoscopy offers the opportunity for more efficient care while reducing procedural risk. Yet, the recommendations against routine gastric biopsies and video capsule endoscopy are helpful for avoiding unnecessary tests.—Michael J. Arnold, MD, Contributing Editor Page 2 Why do some people have painful periods? Many people have some crampy pain with their periods, especially as teenagers. The pain often is low in the pelvis and starts just before your period or at the beginning of your period. It often lasts one to three days. The pain can be bad enough to keep you from doing things you normally do. Painful periods usually do not mean that anything is seriously wrong. Sometimes, though, painful periods can be caused by an infection, cysts, or other problems. Pain can also be caused by a condition called endometriosis (say: en-doe-me-tree-oh-sis). This happens when the lining of the uterus grows outside of the uterus. How are painful periods treated? The most common way to treat painful periods is to take medicines called nonsteroidal anti-inflammatory drugs (NSAIDs). Examples of NSAIDs include ibuprofen (some brand names: Motrin, Advil) or naproxen (one brand name: Aleve). You can buy these medicines without a prescription. Your doctor might also recommend that you try taking birth control pills or getting a birth control shot (brand name: Depo-Provera) or an intrauterine device (IUD; one brand name: Mirena) An IUD is a small T-shaped device that your doctor inserts into your uterus. These medicines can make your periods less painful. You also can try exercising for 45 to 60 minutes at least three days per week or using a heating pad to help make the pain better. Ask your doctor about other treatments that may help. What if these treatments don't work? If the pain with your periods does not get a lot better after taking NSAIDs or birth control pills, your doctor might want to do a pelvic examination and an ultrasound. Your doctor also may want you to see another doctor who can do a minor surgery called laparoscopy (say: lap-uh-rah-ska-pee). These are ways for doctors to see whether you have endometriosis. How can I tell if I have a more serious problem? Tell your doctor if you have any of these symptoms: Your painful periods started after your teenage yearsYou have pain at times other than the first couple of days of your periodYou have unusual vaginal discharge, odor, or bleedingMedicine does not make your pain go away Page 3 To the Editor: The U.S. Preventive Services Task Force (USPSTF) recommendation statement on hypertension in adults reaffirmed the benefits of screening1; however, it missed an opportunity to promote automated office blood pressure (AOBP) measurements as an easier-to-implement alternative to ambulatory blood pressure monitoring (ABPM). The guideline states that AOBP is comparable to ABPM; however, the supporting evidence review discounted the literature on AOBP by stating, "there is substantial heterogeneity and it is unclear if lack of mean mm Hg differences would result in similar diagnostic categorization and treatment decisions."2 The most recent and largest meta-analysis found that this heterogeneity is not clinically significant.3 The Agency for Healthcare Research and Quality evidence synthesis states, "...without analysis of test accuracy outcomes (e.g., sensitivity, specificity), it is not possible to conclude whether AOBP would result in similar clinical screening and diagnostic results as ABPM or [home blood pressure monitoring]."4 This logic is flawed. If blood pressure is a continuous outcome related to cardiovascular risk, and AOBP is similar to ABPM, then it follows that the sensitivity and specificity of AOBP will be similar to that of ABPM. Mathematically, two measures cannot be so closely matched but have different sensitivities and specificities. The only difference will be for a threshold value for hypertension. For example, a person with an average systolic blood pressure of 140.2 mm Hg with one method could have a systolic blood pressure of 139.9 mm Hg with another method. However, there is no clinically significant difference in atherosclerotic cardiovascular disease risk between these two measurements. Multiple studies now recommend treating patients based on atherosclerotic cardiovascular disease risk5; therefore, the USPSTF should acknowledge the close correlation of AOBP and ABPM and recommend using the former. Practicality also needs to be considered. It is logistically challenging to have patients submit multiple home blood pressure readings to diagnose hypertension. It is easier to implement a screening program with AOBP machines in the outpatient setting. Each clinic needs to purchase a device and screen each patient at the desired interval. If the USPSTF wants to optimize the detection of elevated blood pressure, it should recommend AOBP because it is easy to implement and closely resembles ABPM. The USPSTF cited only one randomized trial that reported improvements in clinically meaningful outcomes (i.e., hospitalization) from hypertension screening; this trial used AOBP for screening.6 Page 4 Original Article: Alcoholics Anonymous and Other 12-Step Facilitation Programs for Alcohol Use Disorder [Cochrane for Clinicians] Issue Date: March 1, 2021 To the Editor: Global engagement in Alcoholics Anonymous (AA) is high, with several million members in 180 countries.1 However, the effectiveness of AA has been difficult to study because of a lack of randomized controlled trials (RCTs). The RCTs have not reported a positive effect of AA; however, many cross-sectional and cohort studies have shown improved abstinence with engagement in AA compared with no engagement in 12-step facilitation programs.2,3 The Cochrane review emphasized the positive findings of AA and 12-step program affiliation.4 However, two details of the review should cause primary care physicians to hesitate before referring patients to AA as an alternative to traditional treatment for alcohol use disorder. AA and other 12-step facilitation programs that produced higher rates of continuous abstinence over other established treatments in the Cochrane review were described as manualized, which was defined as following a session-to-session outline offering treatment based on "standardized content delivered in a linear or modular fashion to ensure that the same treatment is delivered across time and different sites".5 Community AA programs would not be considered manualized because each group is autonomous. Significantly positive results were related to the time abstinent from alcohol, continuous period of abstinence, and percentage of days abstinent. The most meaningful patient-oriented outcome examined is the negative impact of consequences of drinking, including physical, social, and psychological consequences. These consequences make up most of the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. criteria for diagnosis of an alcohol use disorder, whereas percentage of time abstinent or length of continuous abstinence plays no role in diagnosing or determining the severity of alcohol use disorder. Unfortunately, none of the reviewed studies showed an advantage for AA or 12-step facilitation programs in reducing the negative consequences of drinking.5 Effective treatments for alcohol use disorder are medications and behavioral therapy. Although this review provides evidence that participation in AA or other 12-step programs may be helpful for people with alcohol use disorder who seek abstinence, the evidence is not compelling enough to consider community AA programs a replacement for formal treatment. Primary care physicians should include counseling on mutual aid groups (including AA) while developing a treatment plan with their patients. Physicians should feel comfortable discussing what to expect at meetings and the benefits of affiliation, and be aware of local mutual aid groups, including being able to provide contact information and meeting availability for patients who express interest. In Reply: Thank you for highlighting these important points. We generally agree with your interpretation of the findings of the Cochrane review. We were not suggesting that AA and 12-step facilitation programs should be recommended instead of licensed addiction treatment services. However, many licensed addiction treatment programs in the United States use 12-step facilitation as a central component of their programming; therefore, the Cochrane review findings provide further support for this practice. Page 5 Original Article: Dysphagia: Evaluation and Collaborative Management Issue Date: January 15, 2021 To the Editor: Strangulation is an important cause of dysphagia and is relevant to family physicians. Strangulation involves applying pressure to the neck with the hands, a constricting band, or an arm. It can diminish cerebral blood flow or occlude the airway and result in carotid artery dissection, making it a potentially lethal act.1 Strangulation is commonly associated with intimate partner violence (IPV), and women are at particularly high risk, with a documented sevenfold increased risk of death from homicide among women experiencing IPV-related strangulation.2 Survivors of strangulation report that when they sought medical attention, symptoms such as difficulty swallowing were often dismissed or incorrectly attributed to more common ailments. Because physicians cannot rely solely on visible findings to identify strangulation, dysphagia is an important presenting symptom. In addition to dysphagia, patients commonly experience neck pain, sore throat, voice changes, and neurologic manifestations.3 Physicians with a high index of suspicion for strangulation should screen patients appropriately. Survivors may not disclose their experience because of impaired memory, lack of knowledge regarding the seriousness and sequelae of strangulation, or unfamiliarity with the term strangulation.4 Questions about strangulation should include terms more familiar to survivors, such as choked, blacked out, jacked-up, or choked-off.5 Inquiry should also be made about a loss of consciousness. Management varies based on the time of presentation and may involve additional imaging, including imaging of the carotid artery.4 Recognizing dysphagia as a symptom of strangulation may also prevent unnecessary interventions, such as prescription of a proton pump inhibitor or invasive procedures. In Reply: We appreciate the thoughtful comments of Drs. Giusti and Ravi and agree that strangulation should be included in the differential diagnosis of any patient, particularly younger women, presenting with dysphagia or hoarseness. This is also a timely reminder that family physicians should routinely screen all women of reproductive age for IPV.1 Although open-ended questions are the best way to begin a trusting dialogue,2 we also agree with Drs. Giusti and Ravi that more directly focused questions are necessary when evaluating patients with new symptoms and with chronic, unexplained functional distress or pain. Page 6 Page 7 Race does not have a biologic definition, but rather a political and social one that is fluid and independent of science.1,2 Nevertheless, the medical community uses race as a scientific variable in several prominent clinical situations, including calculation of atherosclerotic cardiovascular disease (ASCVD) risk and glomerular filtration rate (GFR), decisions on pharmacotherapy for hypertension, and interpretation of pulmonary function testing. These diagnostic and clinical prediction tools do not recognize the social and environmental factors that influence racial differences in health outcomes. Furthermore, they do not highlight the potentially harmful effects of using race as a factor in making medical decisions. Although we may hear about biologic or genetic differences between races, there is more variation within races than there is between them.3 When using identical blood pressure and lipid data in the ASCVD Pooled Cohort calculator, a 40-year-old White male smoker has a lower cardiovascular risk than a 40-year-old Black male nonsmoker. Without considering lifestyle, drug use, or the significant heterogeneity in the Black population, this decision-making tool lumps all Black people together and determines that being a Black man is more dangerous than smoking. The guidelines from the Joint National Committee on the management of high blood pressure recommend against using monotherapy with angiotensin-converting enzyme (ACE) inhibitors in the treatment of Black patients with hypertension.4 This recommendation was heavily influenced by the findings of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which showed worse cardiovascular outcomes for Black patients treated with lisinopril.5 This is sometimes translated into the idea that ACE inhibitors are ineffective in Black people, despite the fact that these questionable findings have not been shown in Black patients treated with combination therapy.6,7 Even taken at face value, a racial difference in the effectiveness of ACE inhibitor monotherapy is explained by social factors, not genetic causes. More than a decade ago, the American Heart Association published a report from the International Society on Hypertension in Blacks that linked poor blood pressure control in Black patients to nonphysiologic factors, such as high stress levels, less physical activity, higher rates of obesity, and low-potassium diets.8 Racial differences in renin-angiotensin activity resolve when Black patients decrease sodium intake, and there is more variation in renin-angiotensin activity within the Black race than there is when comparing Black and White people.8 Treating Black patients as a monolithic group stereotypes them without considering that they are not all obese and that many follow the Dietary Approaches to Stop Hypertension (DASH) diet and exercise regularly. Despite Black patients having worse outcomes for chronic kidney disease, race-based equations assign a higher GFR (i.e., better kidney function) to Black patients with the same creatinine value as people of other races. This is based on questionable racial differences in muscle mass, bone density, and nutritional status.9–11 As is the case with hypertension, these racial differences are often presented without considering nonbiologic causes or the significant variation within individual races. As one expert asserted, the use of race-based GFR equations will "systematically miss a high-risk group of blacks at a time in the disease course when interventions are crucial."12 Inflating GFR in Black patients leads to underdiagnosis of chronic kidney disease in this population and makes it less likely that they will be referred to a nephrologist or become eligible for kidney transplantation. Additionally, the erroneous beliefs about lower effectiveness of ACE inhibitors in Black patients mentioned earlier can prevent those with chronic kidney disease from receiving one of the key medications that can stop disease progression. We should reconsider the use of race in other clinical decision-making tools, such as the calculator for predicting the likelihood of a successful vaginal birth after cesarean delivery (VBAC). Even though Black patients have significantly higher maternal morbidity and mortality, this calculator assigns a lower chance of VBAC success for them compared with White or non-Black Hispanic patients.13 Instead of encouraging a mode of delivery that can improve recovery time and lower the risk of infection or postpartum hemorrhage, this calculator potentially discourages maternity care clinicians from offering Black patients a trial of labor after a cesarean delivery. Instead of treating these patients as a homogeneous group, we should be aggressively studying the social and systemic factors that have historically resulted in more cesarean deliveries. Although the VBAC and ASCVD calculators typically assign higher risk to Black patients, the FRAX tool for estimating osteoporotic fracture risk assigns a 10-year fracture risk to non-White women that is approximately one-half that of White women. Black women are less likely to be screened or treated for osteoporosis, less likely to receive a dual-energy x-ray absorptiometry scan following a hip fracture, and more likely to die or become disabled following a hip fracture.14 Yet, FRAX systematically assigns a lower fracture risk to the entire Black community without considering its diversity. We should focus on the social factors that create the group-level differences that we see among races, and we should also discuss how to screen for these social factors and behaviors instead of making assumptions based on skin color. The rigor that is demanded in evidence-based medicine often eludes studies of race, as exemplified by the studies that led to the Black and Asian correction factors for pulmonary function testing. A systematic review of spirometry revealed that only 17.3% of studies actually defined race and/or ethnicity, and 94% of articles failed to examine socioeconomic status as a potential confounder.15,16 Race is a sloppy, inconsistent proxy for genetics and biology, and we should move toward eliminating it from medical decision-making. None of the calculators and predictor tools mentioned provide any scientific rationale about what race to input if a patient has one parent who is Black and one who is not. There are almost no other aspects of medicine that result in such dramatic differences in medical management simply based on a patient's subjective report about their identity. Race-based approaches to medicine reinforce a system that assumes biologic causes of health inequities, which can lead us to ignore the social determinants of health that are the true drivers for racial disparities in health outcomes.17 This creates a racist system that withholds organ transplants and preventive services from Black patients with chronic kidney disease and ACE inhibitors from Black patients who might benefit from them, and ignores the social or environmental factors that cause differences in the lung function of some Black and Asian people. As family physicians, we should inform patients of these limitations when we use race-based algorithms, and we should look for social explanations to racial/ethnic disparities. As we continue to improve the ways in which we competently address social determinants, members of the American Academy of Family Physicians should be proud that it has joined the ranks of the American Medical Association and other organizations that have declared that race is a social construct instead of a biologic one.18,19 Page 8 Wright J. Introducing AAFP Policy Center One-Pagers. Am Fam Physician. 2000;62(1):19. Accessed May 26, 2021. Mold JW, Fryer GE, Phillips RL, et al. Family physicians are the main source of primary health care for the Medicare population. Am Fam Physician. 2002;66(11):2032. Accessed May 26, 2021. Mold JW, Fryer GE, Phillips RL, et al. Family physicians increase provision of well-infant care despite decline in prenatal services [published correction appears in Am Fam Physician. 2003;68(6):1119]. Am Fam Physician. 2003;67(1):17. Accessed May 26, 2021. Robert Graham Center. Robert Graham CenterThe diminishing role of FPs in caring for children. Am Fam Physician2006;73(9):1518. Accessed May 26, 2021. Keister MCS, Green LA, Kahn NB, et al. What people want from their family physician. Am Fam Physician. 2004;69(10):2310. Accessed May 26, 2021. Wilder V, Dodoo MS, Phillips RL, et al. Income disparities shape medical student specialty choice. Am Fam Physician. 2010;82(6):601. Accessed May 26, 2021. Crothers J, Petterson S, Bazemore A, et al. Family medicine: an underutilized resource in addressing the opioid epidemic?. Am Fam Physician. 2016;94(5):350. Accessed May 26, 2021. Willis J, Antono B, Bazemore A, et al. The state of primary care in the United States: a chartbook of facts and statistics. February 2021. Accessed June 29, 2021. Merrit K, Jabbarpour Y, Petterson S, et al. State level variation in primary care physician density. Am Fam Physician. 2021;104(2):133-134. Accessed August 12, 2021. National Academies of Sciences, Engineering, and Medicine. Implementing high-quality primary care: rebuilding the foundation of health care. 2021. Accessed May 24, 2021. Phillips RL, McCauley LA, Koller CF. Implementing high-quality primary care: a report from the National Academies of Sciences, Engineering, and Medicine. JAMA. 2021;325(24):2437-2438. Stewart AD. Prioritizing primary care can save the U.S. health care system. Am Fam Physician. 2021;104(1):14-15. Accessed July 15, 2021. The Larry A. Green Center. Primary Care Collaborative. Quick COVID-19 primary care survey series 28 fielded April 9–13, 2021. Accessed May 24, 2021. 20Series%2028%20National%20Executive%20Summary.pdf Page 9 The Robert Graham Center, with researchers at IBM Watson Health and the American Board of Family Medicine, published a report examining state-level variation in PCP density.5 Using 2019 data from the American Medical Association Physician Masterfile and the U.S. Census Bureau, the ratio of PCPs per 100,000 residents was calculated. As shown in Figure 1, there is considerable variation by state. Mississippi has the lowest PCP-to-population ratio, with 49.1 PCPs per 100,000 residents, whereas the District of Columbia has the highest ratio at 130.7 per 100,000.5 Differences in retirement trends and rurality of states complicate these data because some states with a higher PCP density, such as Vermont, also have a large percentage of family physicians reaching retirement age. On the other hand, many states with an already low PCP density, such as Mississippi, are at risk of losing even more PCPs to retirement.6 These trends in geographic distribution highlight the gaps in our shrinking national PCP workforce. Policy advances are needed to recruit medical students into primary care, expand residency training programs, engage a rural workforce, and retain current PCPs to address these widening gaps, which intimately affect access to care and national health outcomes. Page 10 Study Population: 1,178 patients, across 11 trials, with suspected small bowel obstruction Efficacy End Points: Diagnosis of small bowel obstruction Harm End Points: Data on harms not reported Narrative: Small bowel obstruction comprises 2% of all patients presenting to the emergency department (ED) with abdominal pain, with more than 300,000 hospitalizations per year.1,2 If not appropriately diagnosed, small bowel obstruction can result in intestinal ischemia, necrosis, and perforation.3 Traditional methods for diagnosing the condition, such as plain radiography, have poor sensitivity and specificity (Table 14,5) and expose patients to radiation.4 Other imaging modalities include computed tomography (CT) and magnetic resonance imaging (MRI). However, they may be expensive, they are not available at all institutions, and CT is associated with radiation exposure. Ultrasonography has demonstrated promise in the diagnosis of small bowel obstruction,6,7 and a meta-analysis including prospective observational studies evaluated the accuracy of ultrasonography for this use.5 The reference standard confirmatory test was determined by individual study definition and included CT, enteroclysis, diagnosis at surgery or discharge, or diagnosis at clinical follow-up. The primary outcome was diagnostic accuracy of ultrasonography for small bowel obstruction, with a subgroup analysis based on specific clinical setting (ED vs. non-ED setting). The authors of the meta-analysis also conducted a sensitivity analysis that categorized inconclusive ultrasound results as false-negatives. The authors of the meta-analysis identified 9,774 records, of which 11 prospective observational studies (n = 1,178) met the inclusion criteria.5 These studies enrolled patients with signs and symptoms of suspected acute small bowel obstruction, with most studies using a convenience sample. Five studies were conducted in the ED, and six were conducted in other settings, including gastroenterology or radiology clinics, or the setting was not reported. The ultrasonography was performed by an ED clinician in three studies and a radiologist in five studies, and the sonographer was not described in the remainder of studies. The mean age of patients was 50 years, and 74% of patients were male. Overall, ultrasonography was 92.4% sensitive (95% CI, 89.0% to 94.7%) and 96.6% specific (95% CI, 88.4% to 99.1%), with a positive likelihood ratio of 27.5 (95% CI, 7.7 to 98.4) and a negative likelihood ratio of 0.08 (95% CI, 0.06 to 0.11).5 Caveats: Although ultrasonography can be a valuable tool in the diagnosis of small bowel obstruction, its usefulness depends on the individual clinician's ability to obtain and interpret appropriate images. This meta-analysis included studies with differences in sonographer experience and diagnostic criteria, which limit the applicability of the data. However, previous literature has suggested good diagnostic accuracy for identifying small bowel obstruction after a 10-minute training session and five practice ultrasound examinations.6 In most studies, ultrasonography was performed by a radiologist or the sonographer was not described. Clinicians in the ED were the primary sonographers in only three studies, limiting the analysis of this subset. Most studies enrolled patients based on a convenience sample, which could be a source of selection bias. Several studies did not state whether clinicians were blinded to the confirmatory CT results, which may have led to potential bias. Inclusion of studies from different clinical settings can also contribute to spectrum bias; however, test characteristics for ultrasonography performed by ED clinicians did not differ significantly from other clinicians based on the authors' subgroup analysis. A 2019 prospective observational study suggests that the diagnostic accuracy of ultrasonography for small bowel obstruction may be lower, with a sensitivity of 88% (95% CI, 80% to 94%) and specificity of 54% (95% CI, 45% to 63%).8 Of note, this study used clinicians with variable ultrasound experience and was performed at centers that did not regularly use ultrasonography to diagnose small bowel obstruction.8 Therefore, further studies evaluating the diagnostic accuracy among clinicians who are not radiologists are needed. The studies included in the meta-analysis were at low to moderate risk of bias, and there were limited data on children.5 There was moderate heterogeneity in patient population and outcome assessment, and studies demonstrated mild heterogeneity for sensitivity and moderate heterogeneity for specificity. Sixteen examinations were nondiagnostic. Assuming all of the nondiagnostic examinations were false-negatives (worst-case scenario), a sensitivity analysis demonstrated a slightly lower sensitivity of 90.9% (95% CI, 86.0% to 94.2%) and positive likelihood ratio of 24.6 (95% CI, 7.2 to 84.3), but specificity and negative likelihood ratio remained similar. Although ultrasonography offers several advantages compared with CT, including the ability to rapidly diagnose small bowel obstruction and assess its progression over time, CT may still be necessary to determine the underlying etiology, which can influence decisions regarding operative management. Conclusion: According to the current available evidence, ultrasonography appears to be highly sensitive and specific in the diagnosis of small bowel obstruction. Although the exact test characteristics for diagnosing small bowel obstruction based on ultrasonography performed by clinicians other than radiologists are less clear, this modality is rapid, repeatable, inexpensive, easily available, and noninvasive; avoids radiation exposure; and can be performed at the bedside. Although we assign a color rating of green (benefits outweigh harms) strictly based on diagnostic accuracy statistics, generalizability to family physicians and others performing point-of-care ultrasonography is limited from this review. Page 11 What vitamins and supplements are recommended in pregnancy? Prenatal vitamins for pregnant patients should contain folic acid, vitamin D, calcium, and iron. Pregnant patients should be counseled on the option to consume two or three servings per week of fish that contains low levels of mercury instead of routinely taking a fish oil supplement. Which muscles should be targeted for strengthening when patellofemoral pain syndrome is present? The American Physical Therapy Association recommends exercises that target muscles of the posterior hip and quadriceps for patellofemoral pain syndrome. Adding patellar taping and foot orthoses to exercise also improves short-term pain. What are the first-line pharmacologic treatment options for alcohol use disorder? Acamprosate and naltrexone should be used as first-line agents for the treatment of alcohol use disorder and are effective for reducing relapse rates. Agent selection should be based on comorbid conditions and adherence to the dosing regimen. Combining the two agents may provide additional benefit early in treatment. What is the recommended first-line imaging modality for inguinal hernias not evident on clinical examination? Ultrasonography is the first-line imaging modality to diagnose suspected groin hernias not evident on clinical examination, with a sensitivity of 33% to 86% and specificity of 77% to 90%. What are the first-line and adjunct pharmacologic therapies used for anaphylaxis? Administer intramuscular epinephrine into the anterolateral thigh as the first-line treatment of anaphylaxis. Use histamine H1 and H2 antagonists and corticosteroids only as adjunct therapies after the administration of epinephrine. Use fluid resuscitation (1 to 2 L of 0.9% isotonic saline at a rate of 5 to 10 mL per kg for adults in the first five to 10 minutes; 10 mL per kg for children) in patients who are anaphylactic with hypotension that does not improve with epinephrine. Which medications are recommended for treating acute gout? Nonsteroidal anti-inflammatory drugs and corticosteroids are equally effective for the treatment of acute gout, with no significant difference in pain relief or adverse effects. Low-dose colchicine (1.2 mg orally followed by 0.6 mg one hour later) is as effective as high-dose colchicine (1.2 mg followed by 0.6 mg every hour for six hours) with fewer adverse effects. Additional Online Only AFP Clinical Answers What are the treatment goals for children with ADHD? Psychosocial interventions should be the first-line treatment in preschool children four to five years of age. Children who are six years and older can be offered stimulant medications for first-line treatment, with psychosocial interventions offered as an adjunct. What initial treatment is recommended for patients with a mechanical globe injury? Patients with a suspected mechanical globe injury should have a metal shield placed over the eye, be given antiemetics, and be referred immediately to an ophthalmologist for surgical repair. Prophylactic systemic antibiotics should be administered to prevent endophthalmitis. How should patients with vulvar lichen sclerosus be treated? Biopsy is indicated for patients with suspected lichen sclerosus because this condition is associated with an increased risk of squamous cell carcinoma. Patients should be treated with a high-potency steroid ointment to alleviate symptoms, prevent architectural damage, and reverse histologic changes. Editor's Note: Several of the answers above first appeared in the new AFP Clinical Answers email, which is sent each month to recipients of the AFP email table of contents. Sign up to receive AFP emails. Page 12 Is the levonorgestrel-releasing intrauterine system (Mirena) safe and effective for reducing heavy menstrual bleeding? The levonorgestrel-releasing intrauterine system is more effective than other medical therapies at reducing menstrual bleeding volume (mean difference [MD] = 67 mL; 95% CI, 43 to 91 mL), with similar rates of adverse effects. The effectiveness of the levonorgestrel-releasing intrauterine system compared with endometrial ablation and hysterectomy has been inadequately studied.1 (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.) Heavy menstrual bleeding is defined by the perception of excessive bleeding affecting a patient's quality of life and is common among those of reproductive age. Numerous medical and surgical therapeutic options exist for heavy menstrual bleeding. The authors of this Cochrane review sought to evaluate the effectiveness and safety of the levonorgestrel-releasing intrauterine system compared with other therapeutic options for heavy menstrual bleeding.1 This Cochrane review included 25 randomized controlled trials and 2,511 patients, with studies comparing the levonorgestrel-releasing intrauterine system with no treatment, placebo, medical therapies (including nonsteroidal anti-inflammatory drugs, antifibrinolytic drugs, and hormone-containing medications), endometrial ablation, and hysterectomy.1 Participants were of reproductive age with regular heavy periods. The study locations and durations were heterogeneous, spanning multiple countries and ranging in length from three months to 10 years. The primary outcomes were effectiveness (reduction in blood loss measured objectively, semi-objectively, or subjectively) and patient satisfaction (measured on a five-point Likert scale). Secondary outcomes were quality of life, adverse effects, withdrawal from treatment, treatment failure, need for subsequent surgery, and cost. The levonorgestrel-releasing intrauterine system consistently reduced heavy menstrual bleeding compared with other medical therapies. The intrauterine system was associated with greater reduction of bleeding volume from baseline compared with an oral contraceptive measured by objective methods (MD = 67 mL; 95% CI, 43 to 91 mL; two studies; 170 women) and a separate analysis of semi-objective methods (MD = 55 mL; 95% CI, 28 to 82 mL; three studies; 335 women; duration of six to 12 months). Most of the remaining six randomized controlled trials also noted reduction in heavy menstrual bleeding volume with the levonorgestrel-releasing intrauterine system compared with other medical therapies, although treatment outcomes could not be pooled because of clinical heterogeneity. Bleeding outcomes were mixed when comparing the levonorgestrel-releasing intrauterine system and endometrial ablation, with two studies showing improvement of bleeding with endometrial ablation, two showing improvement with the levonorgestrel-releasing intrauterine system, and four with no clear difference. Data were insufficient to compare the effectiveness between the levonorgestrel-releasing intrauterine system and hysterectomy. The authors note that the quality of all studies was limited by low participant numbers, and confidence in the findings was also low. The levonorgestrel-releasing intrauterine system caused similar rates of adverse effects and lower rates of treatment failure compared with other medical therapies. The intrauterine system had higher treatment failure rates and more adverse effects, especially progestin-related effects, including mastalgia, weight gain, and acne, compared with endometrial ablation. The authors were unable to adequately compare the levonorgestrel-releasing intrauterine system and hysterectomy. These findings reflect conclusions of previous reviews demonstrating that the levonorgestrel-releasing intrauterine system is likely the most effective medical therapy for heavy menstrual bleeding.2 The National Institute for Health and Care Excellence guidelines for heavy menstrual bleeding recommend considering the levonorgestrel-releasing intrauterine system as first-line treatment for patients with heavy menstrual bleeding with no identified pathology.3 Page 13 How does pioglitazone (Actos) compare with other pharmacologic glucose-lowering agents and lifestyle interventions in the prevention or delay of type 2 diabetes mellitus in individuals with prediabetes? Pioglitazone prevents or delays the incidence of type 2 diabetes in individuals with prediabetes when compared with placebo (absolute risk reduction [ARR] = 11.3%; 95% CI, 0.9% to 15.6%; number needed to treat [NNT] = 9) or no intervention (ARR = 13.3%; 95% CI, 11.6% to 14.9%; NNT = 7). Compared with metformin, however, pioglitazone does not reduce the incidence of type 2 diabetes in those with prediabetes.1 (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.) Prediabetes is a condition with various definitions describing patients whose average blood glucose levels are higher than normal.1 Approximately 34.5% of the U.S. adult population has prediabetes, with a higher prevalence in men and a similar prevalence among all ethnic groups.2 The authors of this review sought to determine the effect of pioglitazone (a thiazolidinedione) on the prevention or delay of type 2 diabetes and its associated complications in individuals with prediabetes. This review included 27 randomized controlled trials with 4,186 participants; most trials were conducted in outpatient settings, three of which were in the United States.1 Primary outcomes of this review were all-cause mortality, incidence of type 2 diabetes, and serious adverse events. Most studies identified individuals with prediabetes using the World Health Organization 1999, American Diabetes Association (ADA) 2003, or ADA 2010 diagnostic criteria for impaired fasting glucose or impaired glucose tolerance. A range of 15 to 30 mg of pioglitazone and varied doses of metformin (38 mg, 250 mg, and 750 mg) were typically used. The length of interventions ranged from six to 36 months. Pioglitazone was compared with metformin, acarbose (Precose), or repaglinide in three studies involving 331 participants. Each comparison group had matching behavior-changing interventions. All-cause mortality was not reported in the included studies, and there were no serious adverse events in the comparison groups. Pioglitazone did not reduce the incidence of type 2 diabetes compared with metformin (low-certainty evidence). Compared with placebo, pioglitazone reduced or delayed type 2 diabetes (ARR = 11.3%; 95% CI, 0.9% to 15.6%; NNT = 9; six studies; n = 1,395; low-certainty evidence). However, this effect was no longer present in three studies after a washout and extended follow-up period ranging between three weeks and one year after the study period. Compared with no intervention, pioglitazone performed better in the prevention or delay of type 2 diabetes (ARR = 13.3%; 95% CI, 11.6% to 14.9%; NNT = 7; 16 studies; n = 2,053; moderate-certainty evidence). Analysis of all-cause mortality revealed no harmful effects (three studies; n = 866; very low-certainty evidence) and no serious adverse events with the use of pioglitazone (seven studies; n = 1,211; low-certainty evidence). Pioglitazone was compared with behavior-changing interventions (diet and exercise) in one study involving 96 participants. There was no significant effect on the incidence of type 2 diabetes or serious adverse events with the use of pioglitazone (downgraded to low-certainty evidence). Limitations of this review include variations in the diagnostic criteria for prediabetes, exclusion of individuals with comorbidities commonly encountered in primary care settings (except for hypertension), and differences in the dosages of administered medications. The ADA recommends yearly testing of individuals who have prediabetes given the estimated annual rate of conversion from prediabetes to type 2 diabetes of 3% to 11%.3,4 Current treatment recommendations for those with prediabetes include intensive behavioral lifestyle intervention (modeled after the Diabetes Prevention Program, a goal-based intervention to achieve and maintain 7% loss of initial body weight and increase moderate-intensity physical activity to at least 150 minutes per week), dietary modification, individualized medical nutrition therapy, and consideration of medications such as thiazolidinediones.5 The cost of 30 tablets of 15-mg pioglitazone is about $15, and the cost of 60 tablets of 500-mg metformin is about $14.6 Pioglitazone carries a black box warning for causing or worsening congestive heart failure. Editor's Note: The ARRs, CIs, and NNTs reported in this Cochrane for Clinicians were calculated by the author based on raw data provided in the original Cochrane review. Page 14 Approximately 19 million full- and part-time students were enrolled in U.S. colleges in 2018.1 Although they are generally healthy, many of these individuals have special health care needs such as asthma, diabetes mellitus, mental health concerns, and learning disorders. Understanding and managing the needs of this dynamic population involve addressing the unique psychosocial stressors related to this life transition that manifest before and while attending college. Common self-reported medical conditions among college students are presented in Table 1.2 College students are often assuming responsibility for their health care for the first time; however, the transition from a childhood model of care to an adult model of care is often given a lower priority than other transitions that students are experiencing.3 Approximately 20% of U.S. youth have special health care needs.4 Although many children and adolescents have taken steps to comanage their diseases, most of these youth do not receive a structured transition to an adult care model,5 and the situation is complicated by poor care coordination.3 Students may have to reconcile recommendations from multiple sources of care, such as an ongoing childhood physician and a new clinician at college if living away from home. Physicians may perceive that youth are poorly informed regarding their own health care matters. Simultaneously, some physicians may be poorly informed about patients' childhood conditions that continue into adulthood, such as cerebral palsy and cystic fibrosis.5 Problems with this transition result in declines in treatment adherence, increased emergency department use, and increased hospitalizations.3 Improved adherence to health care, better patient experience, and increased appropriate use of ambulatory services are reported with structured health care transition visits that prepare the student for self-care and help to transfer the student to the adult model of care6 (Table 2). Under the Patient Protection and Affordable Care Act (ACA), students younger than 26 years have four options for qualifying health coverage: coverage under a parent's insurance plan, school-offered health plans, marketplace plans, and Medicaid and the Children's Health Insurance Program.7 Despite these options, 72% of college students and recent college graduates indicate that finding health care coverage remains difficult, and 1.6 million students remain uninsured.8 A parent's insurance plan may be the least expensive option, but it may also limit confidentiality for the young adult because notices of service are sometimes sent to the primary enrollee. Participation in one of the other three options results in bills and explanations of benefits being sent directly to the student. Many school-offered plans do not provide coverage during summer breaks and may leave the student uninsured if other options are not pursued. Under the ACA, all but the school-offered health plans are regulated by the Department of Health and Human Services. These plans are required to provide the following coverage without an annual or lifetime limit: ambulatory services; emergency services; hospitalization; laboratory tests; maternity and newborn care; mental health care, including substance use treatment; prescription medications; and rehabilitation services.7 Copays for these services vary widely. Institutions of higher education vary with regard to testing, immunization, and prevention practice, depending on state law and exemption practices, in their health care resources and responses to the COVID-19 pandemic.9 Common Learning and Mental Health Issues The learning and mental health needs of college students remain a growing concern. College counseling center directors report an increase in the number of students who arrive on campus already taking a psychotropic medication,10 with at least 40% of these directors reporting increases compared with the previous five years of depression and anxiety disorders, learning disorders, sexual assault, and crisis issues requiring immediate responses.11 In colleges, most health center visits (60%) are to primary care clinics, whereas a smaller proportion of these visits (13%) are to mental health clinics.11 Students in higher education are protected by the Americans with Disabilities Act and Section 504 of the Rehabilitation Act12; however, the ACA does not support costs associated with diagnosis and treatment of learning disorders.13 Students should meet with their college office of disabilities to understand school policies and resources and to self-advocate regarding insurance requirements.14 ATTENTION-DEFICIT/HYPERACTIVITY DISORDER Approximately 8.2% of college students endorse a diagnosis of attention-deficit/hyperactivity disorder (ADHD).2 Pharmacotherapy, including amphetamines, methylphenidate (Ritalin), bupropion (Wellbutrin), and atomoxetine (Strattera), is effective in appropriately diagnosed adults. 15 Associated symptoms are identified by using the Adult ADHD Self-Report Scale (Table 32,10,11,16–20). Cognitive behavior therapy for adults with ADHD, particularly with symptoms of inattention, has been shown to be effective.21 Students should be counseled regarding consequences of drug diversion. Physicians may identify a learning disorder when considering other conditions (e.g., depression, sleep problems, thyroid dysfunction). An estimated 3.6% to 11% of college students self-report a learning disorder.2 Learning disorders may manifest as difficulty listening, thinking, speaking, reading, writing, spelling, or completing mathematical calculations.22 Among those who self-identify with a learning disorder, only 33% reported using accommodations.22 Interventions include neuropsychologic evaluation, assistive technologies (e.g., text-to-speech or speech-to-text), direct assistance (e.g., tutoring and remediation), coursework or testing modifications, strategy instruction (i.e., showing students how to learn the content or skills needed), and comprehensive support (e.g., group and individual instructions).23 It remains unclear whether accommodations result in better academic performance or satisfaction with school22 (Table 32,10,11,16–20). Selected Mental Health and Behavioral Health Issues Anxiety and depression are the most common mental health diagnoses among college students.11 Risk factors for depression among college students are associated with being female, entering college with depression, a pattern of negative thinking or rumination, dysfunctional attitudes, history of childhood abuse or sexual abuse, or stressful life events.24 Prevention programs can decrease the prevalence of anxiety and depression on college campuses.25 Interventions commonly used to treat depression and generalized anxiety disorder, such as pharmacotherapy, cognitive behavior therapy, and mindfulness, work well in collegiate populations, although there is less evidence of success compared with other anxiety disorders (e.g., panic disorder, social phobia, specific phobia).26 An estimated 13.3% of college students reported seriously considering suicide, and 2.4% reported attempting suicide in the past 12 months.2 Among those presenting to a mental health clinic, there has been a 12.7% increase in the number of college students presenting with serious suicidal ideation over the past nine years.27 Family physicians may have a role in identifying these students because most college students (86%) who commit suicide had not sought services in a counseling center.10 POSTTRAUMATIC STRESS DISORDER Lifetime prevalence of posttraumatic stress disorder (PTSD) among college students ranges from 5% to 9%, which is similar to that of the general U.S. population.18 PTSD is associated with other significant mental health problems among college students, including risky alcohol use, medication misuse, disordered eating, and depression.18 Sources of trauma among college students are diverse and warrant screening.11,18 Student veterans and student veterans with PTSD are more likely to engage in high-risk drinking and fighting.28 Risk factors for eating disorders include frequent dieting, weight concerns, body dissatisfaction, and drive

for thinness. College-based programs for preventing and treating eating disorders can be effective.29 Most of these programs are based on cognitive behavior therapy principles or dissonance-based techniques (i.e., learning to act in a way that is contrary to an existing attitude).29 Treatment focuses on medical stabilization, nutritional rehabilitation, normalization of eating behavior, and psychosocial stabilization.30 Poor sleep is associated with other mental health problems, including ADHD, anxiety, depression, and suicidal thoughts and behaviors. As many as 62% of college students experience poor sleep quality.31 Sleep difficulties negatively impacted class performance or delayed progress toward a degree among 22.4% of students.2 Proper treatment of sleep-related problems is based on structured assessment.32 Selected Substance Use and Misuse MEDICATION MISUSE AND DIVERSION The prevalence of nonmedical use of controlled medications among college students within the past year ranged from 1.9% to 21.4%.33 Lifetime rates of diversion range from 16% to 29% among students with stimulant prescriptions.34 Greater risk of nonmedical use of stimulants is associated with being 18 to 25 years of age, being male, being White, having a college grade point average below 3.5, being in a fraternity or sorority, self-reporting more severe ADHD symptoms, and other substance use disorders.35 As many as 33.8% of college students have ever used tobacco or a nicotine-delivery product (e.g., vaping, electronic cigarettes), and 65% of these students have used these products at least once within the past three months.2 Physician-directed interventions and institutional efforts are effective in reducing tobacco use in this population.36 In the prior two weeks, 24% of college students endorsed binge drinking (i.e., five or more drinks per sitting), and 22% indicated that within the past 12 months they did something they later regretted after drinking alcohol.2 Brief interventions using motivational enhancement or motivational interview strategies are effective for reducing alcohol use among college students who drink.37 Physicians can screen for problematic alcohol use with the Alcohol Use Disorders Identification Test–Consumption (AUDIT-C; eTable A). Scores of 5 or above for women and 7 or above for men indicate possible problem drinking in college populations.38 Annual prevalence of using any illicit drug (45%) and any illicit drug other than marijuana (18%) was similar between college students and their noncollege peers.39 College students tend to use MDMA (3,4-methylenedioxymethamphetamine; 4.4%), amphetamines (8.5%; without a doctor's prescription), and cocaine (5.3%) at higher rates than their noncollege peers.39 eTable B summarizes common illicit drugs, their common street names, and related effects. Most colleges require current immunizations before entry. Vaccination guidelines for COVID-19 vary state by state and by individual institution. A second booster dose of meningococcal ACWY vaccine should be given at 16 years of age to prevent the effects of meningitis in the vulnerable college-aged population. Two-dose coverage has been as low as 28.5% in patients who are 17 years of age.40 Immunization for meningococcus B serotype can be separately administered for patients at increased risk and based on shared decision-making.40,41 Annual influenza immunization is important in the dorm-dwelling college-aged population. Immunization for pertussis is important, especially in high-risk populations. Human papillomavirus vaccination status should be verified before or after starting college; it is approved, regardless of sex.42 Table 4 lists other U.S. Preventive Services Task Force (USPSTF) recommendations.43 Public health departments may provide low- or no-cost immunizations for eligible students. The USPSTF has issued several evidence-based screening guidelines applicable to college-aged students, which are also supported by the American Academy of Family Physicians.44 Cervical cytology screening should not be performed until 21 years of age and should then occur every three years until 29 years of age.45 Of note, the American Cancer Society recommends screening with primary human papillomavirus testing (with co-testing or cytology alone as a back-up option) beginning at 25 years of age.46 See the article in American Family Physician on health maintenance for women for more information.47 Screening for chlamydia and gonorrhea is recommended for sexually active women 24 years and younger48; this recommendation is currently being updated to also offer screening for women 25 years and older who are at increased risk of infection.49 Screening for HIV is recommended for adolescents 15 years and older, and hepatitis C screening is recommended for all adults 18 to 79 years of age.50,51 The USPSTF recommends intensive behavioral and contraceptive counseling for all sexually active adolescents and adults at an increased risk of sexually transmitted infections.52 The USPSTF and the American College Health Association (ACHA) also recommend offering pre-exposure prophylaxis with effective antiretroviral therapy to people at high risk of HIV acquisition.53,54 The ACHA has extensive guidelines around best practices for sexual health promotion and the avoidance of sexual and relationship violence.55,56 Physicians start this process by creating a welcoming and inclusive clinic environment for students that considers different sexual orientations and ensures confidentiality. The guidelines recommend first assessing preferred gender identity, followed by assigned sex at birth, and then sexual orientation to determine next steps in preventive health measures.55 Studies have found that 0.5% to 8.4% of college women and 0.6% to 0.7% of college men have been raped and that 1.8% to 34% of college women (most studies found more than 20%) and 4.8% to 31% of college men have had unwanted sexual contact.57 Physicians asking about violence increases the likelihood that students will be willing to report violent relationships.58 The 2019 ACHA survey notes that 82% of students describe themselves as heterosexual. Other students identify as asexual (0.7%), bisexual (8.8%), gay (2%), lesbian (1.3%), pansexual (1.6%), queer (1.2%), and questioning (1.9%).2 Table 5 lists some available resources for physicians who care for these students. This article updates a previous article on this topic by Unwin, et al.59 Data Sources: Specific evidence-based research on college students is relatively limited. PubMed was used as the primary literature search engine. Key words were college student and university student, plus selected content (e.g., alcohol, tobacco). Key sources of data: American College Health Association, review articles in American Family Physician, and federal reports on selected content. Search dates: May, August, and December 2020; May 29, 2021. The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army, Navy, or Air Force Medical Departments; the U.S. Army, Navy, Air Force, or Public Health Service; or Carilion Clinic. Page 15 There are more than 200 types of human papillomavirus (HPV), a DNA virus that infects cutaneous and mucosal epithelial cells. HPV is spread by direct skin-to-skin contact and has tropisms for cutaneous or mucosal epithelial cells.1 A small subset of HPV types can cause cutaneous warts.2 The approximately 40 types that infect mucosal surfaces are typically spread through sexual contact, including vaginal, anal, or oral sex, and can be divided into low-risk and high-risk types based on their associated cancer risk. Low-risk types cause warts, whereas the 15 high-risk types cause cervical intraepithelial neoplasia (CIN) and squamous cell carcinomas of the anogenital tract and oropharyngeal mucosa.3,4 Vertical or horizontal spread of HPV can occur during the perinatal period and is associated with oral infections and respiratory papillomatosis.5,6 Concomitant cervical and anal infections have been demonstrated in women without a history of anal intercourse and may be a result of autoinoculation.7 Vaccination has been demonstrated to reduce the prevalence of vaccine-type HPV in females, anogenital warts, and precancerous cervical lesions. According to a 2018 Cochrane review, vaccinating women, with or without HPV exposure, between 15 and 26 years of age decreases the risk of cervical intraepithelial neoplasia 2 and 3, with a number needed to treat of 39. On June 12, 2020, the U.S. Food and Drug Administration approved adding the prevention of head and neck cancers caused by HPV as an indication for the nonavalent HPV vaccine (Gardasil 9). HPV = human papillomavirus. Epidemiology and Prevalence The Centers for Disease Control and Prevention reports that 79 million Americans are infected with HPV and an additional 14 million are newly infected each year.3 Data from early HPV vaccine trials suggest that the lifetime prevalence of the infection is 85% in women and 91% in men who have had at least one sex partner.8 The prevalence of cutaneous warts is highest in school-aged children (up to 30%), then declines with advancing age.2 HPV infection is the most common sexually transmitted infection in the United States. Genital warts occur in 1% of sexually active adults.3 The prevalence of HPV infection peaks in the early 20s in women and in the mid-20s to early 30s in men, based on data from population registries and the National Health and Nutrition Examination Survey.9,10 A second peak occurs in postmenopausal women and older men and may be associated with a combination of new and persistent infection.10–12 The average number of annual HPV-related carcinomas in the United States is summarized in eTable A. Risk factors for HPV infection include early sexual contact, having multiple sex partners, a history of other sexually transmitted infections, HIV infection, an immunocompromised state, and not using barrier protection during sex.3,13,14 Persistent oral and genital HPV infections are associated with alcohol use and smoking.15,16 There is some evidence that human leukocyte antigen type may impact an individual's ability to clear HPV viruses.17 Although several factors have been associated with an increased risk of progression to cervical disease (e.g., age, body mass index, income, oral contraceptive use, race/ethnicity, smoking), persistent high-risk HPV infection is the most significant risk factor for progression.18,19 Pathogenesis and Subtypes Infection with a low-risk HPV type does not preclude infection with a concomitant high-risk type. One study demonstrated that 31% of genital warts contain both low- and high-risk types of HPV.20 HPV infection can be latent and subclinical or have a presentation ranging from benign cutaneous and mucosal lesions to life-threatening clinical carcinomas (Table 12,3,21–24). The risk of CIN and HPV-related carcinomas is the primary clinical concern. Table 2 summarizes HPV-related carcinomas and associated HPV types.4,22 Natural History and Timeline Most of what is known about the natural history of HPV infections is a result of the extensive study of genital tract disease in women. Data suggest that oral infections have a similar natural history.5 In 90% of individuals with low- or high-risk HPV infection, the immune system clears the virus within two years.25,26 It is unclear whether this represents ongoing infection, which is permanently suppressed, or immune-mediated elimination of the infection.27 Up to 30% of genital warts spontaneously regress within four months, and 50% of cutaneous warts in children spontaneously resolve within one year.28,29 The decision to treat warts depends on the size, number, and persistence of the warts and on patient preference.29 Treatment is up to 80% effective and can result in quicker resolution.30,31 The cervical cytology of HPV infection progresses from atypical squamous cells of undetermined significance (ASCUS) to carcinoma. Because there is a long latent period (10 to 20 years) between cervical HPV infection and diagnosis, the incidence of carcinoma peaks at 40 years of age.11,32 This highlights the importance of screening and testing for HPV-related cervical changes between 30 and 40 years of age.11 Although ASCUS is the most benign pathologic categorization on a Papanicolaou (Pap) smear, approximately 50% of ASCUS findings are associated with high-risk HPV infections.33 CIN (or cervical dysplasia), which typically occurs at the squamocolumnar junction, indicates an active HPV infection and is considered precancerous. CIN is graded histologically from 1 to 3 based on the extent of epithelial involvement, with 3 representing the most severe dysplasia. CIN 1 and 2 often regress or resolve without treatment.34 However, infections that last longer than one or two years are more likely to progress to a higher-grade CIN or carcinoma.35 Between 12% and 30% of CIN 3 lesions will progress to invasive cervical carcinoma.36 Concurrent infection with multiple high-risk types of HPV can have a synergistic effect on the progression to cervical cancer.37 HPV-positive oropharyngeal carcinomas present at a younger age than HPV-negative cancers. Although HPV-positive cancers have a less specific presentation, they are more responsive to treatment and have a higher survival rate than HPV-negative cancers.38 The goal of screening for HPV is to identify precancerous lesions, allowing for treatment to prevent progression to carcinoma. Options for screening include cytology-based testing (Pap smear), high-risk HPV testing, and cotesting (simultaneous cytology and high-risk HPV testing). Recommendations for cervical cancer screening from multiple organizations are summarized in Table 3.39–43 Notably, the American Cancer Society now recommends HPV testing for primary screening beginning at 25 years of age. Table 4 summarizes HPV tests that are approved by the U.S. Food and Drug Administration (FDA) for use in women, all of which have similar sensitivities and specificities.44–49 There are no FDA-approved HPV tests for use in men or the oropharynx. The U.S. Preventive Services Task Force found insufficient evidence to recommend for or against oral cancer screening in asymptomatic individuals, and this finding is supported by the American Academy of Family Physicians.50,51 The American Dental Association recommends that dentists routinely perform visual and tactile examinations for oral and oropharyngeal carcinoma in all patients.52 Anal Pap testing has been considered in people at increased risk of anal cancer, including those with HIV, men who have sex with men, and individuals who have receptive anal intercourse.53,54 However, the Centers for Disease Control and Prevention has found insufficient data about the natural history of anal HPV infection to provide a recommendation for such screening.54 Abnormal findings on anal Pap smear and high-grade disease on cytology are common in these high-risk populations.54 Because cytology may underestimate the level of dysplasia in the anal intraepithelial neoplasia, if anal Pap smear is performed and findings are positive, anoscopy and biopsy should be performed to rule out anal carcinoma.55 Limiting the number of sex partners, delaying first intercourse until a later age, and consistently using condoms reduce the risk of HPV infection.13,14 Smoking and alcohol cessation should be recommended to reduce the risk of HPV persistence and the development of HPV-related malignancies.15,16 Use of male and female condoms and dental dams may decrease the spread of HPV and should be considered for coital and noncoital sexual activity.56 However, vaccination is the primary recommended modality for prevention.57 HPV vaccinations are prophylactic and do not treat current disease or prevent progression.58 Vaccination has been demonstrated to reduce prevalence of vaccine-type HPV in females, anogenital warts, and precancerous cervical lesions.59–61 HPV vaccination is most effective when administered before the onset of sexual activity.57 The FDA has approved vaccination in children and adults between nine and 45 years of age, and the Advisory Committee on Immunization Practices recommends vaccination at 11 or 12 years of age, irrespective of the patient's sex.57,62 Catch-up vaccination is recommended for inadequately immunized individuals 13 to 26 years of age.57 A Cochrane review found that vaccinating females, with or without HPV exposure, between 15 and 26 years of age decreases the risk of CIN 2 and 3, with a number needed to treat of 39.63,64 Although vaccination is not routinely recommended in older individuals because most adults have been exposed to HPV, shared decision-making can guide administration in patients 27 to 45 years of age who have not been previously vaccinated.57 In immunocompetent individuals immunized before 15 years of age, two doses of vaccine given six to 12 months apart are indicated.57 In individuals immunized between 15 and 26 years of age and in individuals of any age who are immunocompromised, three doses given over six months are recommended.57 HPV vaccination is safe, and the only contraindications are known allergy to the vaccine and current pregnancy.57 There are three FDA-approved HPV vaccines: quadrivalent (Gardasil), bivalent (Cervarix), and nonavalent (Gardasil 9). However, only the nonavalent vaccine has been available for use in the United States since 2017. The recombinant quadrivalent vaccine protects against HPV types 6, 11, 16, and 18 and reduces the incidence of cervical, vaginal, and vulvar intraepithelial lesions and adenocarcinoma in situ; penile intraepithelial lesions; and anal warts and intraepithelial lesions.62,65,66 The recombinant bivalent vaccine protects against HPV types 16 and 18 and reduces the incidence of cervical intraepithelial lesions.62,66 These two vaccines are available outside the United States, and data from four Nordic countries demonstrate that the quadrivalent vaccine is 100% effective against HPV-16 and HPV-18 for 12 years and is associated with more than 90% seropositivity for all four HPV types at 14 years.67 The nonavalent vaccine protects against the same HPV types as the quadrivalent vaccine, as well as five additional types: 31, 33, 45, 52, and 58.68 These nine HPV types are responsible for more than 90% of HPV-related carcinomas.57 The nonavalent vaccine reduces the incidence of cervical, vaginal, and vulvar intraepithelial lesions, adenocarcinoma in situ, and carcinoma; penile intraepithelial lesions and carcinoma; and anal warts, intraepithelial lesions, and carcinoma.62,66 The nonavalent vaccine has demonstrated a high level of immunogenicity (93% to 100%).69 On June 9, 2020, the FDA approved adding the prevention of head and neck cancers caused by HPV as an indication for the nonavalent HPV vaccine.70 Data Sources: A PubMed search was conducted using search terms such as human papilloma virus, cervical cancer, anal cancer, oropharyngeal cancer, human papilloma virus vaccination, risk factors, and prevention. An Essential Evidence Plus search included relevant POEMs, Cochrane reviews, clinical decision rules, and a targeted PubMed search. Search dates: January 29, 2020; February 17, 2020; April 6, 2020; June 22 to 24, 2020; and March 12, 2021. The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Uniformed Services University of the Health Sciences or the Department of the Navy. Page 16 Dysmenorrhea, which is defined as painful menstruation, affects up to 50% to 90% of adolescent girls and women of reproductive age.1,2 Nearly one-half of patients (45%) with symptoms of dysmenorrhea will present first to their primary care physician.3 Dysmenorrhea leads to decreased quality of life, absenteeism, and increased risk of depression and anxiety.4,5 Up to one-half of patients with dysmenorrhea miss school or work at least once, and 10% to 15% have regular absences during menses.6–8 A prospective longitudinal study of 400 patients with dysmenorrhea revealed that most have persistent symptoms throughout their years of menstruation, although some improvement in severity may occur, for example, after childbirth.9 Primary dysmenorrhea occurs in the absence of pelvic pathology. It is mediated by elevated prostaglandin and leukotriene levels, with inflammation causing uterine contractility and cramping pain.1,10 Secondary dysmenorrhea is due to pelvic pathology or a recognized medical condition and accounts for about 10% of cases of dysmenorrhea.1 The most common etiology is endometriosis. Other etiologies include congenital or acquired obstructive and nonobstructive anatomic abnormalities (e.g., müllerian malformations, uterine leiomyomas, adenomyosis), pelvic masses, and infection1 (Table 11,11). Age younger than 30 years, body mass index less than 20 kg per m2, smoking, earlier menarche (younger than 12 years), longer menstrual cycles, heavy menstrual flow, and history of sexual abuse increase the risk of primary dysmenorrhea. Nulliparity, premenstrual syndrome, and a history of pelvic inflammatory disease are also associated with the disorder. Protective factors include increasing age, increasing parity, exercise, and oral contraceptive use.9,12 Secondary dysmenorrhea is associated with infertility, especially when caused by endometriosis.13 However, secondary dysmenorrhea associated with increasing gravidity, parity, and body mass index suggests a cause other than endometriosis.14 Dysmenorrhea is typically described as cramping pain in the lower abdomen beginning at the onset of menstrual flow and lasting eight to 72 hours.15 It is often accompanied by nausea, vomiting, diarrhea, headaches, muscle cramps, low back pain, fatigue, and, in more severe cases, sleep disturbance.1,6 In a study of more than 400 patients with dysmenorrhea, 47% reported moderate pain, and 17% reported severe pain on a 0 to 10 visual analog scale.16 Primary dysmenorrhea begins an average of six to 12 months following menarche, corresponding with the initiation of ovulatory cycles, and tends to recur with every menstrual cycle.1 Symptoms of secondary dysmenorrhea may start immediately following menarche or may arise later in life.1 Symptoms more consistent with secondary dysmenorrhea include changes in or progressive worsening of pelvic pain, abnormal uterine bleeding, vaginal discharge, and dyspareunia.1,11 Evaluation should begin with a complete medical, gynecologic, menstrual, family, and surgical history.1 The history should characterize whether pain coincides with menstruation and include which nonprescription therapies the patient has tried. A family history of similar symptoms may suggest endometriosis, and a history of pelvic surgery may suggest adhesions.1 Symptoms should be carefully elicited because many patients assume pain is a normal part of menstruation.8,17 In a study of more than 4,300 patients seeking care for symptoms of dysmenorrhea, nearly two-thirds were told nothing was wrong; this was even more likely when symptoms began during adolescence. 3 A substantial delay from symptom onset to diagnosis is common, ranging from 5.4 years in adolescents to 1.9 years in adults.3 In secondary dysmenorrhea, the time from onset of symptoms to surgically confirmed diagnosis may range from four to 11 years.18 A pelvic examination is not necessary in patients presenting with symptoms consistent with primary dysmenorrhea (Figure 1). Pregnancy should be ruled out in patients who are sexually active. If symptoms consistent with secondary dysmenorrhea are reported, a pelvic examination should be completed and ultrasonography performed to assess for anatomic abnormalities or other pathology 1 (Table 11,11). If a patient's history is consistent with primary dysmenorrhea or with secondary dysmenorrhea due to endometriosis, empiric therapy should be initiated1,19 (Figure 1). Nonsteroidal anti-inflammatory drugs (NSAIDs), which have been shown to be superior to both placebo and acetaminophen, are a first-line therapy for primary dysmenorrhea. NSAIDs act by reducing prostaglandin production.20,21 NSAIDs should be initiated one to two days before the onset of menses and continued in regular dosing intervals through the first two to three days of bleeding, correlating with the highest levels of prostaglandins.21 There is no difference between individual NSAIDs, including cyclooxygenase-2 inhibitors, for pain relief or safety.19,22 Commonly prescribed NSAIDs include ibuprofen (800 mg initially, followed by 400 to 800 mg every eight hours) and naproxen (500 mg initially, followed by 250 to 500 mg every 12 hours)21; both medications can be purchased over the counter, often for less than $10 per month. NSAIDs can also have a secondary benefit of reducing heavy menstrual bleeding.20 Despite the known effectiveness of NSAIDs in the treatment of dysmenorrhea, nearly 20% of patients report minimal to no relief.10 This is likely multifactorial. Up to 25% to 50% of patients do not take the correct dosage to provide adequate relief.10 Variance in menstrual cycles may prevent appropriate timing of treatment. NSAIDS are also associated with adverse effects, including indigestion, headaches, and drowsiness, which may limit use.22 Taking NSAIDs with food reduces gastrointestinal adverse effects. Hormonal therapy is also considered a first-line treatment for dysmenorrhea and can be added or used as an alternative to NSAID therapy in patients who are not planning to become pregnant.1,10 Hormonal therapies improve symptoms of dysmenorrhea by thinning the endometrial lining and reducing cyclooxygenase-2 and prostaglandin production.10 Hormonal therapies may also have secondary benefits, including improvement of heavy menstrual bleeding,23 premenstrual mood,24 acne or hirsutism, and bone mineral density, and decreased risk of endometrial, ovarian, and colorectal cancers.25 Combined estrogen-progestin oral contraceptives are effective in adolescents and adults with primary dysmenorrhea, leading to significant improvement in pain and decreased frequency and dose of analgesics.26,27 There is no difference in effectiveness between low- and medium-dose estrogen preparations.27 Commonly reported adverse effects of combined oral contraceptives include nausea, headaches, and weight gain.27 Continuous combined oral contraceptive regimens with more than 28 days of active hormone may lead to improved and more rapid pain relief but are associated with more weight gain than cyclic regimens.28–30 Progestin-only oral contraceptives are an alternative for those who are not candidates for estrogen therapy. Continuous norethindrone (5 mg daily) is as effective as cyclic combined oral contraceptives for the treatment of dysmenorrhea,2 although this dosing is not currently approved by the U.S. Food and Drug Administration as a contraceptive.1 Other hormonal contraceptives are also acceptable for the management of dysmenorrhea, including transdermal patches, vaginal rings, progestin implants, intramuscular or subcutaneous medroxyprogesterone depot injection (Depo-Provera), and the levonorgestrel-releasing intrauterine system (Mirena).1,25 A systematic review found that the levonorgestrel-releasing intrauterine system is as effective as, if not superior to, oral contraceptives in the treatment of primary dysmenorrhea and secondary dysmenorrhea caused by endometriosis.31 Physicians and patients must weigh secondary benefits with contraindications, U.S. Food and Drug Administration boxed warnings, and adverse effects when considering hormonal treatment options. NONPHARMACOLOGIC THERAPIES Nonpharmacologic therapies and integrative modalities can complement first-line medical therapy or be used as alternatives when first-line interventions are contraindicated or declined. Physical activity reduces intensity and duration of pain in primary dysmenorrhea.32 Based on a Cochrane review, exercise—regardless of intensity but with the goal of achieving 45 to 60 minute intervals at least three times per week—may significantly reduce menstrual pain that is associated with moderate to severe dysmenorrhea.33 Exercise may not reduce overall menstrual flow or pain intensity as effectively as NSAIDs, but given its many benefits beyond managing dysmenorrhea, it should be reviewed with patients as a treatment option.33 High-frequency transcutaneous electrical nerve stimulation is effective for pain reduction in primary dysmenorrhea, with improvement in reported pain level, duration of pain relief, and decreased use of analgesics compared with sham transcutaneous electrical nerve stimulation.34,35 A small randomized controlled study found heat therapy to be effective in improving menstrual pain.36 Self-acupressure, a safe and low-risk intervention, can significantly reduce average menstrual pain intensity, number of days with pain, and use of analgesics over a three-month period37 but is not superior to NSAIDs.38 Manual acupuncture and electroacupuncture are effective at reducing menstrual pain compared with no treatment,39 although they may be no better than sham acupuncture.38,40 No evidence supports the use of spinal manipulation to treat dysmenorrhea.41 Behavioral interventions and pain management training, such as progressive muscle relaxation, imagery, and biofeedback, that focus on coping strategies may help with spasmodic-type pain.42 However, studies were small and of poor methodological quality. There is insufficient evidence to support the use of the dietary supplements fenugreek, fish oil, ginger, valerian, vitamin B1, Zataria multiflora, and zinc sulfate for dysmenorrhea43 or the use of antioxidants for endometriosis-related pelvic pain.44 A small systematic review found that the herbal therapy fennel (Foeniculum vulgare) may be as effective as NSAID therapy in reducing menstrual pain in primary dysmenorrhea, although the quality of evidence was considered low.45 Small studies have found improvement in dysmenorrhea pain with the use of Chinese herbal medicines, but these studies should be interpreted with caution given poor methodological quality and inconsistencies in formulations.46,47 If symptoms persist despite three to six months of empiric treatment or if at any time the symptom pattern suggests a secondary etiology, a more extensive workup should be performed for secondary causes of dysmenorrhea (Figure 1). A comprehensive history and physical examination should evaluate for causes of chronic pelvic pain, including gastroenterologic, urologic, musculoskeletal, or psychosocial etiologies.1 Workup for secondary dysmenorrhea should also include a pelvic examination and ultrasonography.1,19 Normal findings do not rule out endometriosis, which is a surgical and pathologic diagnosis. Referral to an obstetrician-gynecologist may be indicated for diagnostic evaluation, including advanced imaging or laparoscopy.1,19 Gonadotropin-releasing hormone analogues, such as elagolix (Orilissa) or leuprolide (Lupron), used for at least six months with add-back replacement estrogen therapy have been used for treatment of surgically confirmed endometriosis; studies demonstrate up to a 75% reduction of dysmenorrhea symptoms.1,10,48 Adverse effects may include hot flashes, headaches, and hyperlipidemia, which improve with discontinuation of treatment.48 Aromatase inhibitors also require add-back estrogen therapy, and further research is needed to support their effectiveness.10 Alternative treatments, including beta-2 adrenoceptor agonists,49 calcium channel blockers, and vasodilators,10 have the potential to reduce menstrual pain in patients unresponsive to first-line therapies but are often limited by intolerable adverse effects. Surgical options are available for patients whose symptoms do not improve with medical therapies. Laparoscopy is used diagnostically and therapeutically for endometriosis.1 Laparoscopic presacral neurectomy has been found to be more effective than laparoscopic uterosacral nerve ablation for the treatment of primary dysmenorrhea.50 However, a systematic review and a large randomized controlled trial found insufficient evidence to routinely recommend either procedure.50,51 If hysterectomy is performed, pain reduction is similar between total and supracervical laparoscopic hysterectomy.52 Data Sources: We searched Essential Evidence Plus, PubMed, POEMs, the Cochrane Database of Systematic Reviews, and National Institute for Health and Care Excellence guidelines. Key words were dysmenorrhea combined with systematic reviews, clinical decision rules, prevention, natural history, prognosis, diagnosis, and therapy. Search dates: January 2020, May to June 2020, October 2020, and February 2021. Editor's Note: Dr. Fogleman is an assistant medical editor for AFP. Page 17 Breast cancer is the second most common cancer diagnosed in women, exceeded only by nonmelanoma skin cancer. It is the leading cause of death from cancer in women worldwide. In the United States, breast cancer is the second most common cause of death from cancer in women, exceeded only by lung cancer, with approximately 316,000 patients diagnosed with breast cancer annually.1,2 The treatment of breast cancer requires a multi-disciplinary team of specialists in medical, surgical, and radiation oncology. Because most breast cancers are identified by mammography or by physical examination, primary care physicians are often the first contact for patients with a new breast cancer diagnosis.3 Primary care physicians should be familiar with the diagnostic workup for breast cancer and the basics of treatment.3 Breast Cancer Risk Factors and Risk-Reduction Strategies Risk factors associated with breast cancer include older age, female sex, early menarche, late menopause, nulliparity, lack of breastfeeding, positive family history, dense breast tissue, hormone therapy, and a history of radiation therapy to the chest. Genetic variants associated with an increased risk of breast cancer include mutations in breast cancer genes susceptibility 1 and 2 (BRCA1/2) genes.4 Validated risk assessment tools such as the Ontario Family History Assessment Tool or the Seven Questions Family History Screening can help identify women at risk of BRCA1/2 gene mutations or other genetic risks and guide screening and genetic counseling.5 The National Cancer Institute's Breast Cancer Risk Assessment Tool (can provide an estimate of breast cancer risk over the next five years, but the tool is not intended to assess risk in patients with BRCA1/2 gene mutations.6 Patients with a greater than 3% risk of breast cancer over the next five years are considered to be at increased risk. Risk-reducing medications, including the selective estrogen receptor modulators tamoxifen and raloxifene (Evista), or the aromatase inhibitors anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin), may be used to treat postmenopausal women 35 years or older who are at increased risk of breast cancer and at low risk of adverse medication effects7 (Table 18–18). In premenopausal women, only tamoxifen should be used for the prevention of primary breast cancer.6 Bilateral risk-reducing mastectomy may be offered for patients at particularly high risk (e.g., BRCA1/2 gene carriers or carriers of other high-risk, high-penetrance genes).19 There are some data to suggest that bilateral risk-reducing mastectomy results in lower rates of invasive breast cancer and lower mortality rates in high-risk populations.20–22 Breast Cancer Staging and Classification Breast cancer staging is determined by tumor size, nodal involvement, the presence of metastases, and specific biomarkers such as estrogen receptors, progesterone receptors, and the ERBB2 receptor (formerly HER2).23 After a histologic diagnosis of breast cancer, all pathology samples should be tested for estrogen receptors, progesterone receptors, and ERBB2 status.24,25 Breast cancers that express none of these markers are referred to as triple-negative. Ductal carcinoma in situ (DCIS) is stage 0, noninvasive breast cancer. Early invasive cancer describes stages I, IIa, and IIb, and locally advanced describes stages IIIa, IIIb, and IIIc. All of these stages of breast cancer are nonmetastatic. Stage IV is metastatic breast cancer.23 Treatments for the various stages of breast cancer are summarized in Table 2.23,24 Stage 0, DCIS, Noninvasive Breast Cancer DCIS is a form of pure, noninvasive carcinoma and is most commonly identified by mammography showing microcalcifications confined to the breast ducts.26 If left untreated, up to 40% of DCIS cases will progress to invasive breast cancer.27 DCIS is treated with lumpectomy (with a goal of 2-mm surgical margins) and radiation or with mastectomy.28 Sentinel lymph node (SLN) biopsy is done at the time of mastectomy to detect the (unlikely) possibility of lymph node involvement. After mastectomy, an SLN biopsy may not be technically possible. Radiation therapy is offered to patients having a lumpectomy; the combination of lumpectomy with radiation is considered a breast-conserving therapy. Radiation may be deferred for patients with small, low-grade lesions assessed to have a low risk of recurrence. Radiation is not indicated for patients who are treated with mastectomy.24 Patients with estrogen receptor–positive DCIS and residual breast tissue should receive five years of endocrine therapy. This treatment includes tamoxifen if the patient is premenopausal and tamoxifen or an aromatase inhibitor if postmenopausal.24 Lobular carcinoma in situ was previously considered a malignancy. However, despite its name, it is not a carcinoma and is a proliferative disease that confers an increased risk of future breast cancer. It is no longer included in breast cancer staging guidelines.23 Stages I–III, Early Invasive and Locally Advanced, Nonmetastatic Breast Cancer Nonmetastatic breast cancer is treated with preoperative and postoperative systemic therapies that include chemotherapy, endocrine therapies, immunotherapy with monoclonal antibodies directed at tumor receptors, and surgery and radiation. Molecular testing helps guide whether chemotherapy needs to be added to a treatment regimen. For patients with hormone receptor–positive, node-negative breast cancer, including males, a 21-gene expression assay (Oncotype DX) is the preferred assay for disease prognostication and decisions about the addition of chemotherapy.24 When chemotherapy and endocrine therapy are administered postoperatively, chemotherapy always precedes endocrine therapy.24 PREOPERATIVE SYSTEMIC THERAPY The purpose of preoperative systemic therapy is to decrease the size of resectable breast tumors (allowing for better cosmetic and treatment outcomes), to render unresectable tumors operable, and to allow for SLN biopsy instead of axillary lymph node dissection (ALND) if axillary nodes are no longer detectable. Generally, preoperative therapy is not recommended for early invasive breast cancers (I, IIa, IIb) because tumors are often small enough to undergo resection with lumpectomy. Preoperative chemotherapy is used for patients with large primary tumors in relation to breast size who want breast-conserving surgery. It is also used for patients with inoperable disease. Chemotherapeutic drugs are the only systemic therapy available for patients with triple-negative breast cancer.24 Preoperative therapy with trastuzumab (Herceptin) and/or pertuzumab (Perjeta), which are monoclonal antibodies directed against ERBB2, is used in addition to chemotherapy when the cancer is ERBB2 positive. Patients with low-risk estrogen receptor–positive disease, or older adults, may be eligible for preoperative systemic therapy alone, without proceeding to surgery. A complete response (i.e., the tumor is no longer detectable) to preoperative systemic therapies is associated with favorable outcomes for disease-free survival and overall survival.24 The degree of tumor response to preoperative systemic therapies helps determine the need for and response to any postoperative systemic therapies. Lumpectomy with radiation should be offered if negative margins can be achieved with acceptable cosmesis. When the excised tissue is sent to pathology, the specimen's outer surface is marked with ink. A specimen devoid of cancer cells adjacent to the inked surface is considered a negative margin.28 Some tumors may be too large to allow for good cosmesis with lumpectomy and will require a mastectomy. Some women may choose mastectomy over lumpectomy for many other reasons, including family history, gene mutations, peace of mind, or lack of access to health care centers offering radiation therapy.29 In addition to removing the tumor, surgical interventions can also address the potential spread of breast cancer through the lymphatic system. SLN biopsy is done by injecting tracer into the breast and removing the first several axillary nodes into which the tracer drains. An SLN biopsy is preferred over ALND for patients without clinical evidence of nodal disease or with a low nodal burden based on imaging studies.30 The removal of more lymph nodes and adipose tissue of the axilla by ALND is reserved for patients who have positive nodes on SLN biopsy and will have a mastectomy, patients with inflammatory breast cancer (a rare but aggressive cancer that causes redness and swelling of the breast), and patients with positive nodes after preoperative chemotherapy. SLN biopsy does not confer an increased risk of death compared with ALND.31 Radiation. Radiation therapy is used after surgical excision of breast cancer to eliminate any remaining subclinical disease. It is generally recommended for patients who have had a lumpectomy and for patients with high-risk, node-positive disease who have been treated with mastectomy.4 For patients who have a lumpectomy, radiation decreases the 20-year, ipsilateral breast cancer recurrence rate.32 Partial breast irradiation, which involves treating only the site of lumpectomy and surrounding tissue, requires fewer radiation sessions and decreases acute skin toxicity without increasing the risk of local recurrence.33,34 There is evidence to suggest that whole breast radiation therapy may result in better long-term cosmetic results than partial breast irradiation.34 Shared clinical decision-making for radiation should consider patient life expectancy, tumor response to preoperative systemic therapies, and nodal involvement.35 Endocrine. Approximately two-thirds of breast cancers are hormone receptor–positive (express estrogen receptors, progesterone receptors, or both) and are amenable to treatment with endocrine therapies such as tamoxifen and aromatase inhibitors.36 The mechanism of action and adverse effects for these therapies are summarized in Table 1.8–18 Women who are premenopausal at the time of their hormone receptor–positive breast cancer diagnosis should receive five years of therapy with gonadotropin-releasing hormone (GnRH) for ovarian suppression plus tamoxifen or an aromatase inhibitor.24 Ovarian suppression prevents the ovaries from releasing estrogen, which can lead to accelerated growth for hormone receptor–positive breast cancer. Patients who may benefit more from the GnRH plus aromatase inhibitor regimens are those with hormone receptor–positive, ERBB2-negative breast cancer with a high risk of recurrence.37 After five years of tamoxifen therapy, patients who are premenopausal and originally received tamoxifen receive an additional five years of tamoxifen, and patients who originally received tamoxifen and are now postmenopausal may receive tamoxifen or an aromatase inhibitor for an additional five years. Premenopausal patients who were originally treated with aromatase inhibitors may receive an additional three to five years of aromatase inhibitor therapy.24 Women who are postmenopausal at the time of their breast cancer diagnosis may receive up to 10 years total of endocrine therapy. This may consist of tamoxifen alone, an aromatase inhibitor alone, or a sequence of the two medications. GnRH is not necessary after menopause. Targeted. Approximately 15% to 20% of breast cancers involve overexpression of ERBB2.38 These cancers have a poor prognosis; however, outcomes are improved with chemotherapy in conjunction with trastuzumab administered every three weeks for one year.38 There is no increase in long-term, disease-free survival with more than one year of therapy.38 Patients with high-risk ERBB2-positive breast cancer determined by larger tumor size and positive nodal status may benefit from additional agents such as pertuzumab, and neratinib (Nerlynx), an oral tyrosine kinase inhibitor that acts on ERBB2-expressing cells. Treatment with therapies in addition to a trastuzumab-containing regimen has demonstrated a small increase in three-year disease-free survival and five-year disease-free survival for pertuzumab and neratinib, respectively.39,40 Chemotherapy. Chemotherapy is used to decrease tumor size before surgery,24 and is administered after surgery to treat breast cancers that express hormone receptors and ERBB2. Chemotherapy is a core treatment for triple-negative breast cancer because endocrine therapy and immunotherapy have no benefit.4,24 Taxane-based, nonanthracycline regimens are used for lower-risk disease, and anthracyclines are included in regimens that target triple-negative cancers with lymph node involvement.41 There are data supporting the use of capecitabine (Xeloda) for triple-negative cancers with lymph node involvement if residual disease is present at the time of surgery.42 Other Treatments. Postmenopausal women who receive postoperative aromatase inhibitor therapy for nonmetastatic breast cancer should be offered bisphosphonate therapy, which appears to decrease the chance of developing bone metastases and fractures and improves survival.24,43,44 Before starting bisphosphonate therapy, patients should undergo a dental examination and should be taking vitamin D and calcium supplements.24 Stage IV, Metastatic Breast Cancer The median survival rate for patients with metastatic breast cancer has improved over the past several decades with advances in breast cancer therapies. Although metastatic breast cancer is rarely cured, survival is now 24 to 40 months.45 The goals of treatment focus on minimizing symptoms, extending life, and preserving quality of life.4 Endocrine therapy, chemotherapy, and immunotherapy may all be offered to target their respective appropriate breast cancer subtypes. Surgery or radiation following systemic therapy may be appropriate for patients in which tumor burden affects quality of life.46 The 60% to 80% of patients with advanced breast cancer who develop metastases to the bones should be offered treatment with denosumab (Prolia) or bisphosphonates such as zoledronic acid (Reclast) or pamidronate (Aredia).24 These therapies have been shown to decrease the effects of metastases on the bone, such as fractures and hypercalcemia.47 Metastases to the liver, lung, and brain are common in stage IV breast cancer.48,49 Symptomatic treatments should be recommended as needed to provide palliation. The treatment of recurrent breast cancer requires a multi-disciplinary approach that considers all potential options for optimal outcomes.24 For locally recurrent breast cancer initially treated with breast-conserving therapy (i.e., lumpectomy plus radiation), additional radiation is not recommended; total mastectomy is the standard of care.24 However, a 2017 study demonstrated promising data that local resection followed by partial breast reirradiation could be an appropriate alternative treatment approach.50 Local recurrence following a mastectomy usually involves the chest wall and requires wide local excision. If the patient did not previously receive radiation, surgical resection followed by radiation therapy is recommended.51 For regional recurrence involving the axillary lymph nodes, surgical resection and radiation therapy are recommended. Radiation therapy without surgery is the standard of care for supraclavicular or internal mammary node recurrence. The treatment of recurrent disease with distant metastases (i.e., stage IV) is guided by estrogen, progesterone, and ERBB2 receptor status. Treatment algorithms include additional endocrine therapy, chemotherapy, and ERBB2-targeted therapies. Regular assessments with shared decision-making should be implemented to assess ongoing treatment in the setting of palliative and supportive care. Data Sources: A PubMed search was completed in Clinical Queries using the terms breast cancer and treatment. The search included meta-analyses, systematic reviews, clinical trials, and reviews. Also searched were the Cochrane database, U.S. Preventive Services Task Force, DynaMed, American Society of Clinical Oncology Guidelines, Essential Evidence Plus, and UpToDate. Additionally, the search feature on the AAFP website was used with the term breast cancer. Search dates: January 2020, February 2020, and January 2021. The authors thank Melissa Lazar, MD, and Rebecca Jaslow, MD, for reviewing the manuscript. Page 18 Sinus node dysfunction, previously known as sick sinus syndrome, is characterized by abnormal initiation and propagation of electrical impulses from the sinoatrial node (SAN). The resulting abnormalities include bradycardia (less than 50 beats per minute [bpm]), sinus pause (more than three seconds), sinus arrest, and sinoatrial exit blocks, which are sometimes associated with supraventricular tachyarrhythmias in bradycardia-tachycardia syndrome1–4 (Table 15–11). Bradycardia-tachycardia syndrome occurs in approximately 50% of patients with sinus node dysfunction and increases the risk of stroke and death.5,12 Symptoms manifest as end-organ hypoperfusion, including palpitations, decreased physical activity tolerance, easy fatigability, dizziness, and syncope.2,5,6,13 To diagnose sinus node dysfunction, a combination of symptoms and documented electrical abnormalities must be present.5,7 Sinus node dysfunction may occur at any age7,14; however, increasing age is the most significant risk factor with the highest disease prevalence in patients 70 to 89 years of age.2,7,8,14 The incidence of sinus node dysfunction is 0.8 per 1,000 person-years and is expected to double by 2060 due to the aging population.15 Conditions associated with advanced age such as hypertension, chronic kidney disease, diabetes mellitus, and coronary heart disease are overlapping risk factors and potential causes of sinus node dysfunction.2,15 Brugada syndrome, a rare inherited ion channel disorder that results in ventricular tachyarrhythmias and sudden cardiac death, is also associated with sinus node dysfunction.5,16,17 Causes of sinus node dysfunction are generally categorized as intrinsic or extrinsic based on their effect on the SAN (Table 22,5–8,18). It is important to note that sinus node dysfunction is usually a progressive condition and most causes are chronic and irreversible.5 Intrinsic causes originate from structural or functional changes within the SAN. These changes can occur because of fibrosis, ischemia, cardiac remodeling, infiltrative disease, or ion channel dysfunction. 8,18,19 Degenerative idiopathic fibrosis of the SAN is the most common cause of sinus node dysfunction.4,5,7,8,15 Elastic fiber and fatty and fibrous tissue buildup at the SAN and surrounding myocardial tissue increases with age and may lead to prolonged SAN refractory time and, therefore, a decreased intrinsic heart rate.2,4,8 Ischemic heart disease and embolization of the sinus node artery may cause ischemic necrosis of the node, resulting in sinus node dysfunction.8 Acute myocardial infarction may induce a transient sinus node dysfunction caused by autonomic disturbance and increased vagal tone.2,12 Cardiac remodeling following myocardial infarction, congestive heart failure, or advanced age can result in structural changes that decrease cardiac tissue voltage transmission and ultimately delay or block the SAN and result in sinus node dysfunction.3,8,14 Another result of this remodeling is the formation of bradycardia-tachycardia syndrome. It is unclear if a supraventricular tachycardia or sinus node dysfunction is the primary disorder in bradycardia-tachycardia syndrome. The etiology is further complicated by current contradictory evidence about the role of supraventricular tachycardia and atrial fibrillation as a cause of sinus node dysfunction.3 At a minimum, it is clear that these diagnoses are associated even if the causal pathway is unclear. Infiltrative diseases such as sarcoidosis, amyloidosis, hemochromatosis, and connective tissue diseases can disrupt the cardiac tissue and result in abnormal SAN function.2,5 Similarly, sinus node dysfunction has been associated with cardiomyopathy from infection with Chagas disease, with which the arrhythmia may be permanent.6,8 Rhythm abnormalities associated with myocarditis from infections such as diphtheria and typhoid and immune-mediated disorders such as rheumatic fever may cause sinus node dysfunction temporarily.6,8 About 80% of patients younger than 21 years with sinus node dysfunction have a history of congenital heart malformations (e.g., atrial septal defect, transposition of the great arteries) that required surgical intervention.18,20 Genetic mutations in genes responsible for coding ion channels, such as HCN4 and SCN5A, have also been identified as a cause of intrinsic sinus node dysfunction.18 Extrinsic causes are related to external factors causing abnormal conduction at the SAN. These causes include medications, metabolic abnormalities, autonomic imbalances, toxins, and endocrine disorders (Table 22,5–8,18). Extrinsic causes may be reversible, such as electrolyte abnormalities, hypothyroidism, metabolic abnormalities, and certain medications.2,8 Anesthesia (e.g., sympatholytic drugs) has been shown to induce autonomic imbalances that may mimic sinus node dysfunction or may reveal the underlying dysfunction in previously asymptomatic patients.8,21 Other pharmacotherapies known to cause sinus node dysfunction include beta blockers, nondihydropyridine calcium channel blockers, digoxin, lithium, and antiarrhythmics.5,7,8 Toxins such as nicotine and marijuana have also been implicated in sinus node dysfunction.7,8,22 Patients with sinus node dysfunction typically present with end-organ hypoperfusion symptoms from decreased cardiac output caused by the underlying arrhythmia (Table 15–11). The most common symptoms of cerebral hypoperfusion are syncope, presyncope, lightheadedness, and cerebrovascular accidents, with syncope occurring in 50% of patients with sinus node dysfunction.2,5,7,23 Cardiovascular hypoperfusion can present with palpitations, decreased physical activity tolerance, angina, or, less commonly, heart failure. Musculoskeletal hypoperfusion can present with muscle fatigue. Renal hypoperfusion can present as oliguria.2,5,6,13,23 Correlation between symptoms and arrhythmias is considered the diagnostic standard (on electrocardiography [ECG] or other cardiac monitoring).2,5,6 A definitive diagnosis of sinus node dysfunction is established when symptoms are directly associated with cardiac monitoring that demonstrates a bradyarrhythmia2,6 (Table 15–11). The initial assessment should begin with a history and physical examination (Figure 12–4,8,14,17,21,24). Clinicians should focus their history by investigating the intrinsic and extrinsic causes of sinus node dysfunction (Table 22,5–8,18). It should include a medication review to assess for a potential extrinsic cause. Initial diagnostic evaluation should include 12-lead ECG, a basic chemical panel to assess for metabolic abnormalities, and any additional laboratory tests needed to rule out other extrinsic causes that were not excluded by the history or physical examination (i.e., thyroid-stimulating hormone to rule out hypothyroidism or A1C to rule out diabetic atrial myopathy).5,6 Initial evaluation of sinus node dysfunction can be performed in an outpatient setting; patients with hemodynamic instability (i.e., systolic blood pressure less than 90 mm Hg, ventricular arrhythmias) or severe symptoms (i.e., recurrent syncope, anginal symptoms) should be hospitalized because these patients need urgent evaluation and may require temporary transcutaneous pacing for stabilization.2 When a potential extrinsic factor is identified during the workup, further evaluation should focus on confirming the diagnosis followed by a trial of therapy. With successful treatment of the extrinsic factor (e.g., continuous positive airway pressure for confirmed sleep apnea or thyroid supplementation for hypothyroidism) and subsequent resolution of sinus node dysfunction, no further workup is indicated. Patients with history or physical examination findings for underlying structural defects such as a history of valvular disease, new cardiac murmur, bibasilar crackles, lower extremity edema, or concerning ECG findings (e.g., left bundle branch block, second-degree Mobitz type II block, third-degree atrioventricular block) should have transthoracic echocardiography.2 If the results suggest a specific pathology, further workup and treatment should be initiated based on the suspected etiology. Abnormal results may be because of complications from sinus node dysfunction or an alternative diagnosis, and will require further workup and potential specialty referral for evaluation and treatment. Chronotropic incompetence is associated with sinus node dysfunction, with 50% of patients diagnosed with sinus node dysfunction also meeting chronotropic incompetence criteria.25,26 It is a separate diagnosis associated with an array of diseases, including sinus node dysfunction. Chronotropic incompetence is defined as the sinus node's inability to mount a heart rate high enough to meet physiologic demands during exertion, resulting in symptoms of central nervous system hypoperfusion similar to those found in sinus node dysfunction.5,25 When symptoms are associated with exertion, the patient should have an exercise ECG test to assess chronotropic incompetence. A diagnosis of chronotropic incompetence is made if the patient is unable to meet 80% of the maximum heart rate (220 bpm – age) during exertion.2,25 It is important to distinguish that chronotropic incompetence is a separate disease process and alone is not enough to diagnose sinus node dysfunction. Sinus node dysfunction and chronotropic incompetence follow the same treatment algorithm (Figure 12–4,8,14,17,21,24). When initial 12-lead ECG is unable to confirm sinus node dysfunction by correlating symptoms with a definitive bradyarrhythmia (Table 15–11), further electrical monitoring is indicated.2,5,9 There are multiple types of ambulatory monitoring available. These devices include continuous monitoring (e.g., Holter monitor, external patch recorder, ambulatory telemetry) and patient- or event-activated devices (e.g., event monitor, external loop recorder, implantable loop recorder). First-line devices include the original Holter monitor or the external patch recorder.8,9,27–32 The external patch recorder is a smaller second-generation monitor that is water-resistant and can be worn for seven to 14 days. The external patch recorder detected more arrhythmias and was better tolerated by patients compared with the Holter monitor.31,33 The frequency of symptoms, the patient's ability to use the device, and the need for continuous vs. intermittent monitoring should be considered when deciding the best form of monitoring for a patient.9 Table 3 lists cardiac monitoring options with associated indications and pros and cons of use.9,27–31 If sinus node dysfunction cannot be definitively established after ambulatory monitoring is completed, further evaluation for an alternative diagnosis and expert consultation should be considered. Permanent pacemaker placement is the first-line treatment for patients with confirmed sinus node dysfunction,2,5,34–36 accounting for 50% of pacemakers implanted in the United States.5,7,12 Pacemaker therapy has been found to provide symptom relief and improve quality of life, but it is unclear if it provides a mortality benefit.5,36 This treatment includes patients with chronotropic incompetence and patients with pharmacologically induced sinus node dysfunction where continued treatment is clinically necessary. Atrial-based pacing has been established as superior because right ventricular pacing has been associated with an increased risk of arrhythmias and decreased cardiac function.2,37,38 A well-powered randomized controlled trial demonstrated no difference in mortality, stroke, heart failure, or atrial fibrillation hospitalizations when comparing single-chamber atrial pacing with dual-chamber atrial pacing.21 However, over five years of follow-up, 3% to 35% of patients will transition from a single-chamber atrial device to a dual-chamber device with minimized ventricular pacing.2,6 To minimize the risk of these additional procedures, patients with evidence of atrioventricular nodal or bundle branch conduction dysfunction should be considered for initial dual-chamber device placement.2 It is common in the United States for patients to receive a dual-chamber device with right atrial pacing unless otherwise indicated. Overall, permanent pacemaker placement is relatively safe, with complications estimated at less than 1% to 6%. Most common complications include lead dislodgment (5.7% in left ventricular leads), hematomas (3.5%), venous thrombus/obstruction (2%), infections (1%), and pneumothorax (1%).34 Medication control of sinus node dysfunction is a secondary option for patients who decline permanent pacemaker placement. Phosphodiesterase inhibitors (e.g., theophylline, cilostazol [Pletal]) have a positive chronotropic effect, resulting in symptom control for patients with sinus node dysfunction. However, the long-term impact of medication control on disease progression and mortality is unclear.2,35 Other pharmaceuticals (e.g., atropine, dopamine, epinephrine, glucagon) used in advanced cardiac life support protocols for acutely unstable bradycardic patients are effective for short-term control of unstable patients but are not appropriate for long-term management of sinus node dysfunction because of significant adverse effect profiles.2,35 The role of oral anticoagulation in patients with sinus node dysfunction is unclear. There is limited evidence to support its use in patients with sinus node dysfunction who do not have another indication for anticoagulation therapy.2,37,39 Anticoagulation is currently not routinely recommended for the treatment of sinus node dysfunction. Data Sources: We searched Essential Evidence, PubMed, and Google Scholar. Key words included sinus node dysfunction, sick sinus syndrome, causes, bradyarrhythmia, permanent pacemaker indications, chronotropic incompetence, loop recorders, ambulator cardiac monitoring. The search included practice guidelines, randomized controlled trials, a retrospective case control study, and review articles. Search dates: December 2019 to October 2020. The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the Uniformed Services University, the U.S. Air Force Medical Department, the Air Force at large, the U.S. Army Medical Department, the Army at large, or the U.S. Department of Defense. Page 19 Pertussis, or whooping cough, is an acute respiratory tract infection that continues to affect a significant portion of the global population, with more than 24 million estimated cases in 2014.1 Pertussis, a Centers for Disease Control and Prevention (CDC) reportable disease, is caused by Bordetella pertussis. The disease can lead to substantial complications in infants, such as apnea, pneumonia, seizures, other hypoxic complications, hospitalization, or death.2,3 Bordetella parapertussis and rarely Bordetella bronchiseptica can also cause a pertussis-like syndrome. The incidence of pertussis in the United States decreased with universal childhood immunization, but it has rebounded steadily in recent years, from a low of 1,010 reported cases in 1976 to a peak of 48,277 cases in 2012.4 The most recent available data show 15,609 reported cases in 2018.5 What Is the Typical Presentation and Progression of Pertussis? There are three stages of pertussis (catarrhal, paroxysmal, and convalescent), each with a different clinical presentation (Table 1).6–8 However, clinical presentation varies widely depending on age and immunization status, and not every patient has the classic stage progression.9 The key clinical features of the initial catarrhal stage are difficult to distinguish from a viral upper respiratory tract infection and include malaise, rhinorrhea, dry cough, and lacrimation. Fever is usually mild or absent. After one to two weeks, the paroxysmal stage may manifest. Typical features of this stage include paroxysmal coughing, whooping on inspiration after coughing, and posttussive emesis. Other common features of the paroxysmal stage include periods of apnea associated with paroxysms, chest and abdominal soreness from prolonged coughing, and scleral hemorrhage. In between paroxysms, the patient may be asymptomatic. The paroxysmal stage typically lasts up to six weeks before transitioning to the convalescent stage. In this stage, the coughing lessens but typically persists for an additional two to four weeks, with some patients experiencing symptoms for a longer period (e.g., "100-day cough").7,10–12 Can Pertussis Be Diagnosed with Clinical Signs and Symptoms Alone, or Is Laboratory Testing Required? The diagnosis of pertussis requires laboratory confirmation. Because early detection and treatment are critical to reducing transmission, accurate identification of the clinical features of pertussis is important to prompt testing. No validated, accepted clinical decision rule has been established for diagnosing pertussis.13 However, the key clinical features of the infection are included in CDC and World Health Organization (WHO) case definitions. The CDC case definition of pertussis includes coughing of any duration and at least one sign or symptom (i.e., paroxysmal coughing, inspiratory whooping, posttussive emesis, or apnea) and contact with a laboratory-confirmed case of pertussis, or at least two weeks of coughing and one of these signs or symptoms.14 The WHO definition adds the clinical suspicion of pertussis and specifies that apnea is a criterion only in infants younger than one year.15 Although sensitive, the CDC and WHO criteria lack specificity.13 Two 2017 systematic reviews evaluated the clinical features used in the diagnosis of pertussis (Table 2).13,16 One found that the best clinical predictors of pertussis in adults were the presence of whooping (positive likelihood ratio [LR+] = 1.45) and posttussive emesis (LR+ = 1.46), and the best negative predictors were a lack of paroxysmal coughing (negative likelihood ratio [LR−] = 0.33) and presence of fever (LR− = 0.97).16 However, the second systematic review reported minimal value of individual signs and symptoms, with the clinician's overall impression having the highest likelihood ratio out of both reviews (LR+ = 3.3).13 According to a 2019 guideline, pertussis should be considered likely in adults who have posttussive emesis or inspiratory whooping and unlikely if the patient has fever or lack of paroxysmal coughing.17 In children, pertussis should be considered likely if the patient has posttussive emesis, paroxysmal coughing, or inspiratory whooping.17 What Is the Preferred Diagnostic Laboratory Test for Pertussis? Polymerase chain reaction (PCR) is the most accurate test to confirm pertussis (LR+ = 13; LR− = 0.03) and is the diagnostic test of choice in most cases.18 Culture should be used to confirm a positive PCR result during pertussis outbreaks for strain identification or if PCR is not available.7 Serology can be a helpful adjunct late in the course of illness (more than three weeks) but only in patients older than six months who have not been vaccinated in the past year.19,20 The sensitivities of culture and PCR are highest during the catarrhal and early paroxysmal phase, whereas the sensitivity of serology (immunoglobulin G) does not peak until late in the paroxysmal and convalescent phases (Table 3).18,19,21,22 PCR is the preferred test because it provides rapid and accurate results, whereas cultures are limited by antibiotic use and prior immunization, they are challenging to grow, and results take seven to 10 days.7 Serology is primarily used for epidemiology but could be useful in patients who present late in the course of illness because it can help confirm the diagnosis as late as 12 weeks after symptom onset.6,23 Serology is not useful in patients who would be expected to have circulating antibodies (e.g., those who were recently vaccinated).24 Direct fluorescent antibody assays are no longer used because of low sensitivity and specificity.19 In infants younger than three months with a typical clinical presentation, leukocytosis (leukocyte level higher than 20,000 per μL [20.00 × 109 per L]) with greater than 50% lymphocytes can be virtually diagnostic for pertussis.19,20 Why Does Pertussis Remain a Common Disease Despite High Vaccination Rates? Some strains have shifted away from displaying the acellular vaccine antigens (i.e., pertussis toxin, pertactin, fimbriae 2 or 3, and filamentous hemagglutinin). These are known as vaccine antigen deficient strains or escape mutants.4,25,26 Even without this shift, immunity wanes in most patients because of uncertain causes. Unlike with other vaccines, there is not a standardized antibody titer to confirm protection against pertussis.27 Although pertussis vaccines were initially whole cell, the high reactogenicity of the vaccine caused frequent adverse effects (e.g., local reaction, seizure, pain, fever sometimes leading to febrile seizure), resulting in the adoption of acellular vaccines in the 1990s. Immunity typically wanes two to four years after administration of the acellular pertussis vaccine, although this can occur as early as one year postvaccination.28 Individuals with natural infection also experience waning immunity, including children with a history of pertussis.4,29 Because of this rapid decrease in immunity, it is not considered an effective public health strategy to continue recurrent tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) boosters.4 Why Did the Vaccine Recommendations Change for Adolescents in 2005 and Pregnant Patients in 2012? Despite high pertussis vaccination rates in infants and children, there was a significant increase in the incidence of pertussis in the 1990s and early 2000s, especially among adolescents. Infants younger than two months have the highest risk of hospitalization and death; therefore, a passive immunity strategy (placental transmission of maternal antibodies) was adopted to protect this group.4 Because of the increasing incidence of pertussis in the United States and an observed waning immunity regardless of the source of inoculation (whole cell or acellular vaccine or infection), the CDC's Advisory Committee on Immunization Practices (ACIP) published updated pertussis vaccination guidelines in 2005, including introducing a booster of Tdap, rather than tetanus and diphtheria toxoids (Td), at 11 to 12 years of age or once as an adult if not previously received.4 Table 4 summarizes current pertussis vaccine guidelines.4,28 Because more than 85% of pertussis deaths occur in infants too young to receive pertussis vaccination, it is recommended that pregnant patients receive the Tdap vaccine between 27 and 36 weeks' gestation with each pregnancy.4,30 This timing was recommended because of rapid waning of antipertussis antibodies and optimal timing of placental antibody transfer.30,31 If the third-trimester booster is missed, ACIP recommends not vaccinating patients with Tdap postpartum if they have ever received Tdap.4 Should Nonmaternal Caretakers of Infants or Close Contacts of Health Care Workers Be Given Tdap Boosters? No, unless otherwise overdue for the Tdap vaccine. The target is for all individuals to receive a Tdap booster once.28 Although ACIP's 2020 recommendation allows for either Td or Tdap formulations for tetanus prophylaxis or booster, the change is essentially for the convenience of the clinician and patient because there is no identified risk of extra Tdap administrations.28 There is no difference in adverse effects in patients given Td or Tdap at an interval of five to 10 years, and data in pregnant patients given multiple doses in shorter time spans also have not shown an increase in adverse effects.28,32 Cocooning (vaccinating close contacts of infants and others at high risk) was based on a faulty assumption that vaccinated individuals could not transmit the disease.4 It is now known that immunized patients can contract and transmit pertussis, although the vaccine reduces disease severity in the vaccinated individual.27 Models have since shown that household siblings are more significant carriers of pertussis than the mother.4 Therefore, passive immunity through immunization of the mother during pregnancy is the primary public health goal. If a Patient Has a Seizure After Administration of Any Dose of DTaP or Tdap, Are Additional Doses Contraindicated? Seizure after pertussis vaccination was previously a

contraindication for receiving further doses, but the risk of repeat seizure or a complicated neurologic event after subsequent diphtheria and tetanus toxoids and acellular pertussis (DTaP) or Tdap administration is low (0.5 cases of encephalopathy per 10 million doses), and further pertussis vaccination should not be avoided.4,28 Safety concerns with DTaP and Tdap are summarized in eTable A. Immunization should be temporarily delayed in a patient who has uncontrolled seizure disorder or a progressing neurologic disorder, such as infantile spasms, until the disorder is stabilized. Patients with a history of seizures that are currently controlled and patients who had a seizure with previous pertussis vaccines without prolonged symptoms of coma or encephalopathy do not have a contraindication to receiving additional doses of DTaP or Tdap vaccines.4 Children who have had persistent crying or hypotonic-hyporesponsive episodes with DTaP are unlikely to have repeat episodes with further doses; therefore, these are not contraindications to receiving DTaP or Tdap boosters.4 What Antibiotic Should Be Used to Treat Patients with Pertussis? Antibiotics are intended to prevent transmission of pertussis to others and do not shorten the disease course or improve symptoms. Azithromycin (Zithromax) is the preferred treatment for pertussis because of its favorable safety profile, but use of other macrolides (erythromycin, clarithromycin) or trimethoprim/sulfamethoxazole is an acceptable alternative.2,33,34 Antibiotics for pertussis have been shown to provide a microbiologic cure and are prescribed to prevent the spread of the disease within 21 days of cough onset.2,33–35 A Cochrane review did not show that antibiotics significantly reduce mortality, symptom duration, or complications in patients with pertussis.2 Azithromycin has replaced erythromycin as the preferred treatment because of its daily dosing, shorter course, and fewer gastrointestinal adverse effects.2,33,36 In adults, azithromycin can be given as a dosage of 500 mg for three days or 500 mg on day 1, then 250 mg on days 2 to 5. In children, it can be given as a dosage of 10 mg per kg for three days or 10 mg per kg on day 1, then 5 mg per kg on days 2 to 5.2,33,36 Should Pertussis-Related Cough Be Treated with Adjunct Therapies? Treatments aimed at reducing cough, including corticosteroids, antihistamines, beta-2 agonists, and pertussis immune globulin, have not been associated with improved symptoms in patients with pertussis.37 A 2014 Cochrane review evaluating symptomatic treatments for pertussis, including one or two poor-quality studies per intervention, found no benefit in the reduction of coughing episodes or length of hospitalization.37 The use of symptomatic treatments is not recommended. Who Should Receive Antibiotic Prophylaxis? Postexposure prophylaxis should be initiated in household contacts of someone with pertussis and in those exposed to pertussis who are at high risk of severe illness or in close contact with someone who is at high risk of severe illness.38 Postexposure prophylaxis should be initiated within 21 days of exposure.38 The CDC recommends postexposure prophylaxis within 21 days of exposure in household contacts of someone with pertussis and in those exposed to pertussis who are at high risk of severe illness or in close contact with someone at high risk.38 Those at highest risk of severe illness include infants and people who are in their third trimester of pregnancy, are immunocompromised, or who have comorbidities that increase the risk of severe illness (e.g., respiratory disorders). The CDC has limited prophylaxis to only these groups because placebo-controlled studies of erythromycin have not demonstrated effectiveness, and a Cochrane review found no benefit of postexposure prophylaxis in those older than six months who are not in contact with an infant.2,39 Azithromycin is the preferred agent for prophylaxis, at the same dosage as pertussis treatment.2,33 Tdap should no longer be administered for postexposure prophylaxis.4 Data Sources: The primary resources used to identify literature were PubMed and the Cochrane database. Primary search terms included pertussis (free text) or pertussis (MeSH) and one of the following terms: treatment, complications, diagnosis, prevention, vaccination. Limits were used to identify primary literature. Essential Evidence Plus and article reference lists were reviewed to identify further sources. The CDC website was also searched using the terms above and the additional term ACIP. Search dates: April 30, 2020; June 2, 2020; July 7, 2020; October 8, 2020; and March 16, 2021. Page 20 A 23-year-old patient, M.C., comes to your office for a wellness visit with no concerns. On reviewing the patient's medical record, you note that M.C. has a history of polycystic ovary syndrome, blood pressure of 110/70 mm Hg from a visit one year ago, and a body mass index of 28.2 kg per m2. 1. According to the U.S. Preventive Services Task Force (USPSTF) recommendation statement, which one of the following steps regarding screening for hypertension is appropriate for M.C.? A. Screen M.C. for hypertension today because of the patient's history of polycystic ovary syndrome.B. Defer screening M.C. for hypertension for another two to four years because the patient's blood pressure was not elevated one year ago.C. Screen M.C. for hypertension today because the patient's body mass index is in the overweight range.D. Defer screening M.C. for hypertension until 40 years of age.E. Ask M.C. to begin monitoring their blood pressure at home. 2. M.C. had a blood pressure of 143/81 mm Hg upon arrival in the examination room. M.C. reports no headache, blurry vision, chest pain, shortness of breath, or blood in urine. According to the USPSTF recommendation statement, which one of the following steps is correct? A. Prescribe the patient an angiotensin-converting enzyme inhibitor, such as lisinopril, and schedule a follow-up visit in three months.B. Ask M.C. to monitor their blood pressure at home and schedule a follow-up visit to discuss the results.C. Prescribe the patient a calcium channel blocker, such as amlodipine (Norvasc), and schedule a follow-up visit in three months.D. Wait until the next follow-up visit in six to 12 months to confirm the diagnosis of hypertension.E. Repeat the blood pressure measurement today and prescribe an antihypertensive medication if the blood pressure remains elevated. 3. Which of the following blood pressure monitoring methods can you use to confirm a diagnosis of hypertension in this patient? A. Ask M.C. to wear a programmed portable device that automatically takes blood pressure measurements, typically in 20- to 30-minute intervals over 12 to 24 hours, while patients go about their normal activities or are sleeping.B. Ask M.C. to measure their own blood pressure at home with an automated device placed on the upper arm.C. Ask M.C. to follow up in the office in two months to reassess their blood pressure on another day.D. No additional blood pressure readings are necessary to confirm the diagnosis of hypertension. 1. The correct answer is C. Although available evidence on optimal screening intervals for hypertension remains limited,1 the USPSTF suggests annual screening for hypertension in adults 40 years or older and for adults at increased risk for hypertension, including Black people, people with high-normal blood pressure, or people who are overweight or obese. Screening less frequently (i.e., every three to five years) is appropriate for adults 18 to 39 years of age not at increased risk for hypertension and with a previous normal blood pressure reading.2 Polycystic ovary syndrome is not considered, in itself, an indication for annual blood pressure screening. 2. The correct answer is B. For adults 18 years or older without known hypertension, the USPSTF recommends screening for hypertension with office blood pressure measurement. The USPSTF recommends obtaining blood pressure measurements outside of the clinical setting for diagnostic confirmation before starting treatment.2 Selection of treatment can vary depending on severity of blood pressure elevation, age, and other risk factors. 3. The answers are A and B. The USPSTF recommends obtaining blood pressure measurements outside of the clinical setting for diagnostic confirmation before starting treatment.2 Either ambulatory or home blood pressure monitoring with validated and accurate devices can be used to confirm a diagnosis of hypertension before starting treatment. Ambulatory blood pressure monitoring involves wearing a programmed device that automatically takes frequent blood pressure measurements over the course of a day (or day and night). Ambulatory blood pressure monitoring devices are small, portable machines that record blood pressure noninvasively at typically 20- to 30-minute intervals over 12 to 24 hours while patients go about their normal activities or are sleeping. See a related article in FPM about implementing ambulatory blood pressure monitoring for more information.3 Home blood pressure monitoring involves patients measuring their own blood pressure at home with a home blood pressure monitoring device. Home blood pressure monitoring devices are fully automated oscillometer devices that record measurements taken from the patient's brachial artery. Home blood pressure monitoring devices are activated by patients or caregivers, and measurements are taken much less frequently than with ambulatory blood pressure monitoring (e.g., one to two times a day or week, although the blood pressure measurements can be spread out over more time).2 The views expressed in this work are those of the authors and do not reflect the official policy or position of the Johns Hopkins Bloomberg School of Public Health or the U.S. government. Page 21 What are the benefits and harms of diagnostic testing, and what is the effectiveness of treatment options for acute colonic diverticulitis? Computed tomography (CT) accurately diagnoses acute diverticulitis and may make appropriate management more likely compared with clinical diagnosis alone. (Strength of Recommendation [SOR]: B, based on inconsistent or limited-quality patient-oriented evidence.) Misdiagnosis does not increase the risk of poor clinical outcomes. (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) For patients with uncomplicated acute diverticulitis, outpatient management may be as effective as inpatient care, but there is insufficient evidence regarding important clinical outcomes, including treatment failure, mortality, and emergency surgery. (SOR: C, based on disease-oriented evidence.) Antibiotic treatment for patients with uncomplicated diverticulitis does not affect pain symptoms, length of hospitalization, recurrence risk, quality of life, or need for surgery compared with no antibiotic treatment. (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) The evidence is insufficient to guide the choice of antibiotic regimen for patients who do receive antibiotics.1 Colonic diverticulitis is caused by inflammation of abnormal outpouchings (diverticula) in the wall of the large intestine.1 Diverticulosis occurs in 5% to 15% of people older than 45 years and in 80% of those older than 85 years.2 For people with diverticulosis, the lifetime prevalence of developing acute diverticulitis is approximately 25%. Alterations in colonic wall resistance and motility and a low-fiber diet contribute to increased luminal pressure and bowel wall weakness. Aspirin, nonsteroidal anti-inflammatory drugs, obesity, lack of exercise, and increasing age are all risk factors for developing diverticulitis.2 Acute diverticulitis accounts for more than 2.6 million outpatient visits and 200,000 inpatient admissions each year in the United States.3 Diverticulitis can be divided into two categories, uncomplicated and complicated. Complicated diverticulitis is associated with abscess formation, fistula, and bowel obstruction or perforation and may occur in up to 15% of acute diverticulitis cases.3 This Agency for Healthcare Research and Quality (AHRQ) review included 77 primary studies and two systematic reviews on the diagnostic accuracy of CT of the abdomen; harms related to false-positives, false-negatives, and incidental findings on CT; the effectiveness and harms of hospitalization; antibiotics and radiology interventions for the management of acute diverticulitis; the need for follow-up colonoscopy in people with a history of acute diverticulitis; and the effectiveness and harms of pharmacologic and nonpharmacologic interventions and elective surgery for the prevention of recurrent diverticulitis.1 The AHRQ review found that CT of the abdomen has high sensitivity (94%) and specificity (99%) for the diagnosis of acute diverticulitis, but there was insufficient evidence to evaluate staging criteria. Misdiagnosis on CT did not increase the risk of poor clinical outcomes. Incidental findings are common on CT of the abdomen and may prompt further investigation. One study of emergent abdominal CT found that more than 60% of scans included an incidental finding.4 CT can be useful to confirm the diagnosis but is less helpful in directing management. Adverse outcomes such as mortality and emergency surgery were uncommon (0.2% and 1.3%, respectively) regardless of management setting (inpatient vs. outpatient), and there was no evidence to suggest differences in recurrence based on setting. Evidence was insufficient to make conclusions about the effects of inpatient vs. outpatient management on treatment failure, mortality, and the need for emergency surgery. The AHRQ review found low-quality evidence that antibiotic treatment for patients with uncomplicated diverticulitis does not improve pain, length of hospitalization, recurrence risk, or quality of life compared with no antibiotic treatment. The incidence of sigmoid resection at one month and one year is not significantly changed by the administration of antibiotics. Evidence was insufficient to recommend one antibiotic regimen over another. The traditional approach to outpatient management of patients with acute diverticulitis consists of clinical diagnosis with or without imaging, antibiotics, and bowel rest.2,3 The AHRQ review supports recent guidelines from the American Gastroenterological Association and the American Society of Colon and Rectal Surgeons that recommend CT of the abdomen as the most appropriate diagnostic study.5,6 Although most of the evidence was considered low strength or insufficient by the AHRQ review authors, the review and the American Gastroenterological Association guidelines suggest that uncomplicated acute diverticulitis can usually be diagnosed and managed in the outpatient setting without antibiotics. Two U.S. cohort studies published after the end date of the AHRQ literature search found no differences in the effectiveness of outpatient treatment of diverticulitis with amoxicillin/clavulanate or with metronidazole plus a fluoroquinolone.7 In general, patients with complicated acute diverticulitis should be treated as inpatients and receive antibiotic therapy. Editor's Note: AFP SOR ratings are different from the AHRQ Strength of Evidence ratings. Dr. Seehusen is an assistant medical editor for AFP. Page 22 The local hospital has had an influx of patients with COVID-19 admitted. I mentally prepare myself for the first of four days as a physician volunteer for inpatient services. I meet my three interns and find that we have OB/GYN, psychiatry, and dermatology represented. The last time I worked in inpatient medicine was as a resident three years ago. I am feeling out of my element as we begin walking rounds. I realize that a patient I recently evaluated in the office and sent to the ER for leg pain is being transferred to my medical service. The patient was found to have a proximal femoral deep venous thrombosis and multiple small bilateral pulmonary embolisms. In a hospital with almost 700 beds, this welcomed coincidence exemplifies continuity of care at its finest. I conduct a virtual meeting with a patient's legal guardians, the palliative care team, and neurosurgery. The discussion involves a middle-aged patient with Down syndrome who is in severe pain due to a recent L1 compression fracture. A patient's hemoglobin level has dropped precipitously. I evaluate the patient and find they have had an episode of hematemesis. I consult the critical care team, who transfers the patient for a presumed acute upper gastrointestinal bleed. Home, at last, I take a moment to sit down with my husband. We are 33 weeks pregnant and excited to step into the adventure that is parenthood. As we gaze down at our ultrasound photo, I am comforted knowing that at least this is one thing COVID-19 can't take away. I direct fed the baby before I ran out the door. My doorway mental checklist includes bag, wallet, personal phone, work phone, hospital identification, breast pump and parts, ice pack, mask, water bottle, food, food, and more food. They say breastfeeding burns an extra 400 kcal per day. I'm convinced it's higher for doctors. My third-year medical student conducts a telemedicine appointment with a patient while I listen in. The learning curve to precept this type of encounter has been steep and forced. They discuss the results of the patient's pulmonary function tests and devise a treatment plan. Afterward, my student tells me that was the best practice they had at counseling because they could focus completely on a skill that is typically rushed. A patient comes in without an appointment. At the last minute, the patient asks, “Doc, can you test me for STDs?” This is unrelated to the visit. I have not taken a sexual history because I did not see this coming. This is a doorknob moment because it took the whole visit for the patient to work up the courage to ask about what they were really worried about. I call a spouse whose wife is in the hospital with metastatic breast cancer complicated by metastasis to her brain and seizures. He can't visit her because of COVID-19 precautions and worries that she is refusing to eat and is confused. It is a heart-wrenching conversation. The inpatient team talked to them about hospice, but they don't completely understand what it means. I arrange for a virtual meeting with the patient, her husband, the inpatient team, myself, and the primary oncologist. I send my daily text, “When did the baby last get a bottle?” so I know if I should pump again before leaving. On my ride home, I feel a mix of sadness for my sickest patients and relief that the other side of this pandemic is starting to feel within reach. Page 23 A 54-year-old patient presented with a new lesion on the upper chest that had been present for three months. The lesion was solitary and slightly pruritic. The patient had no trauma to the involved area and no family history of melanoma. The patient had a history of skin lesions that were biopsied but determined to be benign. The patient reported multiple severe sunburns over several years and had spent numerous summers playing outside as a child. The patient used sunscreen regularly. Physical examination revealed a red, slightly raised papule on the anterior chest wall, near the left breast (Figure 1). Based on the patient's history and physical examination findings, which one of the following is the most likely diagnosis? A. Actinic keratosis.B. Basal cell carcinoma.C. Bowen disease.D. Lichenoid keratosis.E. Seborrheic keratosis. The answer is D: lichenoid keratosis. Lichenoid keratosis normally occurs in middle-aged and older patients and is more common in those with frequent sun exposure and sun-damaged skin. Lichenoid keratosis typically presents as a solitary asymptomatic lesion on the skin, ranging from 5 to 20 mm in diameter.1 It is a slightly hardened, plaque-like lesion that is normally erythematous but can be brown or sometimes violaceous.1 Because of the wide-ranging clinical appearance, lichenoid keratosis is often misdiagnosed.1 The condition is benign and does not have the histologic characteristics of basal cell carcinoma.2 Because the presentation of lichenoid keratosis is similar to that of basal cell carcinoma, a biopsy may be required to confirm the correct diagnosis. If desired or for cosmetic reasons, lichenoid keratosis can be removed through cryotherapy or excision. Actinic keratosis is a distinct, hyperkeratotic lesion on the skin due to confined proliferation of keratinocytes at the dermoepidermal junction. This proliferation causes a disturbance in the differentiation of the epidermis, which commonly presents as a rough, scaly patch of skin.3 Basal cell carcinoma generally presents on sun-exposed skin, most notably on the head and neck. It presents as a pearly papule or nodule with overlying telangiectasia and a translucent rolled border.4 Bowen disease, the in situ form of squamous cell carcinoma, presents as a nonpigmented, slowly growing, erythematous, well-demarcated plaque with a scaly or crusty surface that may be eroded or ulcerated.5 Bowen disease is common on the lower extremities of older patients with sun-damaged skin. It is more common in women.5 Seborrheic keratoses are a specific type of benign cutaneous tumors, with varying clinical and histopathologic presentations. They develop from the proliferation of epidermal keratinocytes and are common in people 40 years and older.6 Page 24 A 54-year-old patient presented with stiffness and pain in the lower back and both thighs. The pain was worse when sitting and lying down, but there was no pain when standing. The patient described the pain as compression in the flanks that radiated to the right groin and both lateral thighs. The patient had urinary hesitancy but no trauma, fever, weight loss, or blood in the urine. Symptoms were not relieved with ibuprofen and cyclobenzaprine. The medical history was significant for renal stones and gastroesophageal reflux. The patient had no history of back problems or repetitive lifting. Physical examination revealed normal motor strength in the lower extremities and negative findings on the straight leg raise test. There was tenderness on palpation of the right flank. Results of a point-of-care urinalysis were normal. Prostate-specific antigen was mildly elevated at 5.84 ng per mL (5.84 mcg per L). Computed tomography (CT) of the abdomen was performed (Figure 1). Based on the patient's history and physical examination findings, which one of the following is the most likely diagnosis? A. Angiomyolipoma.B. Metanephric adenoma.C. Oncocytoma.D. Renal abscess.E. Renal cell carcinoma. The answer is E: renal cell carcinoma. Renal cell carcinoma is often an incidental finding until the tumor enlarges to an advanced size. Presenting symptoms vary and include hematuria, abdominal pain, or a palpable mass. The likelihood of renal cell carcinoma is higher when all three of these symptoms are present (the classic triad). Approximately 80% to 85% of tumors in the renal cortex are renal cell carcinomas. In these cases, paraneoplastic symptoms may develop because of the production of ectopic hormones such as erythropoietin, parathyroid hormone–like protein, gonadotropins, chorionic somatomammotropin, adrenocorticotropic hormone–like substance, renin, glucagon, and insulin.1 The diagnostic workup for renal cell carcinoma includes CT or ultrasonography, although ultrasonography is less sensitive. Magnetic resonance imaging can be used in some patients. In this patient, CT identified a mass in the right kidney measuring 3.8 cm × 4.0 cm × 3.5 cm. Resection is necessary if imaging studies cannot differentiate benign renal lesions from carcinoma. Tissue biopsy of the mass can establish the diagnosis of malignancy and identify the histopathologic type. Clear cell subtypes, as in this patient, account for up to 75% of cases.2 Angiomyolipoma is a benign renal tumor that can grow to impair renal function. It is strongly associated with tuberous sclerosis, a multisystem autosomal dominant genetic disease, and lymphangioleiomyomatosis. On histology, angiomyolipomas are composed of blood vessels, smooth muscle cells, and fat cells. Patients may be asymptomatic, but rupture of involved blood vessels can result in retroperitoneal hemorrhage accompanied by nausea and vomiting.3 Metanephric adenomas are rare, benign renal lesions. They are more common in women than men (2:1).4 Signs and symptoms may include hematuria, flank pain, and a palpable mass. They can be misidentified on CT as renal cell carcinoma or an epithelial Wilms tumor. Metanephric adenomas are more calcified than other renal tumors. Histopathology reveals small epithelial cells that form small acini in an acellular stroma. Oncocytoma is a benign tumor composed of large epithelial cells rich in granular eosinophilic cytoplasm and excessive numbers of mitochondria. Renal oncocytoma primarily arises from intercalated cells of the collecting ducts in the kidney. Renal oncocytoma is usually asymptomatic, although hematuria, flank pain, and an abdominal mass may be present. Less than 5% of surgically resected renal neoplasms are oncocytomas.5 Renal abscesses arise from an infectious source and are usually associated with pyelonephritis. They may also be associated with diabetes mellitus, pregnancy, and urinary tract abnormalities. Renal abscesses are pus-filled pockets that appear as hypodense regions on contrast-enhanced CT.6 Symptoms may include fever, vague lumboabdominal pain, pallor, fatigue, sweating, and weight loss. Page 25 Is hydrochlorothiazide more effective than chlorthalidone for the treatment of hypertension? Chlorthalidone reduces systolic blood pressure (SBP) by 10 mm Hg more than hydrochlorothiazide at equal dosages (12.5 to 25 mg daily) in patients using monotherapy. (Strength of Recommendation [SOR]: B, meta-analysis of randomized controlled trials [RCTs].) Low-dose chlorthalidone (6.25 mg daily) and controlled-release hydrochlorothiazide (12.5 mg daily; not currently available in the United States) reduce 24-hour ambulatory SBP and diastolic blood pressure (DBP), whereas immediate-release hydrochlorothiazide (12.5 mg daily) may only reduce daytime SBP. (SOR: B, single RCT.) A 2010 meta-analysis (137 RCTs; N = 10,443) evaluated the effect of hydrochlorothiazide and chlorthalidone on SBP and serum potassium.1 Adult patients were on hydrochlorothiazide or chlorthalidone monotherapy. Further patient demographics were not defined. Chlorthalidone dosing ranged from 12.5 to 200 mg daily (mean dosage = 31.6 mg daily) with an average baseline SBP of 166 mm Hg (29 RCTs; n = 4,380). Hydrochlorothiazide dosing ranged from 3 to 450 mg daily (mean dosage = 42.7 mg daily) with an average baseline SBP of 163 mm Hg (108 RCTs; n = 6,063). Studies lasted four to 52 weeks. Pooled results showed that chlorthalidone (12.5 to 25 mg daily) reduced SBP more than hydrochlorothiazide at the same dosage (137 RCTs; N = 10,443; −24 mm Hg vs. −14 mm Hg, respectively; P < .05). However, chlorthalidone also caused larger decreases in serum potassium levels (−0.4 mEq per L [–0.4 mmol per L] vs. −0.2 mEq per L [–0.2 mmol per L], respectively; P < .05). Heterogeneity was not reported. The analysis was limited to patients with hypertension who were on monotherapy. A 2016 RCT (N = 54) evaluated the effect of low-dose chlorthalidone and hydrochlorothiazide on mean 24-hour ambulatory blood pressure.2 Patients were 18 to 65 years of age (mean = 45 years of age) with essential hypertension (SBP of 140 to 159 mm Hg, DBP of 90 to 99 mm Hg) and an average blood pressure of 148/93 mm Hg. Patients were excluded if they had secondary hypertension, diabetes mellitus, hyperuricemia, gout, chronic kidney disease, parathyroid disease, or recent cardiovascular disease. Patients were randomized to receive chlorthalidone, 6.25 mg (n = 16), hydrochlorothiazide, 12.5 mg (n = 18), or controlled-release hydrochlorothiazide, 12.5 mg (n = 20). Ambulatory (24-hour) blood pressure monitoring was done at baseline and after four and 12 weeks of therapy. Chlorthalidone and controlled-release hydrochlorothiazide reduced SBP and DBP during the day and at night at four and 12 weeks. Hydrochlorothiazide showed a significant improvement in SBP only during the day at four weeks. The study was limited by excluding many disease processes often present as comorbid conditions in patients with hypertension. Copyright © Family Physicians Inquiries Network. Used with permission. The opinions and assertions contained herein are the authors' and are not to be construed as official or as reflecting the views of the U.S. Army Medical Department, Army at-large, or Department of Defense. Page 26 Can physical activity prevent the development of depression? Yes. Physical activity appears to be associated with a lower risk of developing depression and depressive symptoms. (Strength of Recommendation: B, based on a systematic review of cohort trials and individual randomized controlled trials [RCTs] and cohort trials.) A 2018 meta-analysis of 49 prospective cohort studies (N = 266,939) examined whether physical activity decreases the risk of developing depression.1 Study participants did not have depression at baseline. Most of the studies enrolled adults, although some also enrolled children and older adults. Physical activity was self-reported and was defined as any bodily movements requiring energy expenditure. Depression was diagnosed using defined cutoffs from a variety of depression screening instruments. Trials were one year or longer. Compared with patients who had low levels of physical activity, those engaged in high levels of physical activity (definition varied by study; included groups with greater frequency, intensity, and volume of physical activity) had a lower risk of developing depression (36 trials; odds ratio [OR] = 0.83; 95% CI, 0.79 to 0.88; I2 = 0). The included studies were conducted in diverse geographic regions, and this meta-analysis found a range of ORs among different areas (0.65 to 0.84); however, in each region, physical activity was found to be protective against developing depression. The protective effect of physical activity against depression was similar among the different age groups (two trials; OR = 0.90; 95% CI, 0.83 to 0.98 for children; eight trials; OR = 0.78; 95% CI, 0.70 to 0.87 for adults; and nine trials; OR = 0.79; 95% CI, 0.72 to 0.86 for older adults). A 2018 prospective cohort study, with 33,908 healthy adults living in a rural area of Norway, examined whether exercise was protective against new-onset depression.2 Patients were followed for an average of 11 years (range = nine to 13). Those who self-reported any physical activity each week were compared with those who reported no physical activity weekly. Depression was assessed using the Hospital Anxiety and Depression Scale, a self-report questionnaire. The authors used multiple models to adjust for age, sex, marital status, social class, tobacco and alcohol use, and body mass index. Across all models, there was a statistically significant increase in the incidence of depression for those who were not physically active, compared with those who had one to two hours of physical activity per week (adjusted OR = 1.4; 95% CI, 1.2 to 1.8). Although the authors identified a dose-response relationship between total physical activity and odds of depression, there was a diminishing benefit of exercising more than one hour per week. A 2018 RCT of 61 university students (72% female; 18 to 30 years of age) evaluated the effect of exercise intensity on the development of depressive symptoms.3 Patients were randomized to six weeks of high-intensity interval training, moderate continuous training, or no exercise. Participants exercised three times a week on a stationary cycle for a total of 18 sessions. High-intensity interval training consisted of 60 seconds of high-intensity intervals with 10 60-second recovery intervals for 20-minute sessions; moderate continuous training consisted of continuous training for 27.5 minutes; the no-exercise group was told to remain sedentary. Before and after the intervention, students completed the Beck Depression Inventory (21 items, scored from 0 to 63, with higher scores indicating worse depression). Compared with the control group's change in depressive symptom scores (from 16.7 before the intervention to 23.1 after), the high-intensity interval training group and the moderate continuous training group had a significant decrease in depressive symptoms (high-intensity interval training: a score of 13.2 before the intervention to 12.2 after; P = .012 vs. no exercise; moderate continuous training: a score of 11.4 before to 9.4 after; P = .005 vs. no exercise). There was no difference in the change of scores between high-intensity interval training and moderate continuous training (P = .77). Students in the control group had a statistically significant increase in depressive symptoms throughout the intervention, which the authors attribute to the stressors of starting a university semester. Copyright © Family Physicians Inquiries Network. Used with permission. Disclaimer: Results are not guaranteed*** and may vary from person to person***. Do you constantly feel exhausted and weak, or are you frequently avoiding activities that require a lot of energy to perform? “Yes,” you may say. “But I’ve been working a lot of hours at the office, so of course I’m tired.” Some people walk around constantly feeling fatigued or indifferent toward life, believing that apathy is simply a daily part of existing. Being overworked is one thing, but continuous symptoms of weakness, fatigue, or dizziness could actually be signs of an iron deficiency. Why Iron Deficiency Occurs The labels “iron deficiency,” “anemia,” and “iron deficiency anemia” are often used interchangeably. An iron deficiency happens when there is little iron in the body. If left untreated, it can quickly progress to a form of anemia called iron deficiency anemia.Anemia transpires when you have a low count of red blood cells in your body—iron deficiency anemia is the most common form of anemia. This kicks in if your blood cells don’t have enough hemoglobin, which is the protein that helps red blood cells carry oxygen from the lungs throughout the body. Iron is imperative for the red blood cells to carry oxygen to the tissues; without the presence of iron, the red blood cells can’t carry the oxygen efficiently.In many cases, the loss of blood can contribute to low iron counts. Common causes of excessive bleeding are: Menstrual periods Cancer in the esophagus and stomach Peptic ulcer disease An iron deficiency can also occur if you have a certain disease or have recently had surgery. Some examples include: Celiac disease Crohn’s disease Gastric bypass surgery Signs and Symptoms of Iron Deficiency Symptoms of iron deficiency generally occur before it progresses to iron deficiency anemia. Mild symptoms of iron deficiency include: Grumpy moods Feeling weak or tired Constant headaches Difficulty keeping focused Moderate cases of iron deficiency can include: If iron deficiency progresses to iron deficiency anemia, the symptoms can include: Dark, tar-colored stool or blood Heavy menstrual bleeding Ulcers Weight loss The Top 10 Iron-Rich Foods If you have an iron deficiency, or if you don’t consume enough iron, I recommend you eat various whole foods, such as grass-fed meats, organic free-range poultry, and organic dairy products. Here is a list of some prime iron-rich foods: Liver: Four ounces contains 9.5 mg of iron. Spinach: One cup contains 6.6 mg of iron. Lamb: A three-ounce piece contains 1 mg of iron. Chickpeas: One cup contains 4.7 mg of iron. White beans: One cup contains 6.6 mg of iron. Kidney beans: One cup contains 5.2 mg of iron. Duck: Half a duck breast contains 3.7 mg of iron. Sardines: One can contains 3.7 mg of iron. Grass fed beef: Three ounces contains 2 mg of iron. Swiss chard: One cup contains almost 4 mg of iron. Iron-Deficiency: The Facts The Centers for Disease Control and Prevention defines iron deficiency as the top nutritional deficiency in the entire world. People in developing countries are more prone to iron deficiencies, but it is extremely common in the U.S. as well. Women who have heavy menstrual periods are more vulnerable to iron deficiencies. In the U.S., the number of people that visited a hospital emergency department in 2011 with anemia listed as their primary discharge was 237,000. In most cases, the visits were from people who were unaware they even had an iron deficiency. In 2011, the percentage of people who were diagnosed with some form of anemia was approximately 10%. In 2011, the number of discharges for first-time anemia diagnoses was 392,000. The average length of stay per patient was four days. The mortality statistics for anemia or iron deficiencies in 2011 were 4,894; this worked out to about 1.5 deaths per every 100,000 Americans. If Left Untreated If iron deficiency anemia is left untreated, it can lead to severe heart problems, chest pains, or even fainting. Without iron, the blood cannot properly carry oxygen to the heart and brain, which will eventually cause both to slow down later on. Untreated iron deficiency anemia can also cause the immune system to become weak, to the point where infectious diseases will become more frequent. If you believe you have an iron deficiency, make sure to visit your doctor to get tested. Sources: “Anemia or Iron Deficiency,” Centers for Disease Control and Prevention web site, April 8, 2015; . “Iron,” The World’s Healthiest Foods web site; last accessed May 14, 2015. “Iron deficiency anemia,” MedlinePlus web site; last accessed May 14, 2015. Pullen, L.C., “USPSTF: Evidence Lacking for Iron Deficiency Screening,” Medscape web site, March 31, 2015; . Rogers, R., “Signs and Symptoms of Low Iron in Women,” Livestrong.com, April 13, 2015; .