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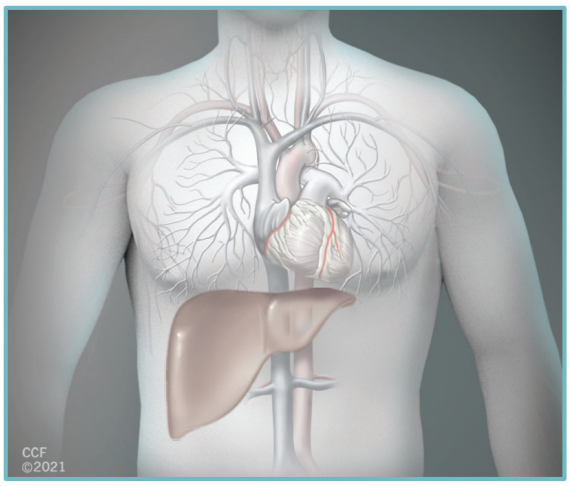

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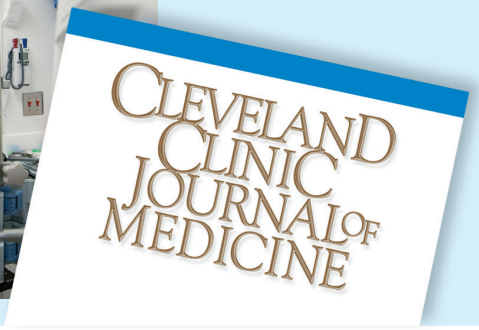

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Sometimes the look is worth the walk

I have always liked looking at blood smears. I am not especially skilled at interpreting them, but I like looking at blood cells under a microscope. And I have had some interesting related experiences. My 7th grade science fair project included the identification of a lectin extracted from a shrub in my front yard that selectively agglutinated type A2 erythrocytes. (Thank you, Harvey, for letting that young boy into your lab in the National Institutes of Health blood bank.) A small piece of personal trivia: "Harvey" is Dr. Harvey J. Alter, the physician scientist who was awarded a Nobel Prize in Physiology or Medicine in 2020 for his work on discovering hepatitis C.

Later, as an undergraduate in Saint Louis, I was repeatedly staring through a microscope counting rabbit neutrophils in chemotactic chambers and synovial fluids from experimentally induced arthritis.

Later still, as a medical intern, it seemed appropriate that I should look at blood smears from patients with unexplained anemia. That is why on my second night on call at the Hospital of the University of Pennsylvania in 1980, looking for the hematology lab, I got lost and locked in a stairwell somewhere behind the pathology department. I was in the stairwell for more than an hour before being rescued by a security guard. Once I found the lab, finding the smear was easy, as blood smears were apparently made at that time for all requested complete blood counts (CBCs) with differential. The stairwell experience was memorable, but so was the patient whose anemia from massive acute hemolysis was attributed to *Clostridium* bacteremia.

Nowadays, even if a physician orders a blood smear, it may not be reviewed by a pathologist unless the CBC is "flagged" by one of the sophisticated automated blood analyzers. This is surely workflow-efficient and appropriate given the relatively low likelihood of a specific diagnosis coming from most smears. But a low likelihood is not zero and, as demonstrated by Candelario and Klein[1] in this issue of the *Journal*, a diagnosis can occasionally be expeditiously made with a few minutes of eyeball time. In 2005, Bain[2] presented a nice discussion on behalf of the simple blood smear, and it is still relevant and worth a read.

Today, residents do not routinely look at blood smears, nor do I. The driving forces of expediency and efficiency are strong. Time spent on activities that have a low yield for influencing care and limited yield in clinical education needs to be limited. Picture a mixture of curiosity and eye-rolling when I take trainees to the microscope. And yet, for some conditions in some patients, going back to the basics can be clinically rewarding, and even memorable.

In the patient presented on page 8 by Candelario and Klein, clues from the history suggested the likely diagnosis, but the constellation of lab findings in their patient (evidence for hemolysis in the setting of pancytopenia and an elevated lactate dehydrogenase) could also suggest diagnoses that might easily have spurred a flurry of imaging and laboratory tests in a 75-year-old patient with "altered mental status" and macrocytic anemia. If this case were presented at a rheumatology clinical conference,

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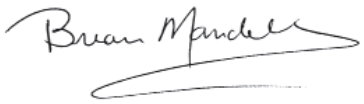
in a patient with these lab abnormalities, consideration would be given to the diagnosis of thrombocytopenic microangiopathic syndrome or myelodysplasia with an associated autoimmune hemolytic anemia. But that was not the case, and the simple blood smear revealed the likely diagnosis. And I think that is a pretty cool message.

As we start 2022, our hospitals here are full and our emergency departments overflowing. Our COVID-19 units are straining, filled mainly with previously unvaccinated patients. Elective surgeries are being postponed in order to preserve bed space. Some days it is impossible to admit even a very ill patient directly to the hospital from my clinic. We are weighing even more carefully than usual the need to immediately initiate immunosuppressive therapies in patients with diseases that threaten organs or quality of life, balancing concern over disease progression vs concern over poor outcome from COVID natural infection or blunting the efficacy of a pending vaccine 3rd dose or booster. Fortunately, it seems that most of our medications are not adversely affecting the outcome from COVID infection.

Yet we are not sanguine about this. There is concern over what the omicron variant, influenza, and continued social resistance to vaccination and masking will bring. A few visible members of our medical community continue to put forth profound misinformation without receiving professional or social sanctions. This is not attributable to academic difference of opinion or open discourse any more than yelling "fire" in a crowded building is free speech. It is rare but ongoing, while our ICUs are packed and frontline physicians, nurses, and other healthcare workers are suffering enormous physical and emotional stress caring for patients whose severe disease may well have been preventable.

Still, there is hope from knowing that antivirals with efficacy in preventing severe disease are coming out of clinical studies, and the vaccination rates are still rising, even if slowly. And there is comfort in seeing the genuine kindness and compassion offered by medical caregivers to patients who would otherwise be isolated and alone.

On behalf of all my editorial colleagues, I wish you—our readers and fellow passengers on this strange roller coaster of life—a safe, healthy, and peaceful 2022.



Brian F. Mandell, MD, PhD
Editor in Chief

1. **Candelario N, Klein C**. Megaloblastic anemia due to severe vitamin B_{12} deficiency. Cleve Clin J Med 2022; 89(1):8–9. doi:10.3949/ccjm.89a.21041
2. **Bain BJ**. Diagnosis from the blood smear. N Engl J Med 2005; 353(5):498–507. doi:10.1056/NEJMra043442

2022

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Cleveland, OH

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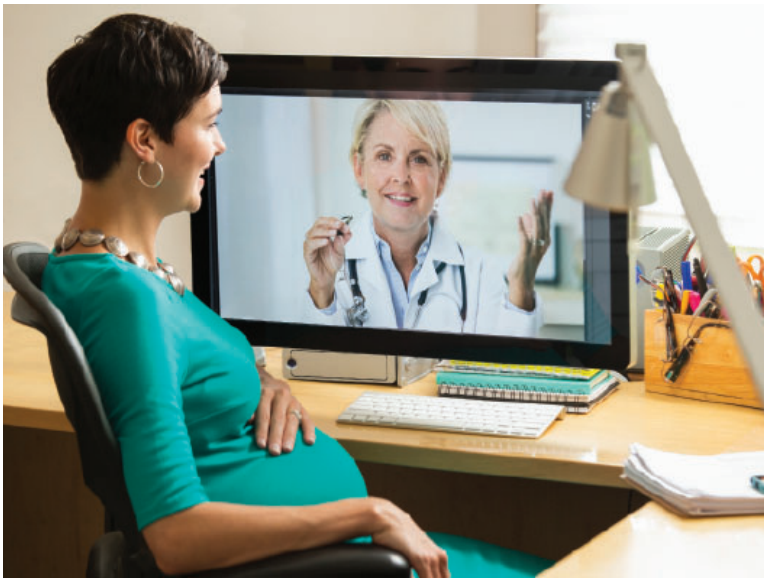
Improve Your Virtual Patient Visit Skills



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With the exception of the physical examination module, these activities have been approved for *AMA PRA Category 1 Credit™*.

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Megaloblastic anemia due to severe vitamin B_{12} deficiency

Megaloblastic anemia is commonly related to vitamin B_{12} or folate deficiency

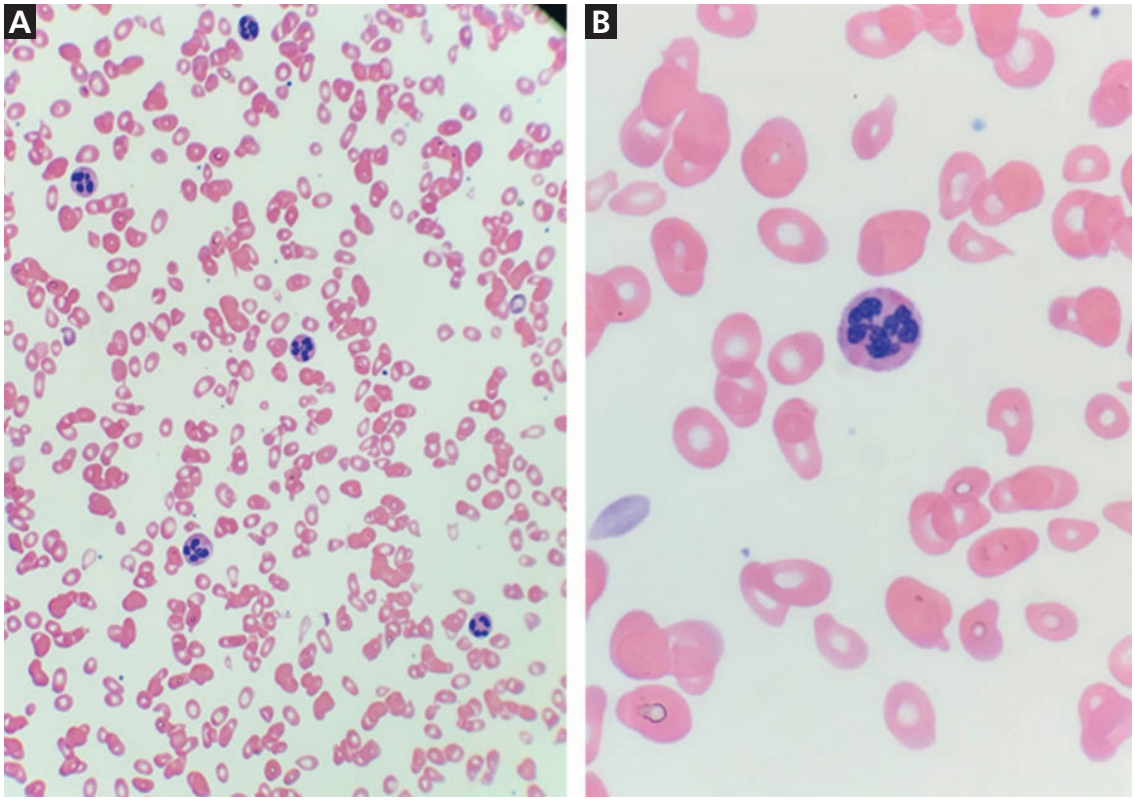

Figure 1. Peripheral blood smears show hypersegmented neutrophils consistent with megaloblastic anemia. Panel A (hematoxylin and eosin, magnification × 40) shows neutrophils with hypersegmented multilobed nuclei (more than 5 lobes, dark blue stain) in a background of anisocytosis with macrocytes, ovalocytes, and thrombocytopenia. Panel B (hematoxylin and eosin, magnification × 100) shows a neutrophil (stained dark blue) with multilobed nuclei.

A 75-year-old man presented to the hospital with altered mental status and pancytopenia. He had a history of schizophrenia and gastrointestinal bleeding due to peptic ulcer disease, for which he had undergone subtotal gastrectomy.

Results of a complete blood cell count at presentation showed the following:

- Hemoglobin 5.5 g/dL (reference range 14.5–18.1)
- Hematocrit 17.5% (42.0–54.0)
- Mean corpuscular volume 108.7 fL (80–100)
- White blood cell count 3.5 × 10^9/L (4.41–10.05)
- Platelet count 54 × 10^9/L (150–400)
- Lactate dehydrogenase 3,320 U/L (90–285)

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- Haptoglobin < 10 mg/dL (33–171)
- Total bilirubin 2.6 mg/dL (< 1.2)
- Indirect bilirubin 1.8 mg/dL (< 1.2).

Results of an iron panel study were consistent with anemia of chronic inflammation with serum iron 177 µg/dL (40–150), total iron binding capacity 179 µg/dL (280–500), iron saturation 98.89%, and ferritin 408 ng/mL (40–400). The reticulocyte percentage was 1% with a reticulocyte index of 0.17%, indicating a hypoproliferative type of anemia.

In addition, the vitamin B_{12} level was low at 93 pg/mL (220–600), serum folate was normal at 8.2 ng/mL (> 3), homocysteine was elevated at 138 µmol/L (0.0–19.2), and methylmalonic acid was elevated at 25,024 nmol/L (0.0–378). A peripheral blood smear (**Figure 1**) showed the presence of macrocytosis, thrombocytopenia, and hypersegmented neutrophils (ie, with multiple lobes in nuclei). These findings, consistent with megaloblastic anemia, confirmed the diagnosis of megaloblastic anemia due to vitamin B_{12} deficiency.

MEGALOBLASTIC ANEMIA: DIAGNOSTIC CLUES

Macrocytic and megaloblastic anemia from vitamin B_{12} deficiency leads to defective DNA synthesis in hematopoietic precursors manifesting as pancytopenia and hemolysis owing to ineffective hematopoiesis. Megaloblastic anemia is commonly related to vitamin B_{12} or folate deficiency.[1–4] Important differential diagnoses to consider include medication side effects (eg, methotrexate, chemotherapy, or antibiotics such as trimethoprim), and malabsorption due to an anatomic or autoimmune cause (pernicious anemia), as well as a primary bone marrow pathology such as myelodysplastic syndrome.

In this patient, megaloblastic anemia was diagnosed based on clinical and laboratory findings of severe vitamin B_{12} deficiency, for which subtotal gastrectomy is a known predisposing factor.

CASE CONCLUSION

The patient was immediately started on vitamin B_{12} 1,000 µg weekly by intramuscular injection. Several days after the start of treatment, repeat testing showed improving bone marrow recovery, with an increase in reticulocyte count and normalization of lactate dehydrogenase. At 2 weeks, the patient experienced significant improvement in complete blood cell count and mental status. ■

At 2 weeks, the patient experienced significant improvement in complete blood cell count and mental status

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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A large, painless bulla on the right foot

Bullosis diabeticorum is a noninflammatory blistering condition that affects patients with prediabetes and diabetes

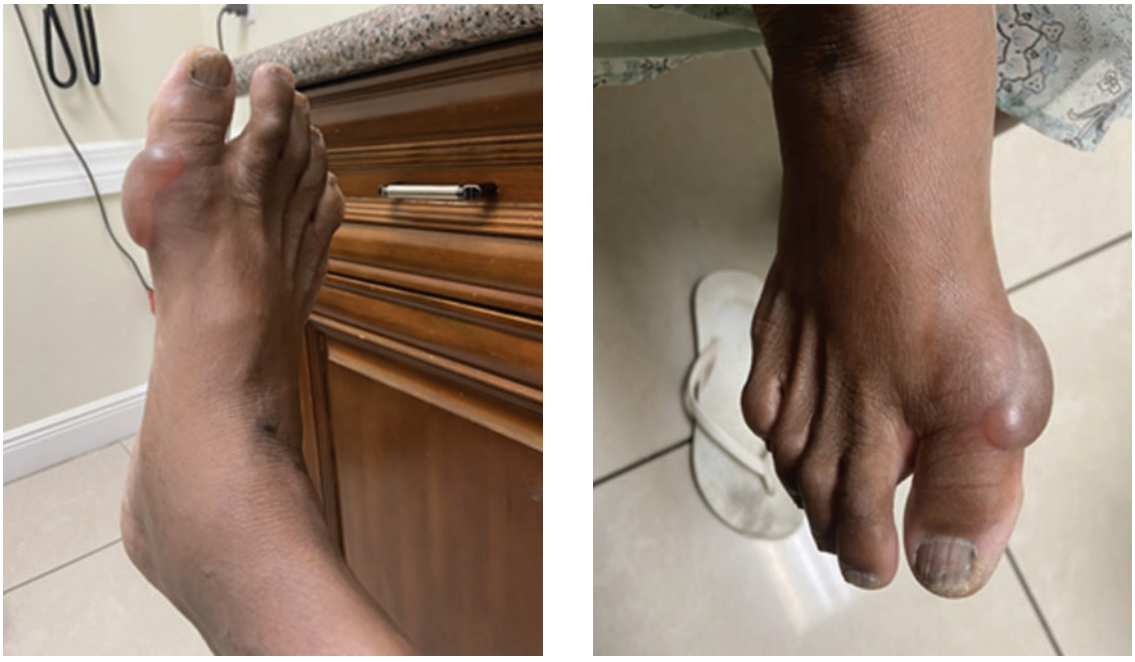

Figure 1. A large, tense, noninflammatory bulla 3.75 cm in diameter at the base of the first metatarsal joint of the right foot. The bulla contained clear fluid.

A 71-year-old woman with a history of diabetic neuropathy presented with a large, painless bulla on her right foot. She said it had started as a small vesicle but had slowly enlarged over the past 3 days. She had been working in her yard for several days prior to the development of the vesicle but did not sustain any insect bites or local trauma. She reported no fever or chills, and she had no history of skin vesicles or bullae or similar lesions on other parts of her body. No new medications had been recently prescribed.

Her medications at the time of presentation included metformin extended-release 500 mg once daily, insulin lispro protamine–insulin lispro (75/25) 35 units twice daily, anastrozole 1 mg daily, and gabapentin 600 mg twice daily. She was not employed, mostly stayed at home, and had no history of smoking or alcohol or drug use. Comorbidities included breast cancer treated with chemotherapy and radiotherapy 1 year previously, type 2 diabetes mellitus with peripheral neuropathy, and hyperlipidemia.

On physical examination, the patient's vital signs were normal, and examination of the extremities revealed a large, tense, noninflammatory bulla at the base of the first metatarsal joint of the right foot, 3.75 cm in diameter and containing clear fluid (**Figure 1**). There were

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no other lesions on the extremities or trunk and no signs of local inflammation or spontaneous drainage. She had decreased perception to monofilament on both feet with normal peripheral pulses. As the bulla contained clear fluid, it was presumed to be sterile and thus, to avoid the risk of secondary infection, aspiration was not attempted. At a 4-week follow-up visit, the lesion had completely resolved, and the patient did not report any recurrence (**Figure 2**).

Laboratory testing during the follow-up visit revealed a hemoglobin A1c of 10.3% (reference range < 5.7%), serum creatinine 0.87 mg/dL (reference range 0.60–0.93 mg/dL), and albumin-to-creatinine ratio 12 µg/mg creatinine (reference range < 30 µg/creatinine). Results of other laboratory testing were normal, including complete blood cell count, alanine transaminase, aspartate transaminase, total protein, and albumin.

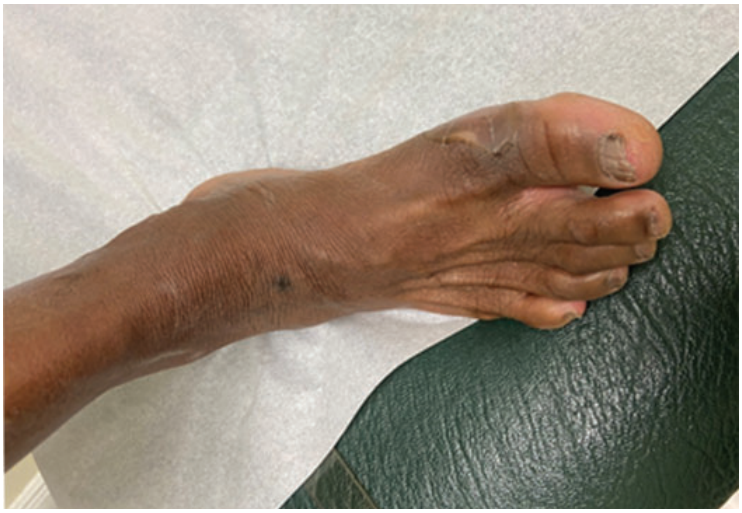

Figure 2. At a 4-week follow-up visit, the lesion had completely resolved with no signs of recurrence.

BULLOUS DISEASE OF DIABETES

Bullosis diabeticorum is a noninflammatory blistering condition that affects patients with prediabetes and diabetes.[1] The condition was first reported by Kramer in 1930, and the name was coined by Cantwell and Martz in 1967.[2] The blisters are tense with serous content. They are recurrent and spontaneous around acral regions, particularly on the lower extremities, including the toes and plantar area of the feet. They can also be present on the hands and forearms. They seldom present on the trunk.[3–7] Vesicles and bullae can range in size from 0.5 cm to several centimeters. It is a rare disease, affecting approximately 0.5% of diabetic patients. Men are twice as likely as women to develop the condition.

Because bullosis diabeticorum mostly affects patients with diabetes mellitus who have associated nephropathy and neuropathy, it has been postulated that microangiopathy and disturbances in carbohydrate metabolism may lead to premature aging of connective tissue and other structural alterations in connective tissue,[8] increasing the risk of spontaneous appearance of these lesions.[2] The lesions are usually self-limited and heal within 4 to 6 weeks without scarring.[5]

Treatment is conservative, and the blister should be kept clean and protected to avoid secondary infection. No antibiotic therapy is required, although fluid aspiration and culture with use of oral antibiotics may be considered if secondary bacterial infection is suspected.[6] Signs of possible infection include erythema, warmth, edema with surrounding inflammation, the presence of purulent fluid or drainage, and fever. The etiology is unclear.

Men are twice as likely as women to develop bullosis diabeticorum

The differential diagnosis for bullosis diabeticorum includes insect bite reaction, contact dermatitis with bullae, poison ivy dermatitis, bullous drug eruption, bullous impetigo, edema bullae, burns, and friction blister.[7] Unlike friction blisters, bullosis diabeticorum often develops overnight and in the absence of known trauma.[2] Friction blisters are generally associated with high levels of exercise and activity and are often seen in active military personnel or athletes with no underlying health issues, whereas bullosis diabeticorum commonly presents in the absence of foot trauma or pressure in vulnerable populations. Although rare, recurrent episodes leading to severe infection and ulceration have been described, with some bullae recurring years after the initial appearance.[9]

TAKE-HOME POINTS

Bullosis diabeticorum may be the first clinical presentation of hyperglycemia.[2] Bullosis diabeticorum in patients with diabetes often signals poor diabetes control or the existence of associ-

ated neuropathy or nephropathy. Patients with this condition should be routinely screened for diabetes and for microscopic proteinuria and assessed for findings of peripheral neuropathy. Supportive care of the lesions with monitoring for signs of secondary infection is advised.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Clinical impact of 2020 American Heart Association statement on menopause and cardiovascular disease risk

ABSTRACT

The American Heart Association published a 2020 scientific statement on cardiovascular disease risk for women transitioning through or experiencing menopause. The report reflects scientific evidence on menopause and cardiovascular risks, and this article reviews the statement with a focus on what is new and what is clinically important for healthcare providers treating this patient population.

KEY POINTS

The American Heart Association 2020 scientific statement supports the notion that the transition of menopause itself, independent of chronological and ovarian aging, leads to increased cardiovascular risk and mortality.

The physiological changes that take place during the female reproductive life span (extreme early age at menarche, pregnancy disorders, preterm births, adverse pregnancy outcomes, early age at menopause, and menopause) are associated with cardiometabolic risk.

Female patients in midlife should be routinely counseled on lifestyle interventions aimed at achieving ideal cardiovascular health: smoking cessation, weight management, optimization of cholesterol levels and blood pressure and fasting blood glucose, daily physical activity, and dietary approaches to stop hypertension.

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Cardiovascular disease (CVD) is the leading cause of mortality for women worldwide.[1,2] Women typically develop CVD several years later than men, although "this female advantage gradually disappears with aging, particularly after menopause when cardiometabolic risk factors accumulate."[3] The physiological changes that take place during the different stages of the female reproductive life span, such as extreme early age at menarche, pregnancy disorders, preterm births and adverse pregnancy outcomes, early age at menopause (< 40 years), and menopause, are factors associated with cardiometabolic risk.[2,4,5]

In December 2020, the American Heart Association (AHA) published a scientific statement focused on menopause and CVD risk with the intent of increasing awareness of adverse cardiometabolic health-related changes accompanying female patients midlife.[1] Adverse changes in body fat distribution, lipids, lipoproteins, and structural and functional measures of vascular health take place during the transition to menopause, seen as a time of accelerating CVD risk.[1,6]

CLINICAL SETTING

The field of menopause is continuously evolving as studies are completed regarding best treatment options for female patients dealing with menopause-related symptoms and risk for CVD. This review focuses on the 2020 AHA scientific statement for the purpose of raising

clinician awareness of the significant adverse cardiometabolic health-related changes and mitigation of CVD risk in this patient population.[1]

INTENDED AUDIENCE

This review is intended for healthcare providers who manage female patients in the middle of their lives transitioning to or experiencing menopause in the outpatient setting including the primary care, cardiovascular, endocrinology, and gynecology environments.

WHO WROTE THE GUIDELINES?

The guidelines were completed by the American Heart Association Prevention Science Committee of the Council on Epidemiology and Prevention and the Council on Cardiovascular and Stroke Nursing, composed of a collaboration of physicians and researchers. The documents were peer-reviewed by the American Heart Association Office of Science Operations.

WHAT ARE THE MAIN RECOMMENDATIONS?

Menopause, independent of chronological and ovarian aging, leads to increased cardiovascular risk and mortality

The December 2020 AHA scientific statement reviewed longitudinal research supporting the notion that the transition of menopause itself, independent of chronological and ovarian aging, leads to increased cardiovascular risk and mortality.[1] Previous AHA guidelines for the prevention of CVD recommended that female patients in midlife should be evaluated for potential contributors to poor cardiovascular health (ie, smoking, overweight or obesity, hypertension, diabetes, etc.), stratified into categories of risk (ie, ideal cardiovascular health, at risk, and high risk), and then counseled accordingly.[7,8] While previous studies have noted that premature menopause (< 40 years old) and early menopause (40 to 45 years old) can increase the risk of CVD, clinicians should now also recognize menopause in general as a risk factor.[1–5]

The clinical recommendations highlighted in the scientific statement focus on the role of lifestyle intervention, lipid-lowering medications, and menopausal hormone therapy (HT) in the prevention of CVD during the critical window of midlife of the female patient.[1]

Lifestyle interventions

Female patients traversing menopause in midlife should be routinely counseled on lifestyle interventions aimed at achieving ideal cardiovascular health. In accordance with the AHA Life's Simple 7 components,[1,9] to achieve ideal cardiovascular health, interventions should involve the following:

- Smoking cessation
- Weight management to achieve an ideal body weight (body mass index < 25 kg/m^2)
- Optimization of cholesterol levels: total cholesterol < 200 mg/dL, low density lipoprotein cholesterol (LDL-C) < 100 mg/dL, high density lipoprotein cholesterol (HDL-C) > 50 mg/dL, triglycerides < 150 mg/dL, non–HDL-C < 130 mg/dL)
- Optimization of blood pressure levels (< 120/80 mmHg)
- Optimization of fasting blood glucose (goal < 100 mg/dL)
- Engaging in at least 150 min/week of moderate-intensity exercise or 75 minutes per week of vigorous exercise (or a combination of both)
- A DASH (Dietary Approaches to Stop Hypertension) diet.[1,7–9]

Aspirin use

While not discussed in detail in this scientific statement, previous AHA guidelines have outlined that aspirin use in female patients without cardiac risk factors and under the age of 65 is not recommended for primary prevention of heart attack.[7,8]

Lipid-lowering interventions

First-line intervention strategies for the optimization of lipids in midlife female patients include lifestyle modifications such as regular exercise, maintaining ideal body weight, smoking abstinence, and eating a heart-healthy diet.[1,7,8]

It is unclear whether supplementation and/or dietary intake of foods rich in omega-3 and omega-6 fatty acids are associated with reduced coronary heart disease, myocardial infarction, reduced total cholesterol levels, or decreased rates of cardiovascular or all-cause mortality, leaving it uncertain what effects, if any, omega-3 and omega-6 fatty acids have on CVD prevention in midlife women.[7] Con-

sumption of omega-3 fatty acids in the form of fish or in capsule form (eg, eicosapentaenoic acid 1800 mg/d) may be considered in women with hypercholesterolemia and/or hypertriglyceridemia for primary and secondary prevention.[7]

The role of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (ie, statins) for CVD risk reduction in women in midlife remains controversial. Current guidelines still recommend statins as first-line therapy for risk reduction of CVD in patients with LDL-C ≥ 190 mg/dL, diabetes, and patients 40 to 75 years old at sufficiently elevated CVD risk.[1,8] However, the literature surrounding these recommendations is conflicting and not well-differentiated by gender. While there have been several randomized controlled trials demonstrating reduced atherosclerotic CVD risk in patients using statin therapy for primary prevention in mixed gender studies, there have also been multiple studies that have not shown significant reductions in women specifically.[10–16] The Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial demonstrated a reduction in arterial revascularization in a subgroup of female patients > 60 years old, but did not find a statistically significant decrease in myocardial infarction or all-cause mortality with statin use across the entire female cohort.[1,10] In the Management of Elevated Cholesterol in the Primary Prevention Groups of Adult Japanese (MEGA) study that followed a large female cohort for >5 years of statin therapy, the impact on CVD and all-cause mortality was null.[1,11] The Heart Outcomes Prevention Evaluation-3 (HOPE-3) trial also looked at sex-specific data and found that statin therapy had a nonsignificant effect on CVD and all-cause mortality.[1,12] Multiple meta-analyses found mixed results regarding lipid lowering medications affecting prevention of total or CVD mortality or risk factors in general; for female patients with known CVD, medications reduced cardiovascular events and mortality as well as nonfatal myocardial infarction but did not impact total mortality.[13–16]

The AHA scientific statement noted that data for primary and secondary prevention and improved survival with lipid-lowering medications in women remains elusive, and nonpharmacological therapies are currently first-line strategies for improving lipid profiles.[1] Additionally, given diabetes is a known risk factor for CVD, it is important to note that there have been studies suggesting an increased risk of diabetes associated with statin use in postmenopausal female patients.[17]

The most common nonstatin therapies are bile acid sequestrants, cholesterol absorption inhibitors, and proprotein convertase subtilisin/kexin type 9 inhibitors that may be used in addition to or instead of statins for cholesterol reduction in select patients.[1,7,8] The use of these medications in the primary prevention of CVD in both men and women is still in question and warrants sex-specific trials to determine efficacy.

Supplements

There are currently no vitamin or antioxidant supplements recommended for primary or secondary prevention of CVD.[1,7,8]

Menopausal hormone therapy

Currently, no data are available on the effects of menopausal HT on the cardiometabolic health of perimenopausal women.[1] Evidence varies regarding the effects of HT on atherosclerosis and CVD event progression by age and timing of HT initiation.[1] The use of HT and selective estrogen receptor modulators for primary or secondary prevention of CVD and stroke in postmenopausal women is not currently recommended.[1] However, according to the AHA scientific statement, post-hoc and longitudinal research suggests that HT initiated early among patients with premature or surgical menopause and within 10 years of natural menopause is associated with cardiovascular benefit.[1] Additionally, the use of hormone replacement therapy to mitigate certain deleterious effects of early estrogen loss is currently considered the standard of care.[18]

Significant adverse cardiometabolic changes occur in women in midlife

WHAT IS DIFFERENT FROM PREVIOUS GUIDELINES?

The most paramount distinction introduced in the 2020 AHA scientific statement is the identification of the menopause transition as a risk factor for CVD.[1] The 2011 AHA Guidelines did not classify menopause, early meno-

pause, or surgical menopause as a risk factor for CVD, nor did it address menopause and its cardiometabolic significance.[7] While the 2019 AHA guidelines on primary prevention of CVD identify early menopause as a possible risk factor for CVD, it does not address the consequences of natural menopause.[8]

DO OTHER SOCIETIES AGREE OR DISAGREE?

The current AHA scientific statement stands in agreement with multiple other national medical societies in the field of menopause, including the North American Menopause Society, the American College of Obstetricians and Gynecologists, the Endocrine Society, the American College of Endocrinology, and the American Association of Clinical Endocrinologists.[18–20] These prominent organizations recognize the cardiometabolic changes of menopause as a risk factor for CVD and suggest that for healthy, recently menopausal patients, the benefits of HT outweigh the risks.[18–20] In congruence with the AHA, none of these societies currently recommend the use of HT for primary prevention of CVD.[18–20] The North American Menopause Society does, however, recommend the use of HT, to mitigate physiologic consequences of early estrogen loss, until at least the median age of menopause (52 years old) in patients without contraindications who undergo menopause early or prematurely.[18] All of these societies endorse lifestyle modifications and statin therapy, when appropriate, for reduction of CVD risk in midlife women.[18–20]

Midlife female patients should be counseled on lifestyle interventions to achieve ideal cardiovascular health

HOW WILL THIS CHANGE DAILY PRACTICE?

The 2020 AHA scientific statement identifies a crucial gap in the healthcare of female patients in midlife.[1] Currently, there is a widespread missed opportunity to educate women about the health risks associated with menopause. The AHA recommends that female patients be routinely counseled on lifestyle interventions aimed at achieving ideal cardiovascular health and suggests clinicians explain to patients that these lifestyle modifications are important to help counteract the consequences of the estrogen loss that occurs at the menopausal transition.[1]

There is also a current critical unmet need for individualized counseling on the indications and benefits of HT as a treatment option for menopausal women. The ramifications of menopausal HT on the cardiovascular health of female patients has been a source of great debate among healthcare providers in recent decades and first arose in 2002, when the Women's Health Initiative published its initial results suggesting an increased risk of cardiovascular events among postmenopausal patients treated with HT.[21] Post-hoc analyses of the data and other subsequent studies showed no risk or a reduction in cardiovascular risk when HT was initiated at or before the age of 60, and/or within 10 years of the last menstrual period.[22–25] Despite this, controversy around the safety of HT has remained prevalent, resulting in a sharp decline in the number of HT prescriptions written since 2003.[26] For this reason, the 2020 AHA scientific statement regarding cardiometabolic changes and CVD risk throughout the transition into menopause will be an important milestone in the healthcare of female patients in midlife.[1] This is a significant clinical consideration because the development of chronic disease states are commonly diagnosed around the menopause transition, often coinciding with the time that patients are seeking medical treatment for menopausal symptoms.

The updated position of the AHA on menopause represents a turning point in the healthcare of female patients that should not be underestimated. The scientific statement published by the AHA will hopefully go a long way in facilitating the dissemination and understanding of decades of evidence-based research regarding the treatment of menopause.

WHEN WOULD GUIDELINES NOT APPLY?

The AHA recommendations to recognize the cardiometabolic changes during the transition to menopause, menopause, and the midlife of women as important risk factors for CVD and mortality would apply to all patients who lose ovarian hormone production, regardless of when this loss occurs. Guidelines on the use of HT would not apply to patients with possible contraindications to estrogen therapy, such as medical history of unexplained vaginal bleeding, severe active liver disease, porphyria

cutanea tarda, estrogen-sensitive malignancy, stroke, pulmonary embolism, deep vein thrombosis, dementia, and unstable coronary heart disease.

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Discontinuing antidepressants: Pearls and pitfalls

ABSTRACT

Stopping antidepressants can be challenging due to the high rate of discontinuation symptoms. Patients with antidepressant discontinuation syndrome (ADS) commonly experience insomnia, flu-like symptoms, mood disturbances, dizziness, and paresthesias, but a broad array of adverse effects is possible. Symptoms can last for days to months, and different symptoms have different durations. Patient education, identification of patients most at risk for developing symptoms, and a slow antidepressant taper or cross-taper are important steps in mitigating the risk of ADS and managing patient concerns about ADS. Tapers should be carried out over weeks to months. Discontinuation symptoms should be managed with restarting the prior dose of antidepressant and then tapering even more slowly, with additional symptomatic management as needed.

KEY POINTS

Changing or stopping antidepressants, especially if done abruptly, can be associated with ADS.

Symptoms can present within hours and last for months due to the complex mechanisms of antidepressants.

Slow tapers should be carried out over weeks to months to minimize the risk of ADS.

Knowing risk factors for ADS can identify the most vulnerable patients.

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An ever-increasing number of patients are prescribed antidepressant medications, most often by primary care physicians,[1] with approximately 12.7% of the adult population in the United States prescribed a daily antidepressant.[2] Antidepressants are used to treat a variety of conditions other than mood and anxiety disorders, such as chronic pain syndromes, tobacco use disorder, and obsessive-compulsive disorder. Common scenarios prompting discontinuation of an antidepressant include the following:

- The condition for which the antidepressant was started is in remission for an appropriate maintenance period
- The antidepressant does not achieve a satisfactory effect[3,4]
- Intolerable side effects emerge
- New drug-drug interactions occur due to additional medication the patient must take
- The patient's prescription drug insurance coverage changes.

In the case of insurance coverage, clinicians are encouraged to advocate for the patient whenever a coverage issue arises in order to avoid changing antidepressants. Additionally, patients may choose to stop an antidepressant of their own accord.

Stopping antidepressants can be challenging because of the frequency of antidepressant discontinuation syndrome (ADS). Discontinuation symptoms occur commonly and vary in severity.[5] Symptoms will often surprise and frighten patients who are not forewarned, leading them to seek emergency medical care. Discontinuation symptoms include insomnia, flu-like symptoms, mood disturbances, dizziness, paresthesias ("brain zaps"), and a broad array of other adverse effects.[6,7]

TABLE 1

Clinical syndromes after discontinuing antidepressants

Condition	Category	Onset, duration	Symptoms
Discontinuation syndrome	Acute withdrawal	Onset 36–96 hours Duration < 6 weeks	New symptoms not present before antidepressant was started or stopped
	Rebound	Onset 36–96 hours Duration < 6 weeks	Greater severity of original symptoms
	Persistent withdrawal syndrome	Onset 24 hours to 6 weeks Duration > 6 weeks	New symptoms and/or greater severity of original symptoms
New episode	Relapse	Onset < 6 weeks Duration variable	Original symptoms at original severity
	Recurrence	Onset > 6 months Duration variable	Original symptoms at original severity

Based on information in reference 9.

The range of risk factors for ADS indicates the complex mechanisms underlying discontinuation symptoms beyond acute medication cessation. But despite the frequent morbidity associated with stopping antidepressants, there is a notable lack of guidance for clinicians on tapering antidepressants or managing ADS,[8] and the majority of available guidelines are not considered evidence-based.[5] The following narrative review describes the array of discontinuation symptoms and their causes and provides practical clinical guidance for discontinuing antidepressants to minimize the risk of ADS. The principles discussed regarding medication discontinuation and switching to another antidepressant can be applied regardless of the antidepressant indication.

SYMPTOMS AND RISK OF ANTIDEPRESSANT DISCONTINUATION

ADS can pose diagnostic challenges because many symptoms of discontinuation overlap with those of toxicity and recurrence. ADS should be suspected if the patient reports either new symptoms that were not part of the original presentation or symptoms noted in the original presentation but at greater severity.[9]

ADS can be conceptualized into 3 categories: acute withdrawal (new symptoms for < 6 weeks), rebound (same symptoms with greater severity for < 6 weeks), and persistent withdrawal (new symptoms or same symptoms with greater severity for > 6 weeks). By contrast, new episodes of the original condition can occur after discontinuation, including relapse (same symptoms at the same severity emerge < 6 weeks) and recurrence (same symptoms at the same severity emerge > 6 months).[9] These definitions are summarized in **Table 1**.[9]

ADS can pose diagnostic challenges because symptoms of discontinuation may overlap with those of toxicity and recurrence

Risk of relapse

Patients who stop antidepressants, regardless of the specific psychiatric indication or duration of taper, are at a greater risk of relapse of psychiatric illness than those patients who remain on antidepressants.[10] A large meta-analysis[10] found the rate of 12-month relapse was 2.3 times higher in patients who had stopped antidepressants compared with those who continued treatment. Of patients who stopped antidepressants, 44.8% experienced a relapse or recurrence within 12 months compared with 19.5% of patients who continued antidepressants. The patients who stopped antidepressants also demonstrated a median time

to recurrence of about 14 months, compared with 48 months for patients who continued antidepressants.[10] Therefore, it is especially critical to distinguish between a recurrent episode and ADS.

Studies have shown that 27% to 86% of patients who attempt to stop antidepressants, whether on their own or under supervision of a physician, experience ADS.[11] One review[11] included studies ranging from randomized clinical trials to online surveys, with a weighted average of 56%. Of patients experiencing discontinuation symptoms, 86.7% reported ongoing symptoms at 2 months, 58.6% at 1 year, and 16.2% beyond 3 years.[11] Persistent discontinuation symptoms, often termed protracted withdrawal syndrome, is not formally defined but should be diagnosed when discontinuation symptoms persist beyond several months. Data from an Internet forum for patients[12] identified a mean duration of 37 months and a median duration of 26 months in persistent symptoms. Of forum users identified as having protracted withdrawal, 73.9% experienced various physical symptoms, 82.6% experienced affective symptoms, and 63.8% experienced both physical and affective symptoms. Sleep disturbances (43.5%) and cognitive symptoms (31.9%) were also very common.[12]

To simplify recognition of ADS, use the mnemonic FINISH: flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal

Symptoms vary by drug class

Symptoms of ADS present across a range of organ systems and vary based on the antidepressant class and individual medication. **Table 2** summarizes the most typical symptoms, though symptoms can vary by individual medication since many medications, even within the same class, have different receptor profiles and affinities.[6,7,13,14] There is relatively little information available on tricyclics, tetracylics, and monoamine oxidase inhibitors (MAOIs) relative to selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), in part because symptoms were often thought to be psychosomatic[13] and not of much importance at a time when tricyclics, tetracyclics, and MAOIs were more commonly used.[9]

There are also only limited data on atypical antidepressants such as mirtazapine and bupropion and newer medications such as vortioxetine and levomilnacipran.

A useful diagnostic mnemonic

To simplify recognition of ADS, clinicians can use the mnemonic FINISH for flu-like symptoms, insomnia, nausea, imbalance (dizziness), sensory disturbances (parasthesias, including brain zaps), and hyperarousal (anxiety, irritability),[15] which are fairly generalizable across antidepressant classes.

Suicidal ideation, panic, and other risks

Discontinuation of antidepressants can carry significant risk, including suicidal ideation, suicide, and mania. One study[16] of 73 patients investigating the role of adjunctive psychotherapy in antidepressant discontinuation had to be stopped due to ethical concerns stemming from lack of efficacy and a patient suicide. Another study[17] observed 28 patients undergoing antidepressant discontinuation and found suicidal ideation in 4 patients, all of whom were stopping paroxetine.

Panic and restlessness due to ADS likely exacerbate suicidal ideation, which in most cases is probably due to ADS rather than relapse.[6] Patients treated for panic disorder should be closely monitored for rebound.

Cessation of antidepressants can also elicit mania or hypomania. Although it is more frequent that patients experience depression following antidepressant discontinuation, the phenomenon of mania due to antidepressant cessation has been observed in at least 24 cases across various antidepressants.[18]

Brain zaps: Unpleasant, sometimes disabling

Another notable discontinuation symptom is a type of paresthesia known colloquially as "brain zaps," unpleasant and sometimes disabling electric shock-like sensations. These sensations may be due to adrenergic withdrawal. Therefore, SNRIs are expected to have a higher likelihood of causing brain zaps than SSRIs. Disproportionately higher rates of brain zaps are reported with venlafaxine but also with paroxetine, and they have been reported with many antidepressants.[19]

Electric shock-like sensations are most often seen in patients who have abruptly stopped antidepressant treatment or missed doses, though more than 30% of patients with brain zaps report these symptoms either while undergoing a taper or after completing a taper. Some patients may experience the zaps during normal treatment.

TABLE 2

Discontinuation symptoms by antidepressant drug class

System	SSRIs	SNRIs	TCAs	MAOIs	Atypicals
General	Flu-like symptoms Fatigue	Flu-like symptoms Fatigue Diaphoresis	Flu-like symptoms Fatigue	Flu-like symptoms Fatigue	Flu-like symptoms Fatigue
Cardio-vascular	Tachycardia Flushing	Tachycardia Hypertension, hypotension Syncope	Tachycardia Arrhythmia	Tachycardia Arrhythmia	(Limited data)
Gastro-intestinal	Nausea, vomiting Diarrhea Anorexia	Nausea, vomiting Diarrhea Anorexia	Nausea, vomiting Diarrhea Anorexia	Nausea, vomiting Diarrhea Anorexia	Nausea, vomiting Diarrhea Anorexia (mirtazapine)
Neurologic	Headache Gait instability Dizziness Paresthesias, brain zaps Tremor, ataxia Myclonus, muscle jerking Parkinsonism	Headache Gait instability Dizziness Parasthesias, brain zaps Tremor, ataxia Stroke-like symptoms Seizure, myoclonus, muscle jerking	Headache Paresthesias Tremor, ataxia Seizure Parkinsonism	Headache Paresthesias Tremor, ataxia Seizure, myoclonus, muscle jerking Parkinsonism Dystonia Catatonia	Headache Dizziness Paresthesias Tremor Dystonia (bupropion)
Psychiatric	Anxiety, panic Depression, mania Suicidal ideation Anger, irritability Mood swings Depersonalization, derealization Hallucinations	Anxiety, panic Depression, mania Suicidal ideation Anger, irritability Mood swings Depersonalization, derealization Hallucinations	Anxiety, panic Depression, mania Suicidal ideation Anger, irritability Mood swings Derealization Hallucinations Delusions	Depression, lability Suicidal ideation Anger, irritability Aggression, agitation Hallucinations Delusions	Anxiety, panic Depression, mania Suicidal ideation Anger, irritability Mood swings Depersonalization, derealization
Cognitive	Confusion, delirium Inattention	Confusion, delirium Inattention	Confusion, delirium Inattention	Confusion, delirium Inattention	(Limited data)
Sleep	Sleep disturbances Nightmares, vivid dreams	Sleep disturbances Nightmares, vivid dreams	Sleep disturbances Nightmares, vivid dreams	Sleep disturbances Nightmares, vivid dreams	Sleep disturbances Nightmares, vivid dreams
Visual	Vision changes	Vision changes	Vision changes	Vision changes	(Limited data)
Sexual	Dysfunction	Dysfunction	Dysfunction	Dysfunction	Dysfunction

MAOIs = monoamine oxidase inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic and tetracyclic antidepressants

Based on information in references 6,7,13,14.

The sensations typically last a few weeks but can persist for years and may be associated with dizziness, the perception of crackling or sizzling noises, and various other symptoms such as depersonalization (feeling detached from and outside of one's own body) and derealization (the sensation that the external world is unreal). Common triggers are eye and head movements, but patients note many other triggering activities. There are no known treatments that successfully and specifically target brain zaps other than resuming the medication at the previous dose.[19]

DISCONTINUATION SYNDROME VS WITHDRAWAL

There is controversy surrounding the terminology of ADS vs antidepressant withdrawal. While clinically the terms are often used interchangeably, it is important to appreciate the nuanced meaning of each term.

Withdrawal from antidepressants may imply addiction.[3,20] However, patients do not crave antidepressants, experience intoxication, or exhibit other hallmarks of a substance use disorder, such as using more and more drug despite negative consequences.[17] Therefore, clinically, the term discontinuation is preferred over withdrawal. Some other authors argue that the term discontinuation downplays the severity of the emergent symptoms, which can be intensely uncomfortable and impairing.[21] These authors strongly favor the use of antidepressant withdrawal because the syndrome of antidepressant discontinuation is consistent with withdrawal from other substances,[6,7,21,22] and because antidepressants cause dependence.[12]

There are no known treatments for brain zaps other than resuming the medication at the previous dose

ADS has been clinically recognized for decades,[13,23–25] demonstrating emergence of symptoms within days or even hours of abrupt cessation. Clinical trials that transitioned patients on antidepressants to placebo observed discontinuation symptoms, especially in antidepressants with shorter half-lives.[23,24] However, many patients experiencing such symptoms are misdiagnosed as experiencing a relapse or a psychosomatic reaction.[13,25] With growing recognition of the difficulty in stopping antidepressants, the risk of ADS should be discussed with patients as part of an informed-consent process when starting antidepressants.[25]

THE PHARMACOKINETICS BEHIND DISCONTINUATION SYNDROME

Straightforward pharmacokinetic explanations of discontinuation symptoms are inadequate since symptoms continue to emerge over a period of weeks and can last for months and even years.[22] Antidepressants are believed to exert their effect partly through chronic medication exposure leading to receptor downregulation to create a more favorable neurotransmitter-to-receptor ratio.[6,7,26–28] It should be noted that each class of antidepressants exerts its effect in different ways; therefore, broad statements about antidepressant mechanisms of action tend to be overgeneralizations. Still, the mechanism of receptor downregulation, which requires weeks to months and may over time contribute to medication desensitization, likely accounts in part for prolonged discontinuation symptoms.[12]

Furthermore, it is also hypothesized that antidepressants with anticholinergic properties may lead to receptor upregulation rather than downregulation and thus can contribute to desensitization.[13] The theory of "oppositional tolerance" incorporates both upregulation and downregulation,[22] because discontinuing antidepressants may lead to diverse rebound symptoms due to the widespread distribution of serotonin throughout the body. Oppositional tolerance that develops and increases over time may explain why patients treated with antidepressants at higher doses and for longer periods are at greater risk for ADS.[29]

WHO IS MOST AT RISK OF DISCONTINUATION SYMPTOMS?

Despite extensive literature on ADS, there is still little known about the patient characteristics that pose the most risk.[7,14] Nevertheless, though the risk of ADS cannot be eliminated, it can be reduced through awareness of known risk factors (**Table 3**).[6,7,14,23,24,26,28–32]

Some patients may have a genetic predisposition,[7] although this is yet to be determined. Younger patients may be more at risk, but younger patients are also more likely to abruptly discontinue their antidepressants.[30] Patients who report discontinuation symptoms during missed doses are also at higher risk of withdrawal during a taper,[28] and pa-

tients should be asked about this experience during an appointment to plan a taper.[31]

Treatment of longer duration[6,26,29] and at treatment at higher doses[29] have proven to be risk factors for ADS. Medications with higher receptor affinity such as paroxetine carry greater risk.[26] Abrupt discontinuation of antidepressants increases the risk of ADS.[32] The indication for the prescribed antidepressant does not appear to affect the likelihood of ADS symptoms.[6]

Medication half-life inversely predicts the risk of discontinuation.[6,23,24] Of the SSRIs, paroxetine and fluvoxamine have the shortest half-lives and therefore are associated with the highest risk. Citalopram, escitalopram, and sertraline carry moderate risk, while fluoxetine carries the lowest risk due to the long half-life of its active metabolite (approximately 7 days).[7] Among SNRIs, venlafaxine and desvenlafaxine carry the highest risk for ADS. Duloxetine carries a high risk and milnacipran a low risk, with levomilnacipran carrying the lowest risk.[14] MAOIs and tricyclic and tetracyclic antidepressants generally carry a relatively high risk for ADS. Although mirtazapine and bupropion carry some risk, the data on this are limited.[6]

To date, there are only minimal prospective data comparing the risk of ADS with different antidepressants. A recent review[9] concluded that paroxetine and venlafaxine pose the greatest risk among antidepressants most commonly prescribed today. **Table 4** stratifies antidepressants by the risk of ADS.

PREVENTING AND MANAGING DISCONTINUATION SYMPTOMS

To date, no formal schedules for tapering antidepressants have been validated. The maxim "slower is better" applies to tapering antidepressants. Most authors now agree that a longer taper, defined as at least 14 days, may reduce the risk of discontinuation symptoms compared with a rapid taper, defined as 1 to 10 days.[17] Current recommendations advise antidepressant dose adjustments every 1 to 4 weeks.[26] Data from the field of sleep medicine, where patients are often instructed to hold antidepressants, suggest tapers over 3 to 4 months.[33] Some have suggested the "10% rule," which recommends reducing the dose by 10% weekly.[26] Switching to a liquid formulation can facilitate slow tapers by enabling precise dosing. However, neither paroxetine nor venlafaxine, common antidepressants very likely to cause ADS, is readily available in liquid formulation. Patients report opening capsules to divide up beads, as well as breaking unscored tablets with pill cutters to slowly taper off medication.[11,28] Patients can also utilize compounding pharmacies to access custom formulations.

TABLE 3

Risk factors for antidepressant discontinuation syndrome

Longer duration of treatment
Higher dose of drug
Shorter half-life of drug
Higher receptor affinity of drug
Younger patient age
History of discontinuation symptoms
Abrupt discontinuation
High-risk medication (see Table 4)

Based on information in references 6,7,14,23,24,26,28–32.

TAPERING TO CHANGE ANTIDEPRESSANT MEDICATIONS

When switching from one antidepressant to another, taper considerations are different. Cross-tapering is generally recommended[4] and can be carried out over 1 to 4 weeks or longer depending on the dosing of the original medication. Cross-tapering involves incrementally decreasing the current antidepressant while incrementally increasing the new antidepressant (**Table 4**).

Other ways to change antidepressants include starting the new antidepressant immediately after stopping the previous drug (direct switch), starting the new drug after 2 to 3 days off the prior drug (moderate switch), and starting the new drug after 5 half-lives off the prior drug (conservative switch). A direct switch can be considered when changing an SSRI to another SSRI or SNRI at an equivalent dose, unless the current SSRI is at a high

To date, there are only minimal prospective data comparing the risk of ADS with different antidepressants

TABLE 4

Risk of antidepressant discontinuation syndrome (ADS): A summary of antidepressant dosing

Risk of ADS	Name (brand name)	Starting daily dose (mg)	Daily dose range (mg)	Typical dose increment (mg) (conservative dose increment)
Low	Bupropion XL (Wellbutrin XL)[a]	150	150–450	150
	Doxepin (Silenor)	3	3–6	3
	Fluoxetine (Prozac)[a]	10	10–80	10
	Levomilnacipran (Savella)	20	20–120	40 (20)
	Milnacipran (Fetzima)	25	50–300	25–50 (12.5)
	Vilazodone (Viibryd)	10	10–40	10
	Citalopram (Celexa)	10	10–40	10
	Escitalopram (Lexapro)	5	5–30	10 (5)
	Mirtazapine (Remeron)	7.5–15	7.5–60	15 (7.5)
Intermediate	Sertraline (Zoloft)	25	25–300	50 (12.5–25)
	Trazodone (Deseryl)	25–50	25–400	50 (25)
	Vortioxetine (Trintellix)	5	5–20	5
	Amitriptyline (Elavil)	10–25	10–300	50 (10–25)
	Clomipramine (Anafranil)	25	25–300	50 (25)
	Desipramine (Norpramin)	25	25–300	25–50 (10–25)
	Desvenlafaxine (Pristiq)	25	50–400	50 (25)
	Doxepin (Sinequan)	25	25–300	25–50 (10–25)
	Duloxetine DR (Cymbalta DR)	20–30	30–120	30 (20)
High	Fluvoxamine (Luvox)[b]	25	25–300	50 (12.5–25)
	Imipramine (Tofranil)	25	25–300	25–50 (10–25)
	Nortriptyline (Pamelor)	10–50	10–150	25–50 (10–25)
	Paroxetine (Paxil)[a]	10	10–50	10 (5)
	Phenelzine (Nardil)	15	7.5–90	15
	Tranylcypromine (Parnate)	10	10–60	10
	Venlafaxine ER (Effexor ER)	37.5	75–375	37.5

[a]Potent CYP 2D6 inhibitor.
[b]Potent CYP 1A2 inhibitor.

dose. Moderate and conservative switches carry the risk of ADS due to the time spent completely off an antidepressant.[4] Alternatively, cross-tapering carries the risk of causing drug-drug interactions, and clinicians should be aware of potential risks such as serotonin syndrome. None of these switching methods are appropriate for MAOIs, which require a 14-day washout both pre- and post-treatment, and at least a 5-week washout if MAOI treatment is preceded by fluoxetine.[34]

Studies have suggested discontinuing antidepressants by switching patients to fluoxetine due to its 7-day half-life and rela-

tively low risk of ADS.[23,35] There are no formal guidelines on fluoxetine-assisted tapers, but the strategy consists of cross-tapering to fluoxetine (slowly decreasing the original antidepressant while increasing fluoxetine to a dosing required for ADS remission) followed by discontinuation of fluoxetine,[26] which can self-taper due to its long half-life. Such a strategy can be helpful when tapering off venlafaxine, desvenlafaxine, paroxetine, and tricyclic and tetracyclic antidepressants. However, clinicians must be wary of drug-drug interactions due to fluoxetine's CYP 2D6 inhibition, which can raise drug levels.

Additional practical guidance on discontinuing and switching antidepressants can be found online.[36,37]

Patient education and other management tools

Perhaps the most pragmatic and effective measure in managing ADS is to proactively educate patients about FINISH symptoms with missed doses or abrupt discontinuation. This prepares patients to better cope with ADS during planned antidepressant discontinuation and may prevent unnecessary visits to the emergency room. It is also important to reassure the patient that ADS is neither life-threatening nor indicative of addiction, and that it will eventually resolve.

If ADS does occur, the antidepressant being tapered can be rapidly resumed at the previous dosing and then tapered more slowly. This intervention is the simplest antidote and is highly effective in most cases within 24 hours.

Symptom management is another treatment strategy.[35] For example, headaches can be managed with ibuprofen 400 mg or acetaminophen 650 mg every 4 to 6 hours. Nausea can be addressed with ondansetron 4 mg every 8 hours. Anxiety and insomnia can be managed with hydroxyzine 50 mg every 6 hours or with benzodiazepines. In some cases, diphenhydramine can be recommended if the patient is stopping a particularly anticholinergic antidepressant, such as paroxetine.

Additionally, antidepressants can have extensive drug-drug interactions. These interactions can occur from enzymatic induction or inhibition of the cytochrome P450 system or from medication side effects that overlap with the effect of other medications, such as additive effects in anticoagulation. The cessation of an antidepressant therefore requires the reevaluation of other concurrently prescribed medications.[22] While it is always recommended to complete a medication review, changes in bupropion, fluoxetine, and paroxetine (potent CYP 2D6 inhibitors), fluvoxamine (a potent CYP 1A2 inhibitor), tricyclic and tetracyclic antidepressants, and MAOIs should prompt an especially close medication review.

FUTURE DIRECTIONS

Translational efforts including the further development of animal models for ADS are needed to enhance our understanding of the pathogenesis, phenotypic variance, and role of genetic and environmental modulation in ADS. Such efforts will help the clinician screen for a medication's potential to induce ADS and will contribute to developing agents that reduce the symptoms and severity of ADS.[38]

TAKE-HOME POINTS

- Discontinuing or changing antidepressants, especially when done quickly, can be associated with ADS, and symptoms can emerge within hours and last for months.
- The mnemonic FINISH is useful for recognizing ADS: flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances (eg, brain zaps), and hyperarousal.
- Dosing adjustments should be made every 1 to 4 weeks and may require months to complete. Patients unable to tolerate a tapering schedule should be tapered more slowly with supplemental symptomatic management.
- Risk factors for ADS are higher dose and longer duration of treatment, medication with shorter half-life and greater receptor affinity, abrupt discontinuation, prior symptoms with missed doses or previous antidepressant discontinuations, and younger patient age. ■

It is important to reassure the patient that ADS is neither life-threatening nor indicative of addiction, and that it will eventually resolve

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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A painful mass in the jaw

A 64-year-old woman who had recently immigrated to the United States from Vietnam came to the emergency department because of a painful mass in the left side of her jaw, which she had first noticed 3 weeks earlier. Because the pain kept getting worse and the mass kept getting bigger, she had gone to her dentist, who gave her amoxicillin, which did not help. She also reported headache, severe trismus ("lockjaw"), odynophagia (painful swallowing), night sweats, and unintentional loss of 6 kg (13 lb) over several months. She said she had experienced no recent trauma or fever, had never used tobacco, alcohol, or illicit drugs, and had never been seriously ill before.

INITIAL EVALUATION AND MANAGEMENT

In the emergency department, her temperature was 98.1°F (36.7°C), pulse 74 beats per minute, blood pressure 132/66 mm Hg, respiratory rate 18 breaths per minute, and oxygen saturation 99% while breathing room air.

On examination, she had a large, tender mass at the left mandibular angle and marked tenderness to palpation in the back of the left side of her neck. Her teeth could not be well visualized due to trismus. She also had swollen submandibular lymph nodes on the left side, ulceration and erythema along the left retromolar trigone, and numbness on the left side of her face in the area supplied by the mandibular nerve. The rest of the physical examination was unremarkable.

Laboratory test results at presentation were the following:

- White blood cell count 3.1 × 10^9/L (reference range 4.5–11.0 × 10^9/L)
- Absolute neutrophil count 1.6 × 10^9/L (1.8–7.7 × 10^9/L)
- Absolute lymphocyte count 0.7 × 10^9/L (1.0–4.8 × 10^9/L)
- Absolute monocyte count 0.6 × 10^9/L (0.2–0.4 × 10^9/L)
- Absolute immature mononuclear cell count 0.1 × 10^9/L (0.0 × 10^9/L)
- Hemoglobin 11.9 g/dL (12–16 g/dL)
- Hematocrit 34.0% (36%–46%)
- Mean corpuscular volume 101.5 fL (80–100 fL)

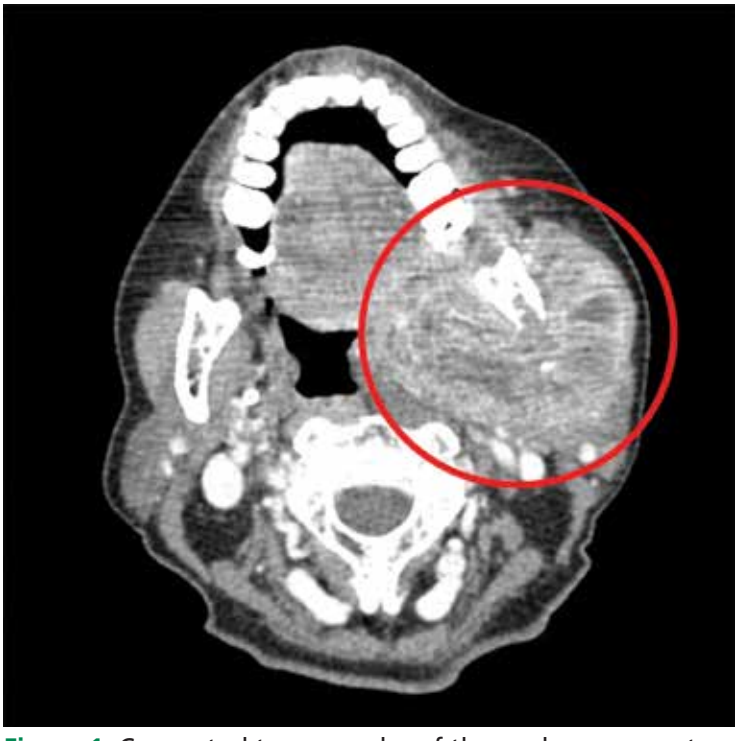

Figure 1. Computed tomography of the neck on presentation was notable for a mass in the ramus of the left mandible with a large soft-tissue component (circle) within the left masticator space.

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- Platelet count 705 × 10^9/L (130–400 × 10^9/L)
- Peripheral smear: Macrocytes present. Leukocytes were decreased with rare blast cells. Platelets were increased, with scattered large forms.

Computed tomography (CT) of the neck revealed a permeating mass in the ramus of the left mandible with a large soft-tissue component, measuring 6.2 cm in the anteroposterior dimension, 5.8 cm in the transverse dimension, and 6.3 cm in the craniocaudal dimension (**Figure 1**). Inseparable from the left muscles of mastication, the mass displaced parapharyngeal fat medially and extended posteriorly, abutting the left parotid gland.

CT of the chest showed several hypodense lesions in the liver. One lesion with mixed hyperdense and hypodense material measured 4.6 by 5.0 cm.

DIFFERENTIAL DIAGNOSIS

1 In light of these findings and the uniquely high incidence of specific cancers in the Southeast Asian population, which of the following is the least likely cause of this patient's mandibular mass?

A 64-year-old woman presents with a mandibular mass: What is the cause?

- ☐ Nasopharyngeal carcinoma
- ☐ Odontoma (a benign tumor of dental tissue)
- ☐ Metastatic lung cancer
- ☐ Squamous cell carcinoma of the oral cavity

Mandibular lesions are often classified by the tissue of origin (odontogenic, nonodontogenic), and CT is crucial in guiding the initial diagnostic workup. Odontogenic lesions usually surround a component of the tooth. Additional features such as location within the mandible, cystic vs solid appearance, border contour with lytic or sclerotic features, and compression of surrounding tissues help to delineate the etiology of these lesions.[1,2] Other clinical information such as the patient's age, comorbidities, and risk factors may help to narrow the diagnosis. Nevertheless, tissue biopsy is often required to obtain a definitive pathologic diagnosis.

Odontomas are the most common odontogenic tumor of the mandible and are usually diagnosed during the second decade of life. Nearly 50% of these tumors are associated with an impacted tooth, and they often resemble normal teeth, as the lesion consists of various odontogenic components including dentin and enamel.[2] This diagnosis was unlikely in our patient, given the lack of association with teeth and the large soft-tissue component seen on CT of her neck.

Mandibular masses related to primary head and neck cancer are typically the result of direct invasion. In view of our patient's ethnic background, we considered primary nasopharyngeal carcinoma and squamous cell carcinoma of the oral cavity as potential diagnoses. While nasopharyngeal carcinoma is rare in the United States and Western Europe, it is endemic in Southern China and has intermediate incidence in Southeast Asian populations.[3] It frequently originates from the posterolateral recess of the pharyngeal wall and presents as a cervical mass in the apex of the posterior cervical triangle.[4] Additionally, more than half of oral cancers occur in Asia, with 11% of these occurring in Southeast Asia.[5] Typically, these cancers metastasize to cervical lymph nodes and the lungs, although spread to the liver and bone has also been described.[6]

Rarely, mandibular masses can be a sign of a widespread metastatic disease process, most commonly breast, lung, or renal cell cancer.[7] Of these, lung cancer is the most common cancer type and a leading cause of death in South, East, and Southeast Asia.[8,9] Moreover, 20% to 40% of patients with lung cancer have bone metastases at the time of presentation.[10,11]

CASE CONTINUED: A REVELATION FROM THE PATIENT'S FAMILY

To identify the etiology of the patient's mandibular mass, we performed fine-needle aspiration of the lesion. When we discussed the initial findings with the patient and her family, her children revealed that she had undergone treatment for liver cancer in Vietnam but that they had not disclosed the diagnosis to her. Given this additional information, we pursued further workup to evaluate for potential metastatic and recurrent hepatocellular carcinoma.

The results of further laboratory testing and imaging were as follows:

- Carcinoembryonic antigen < 0.5 ng/mL (reference range < 5.0 ng/mL)

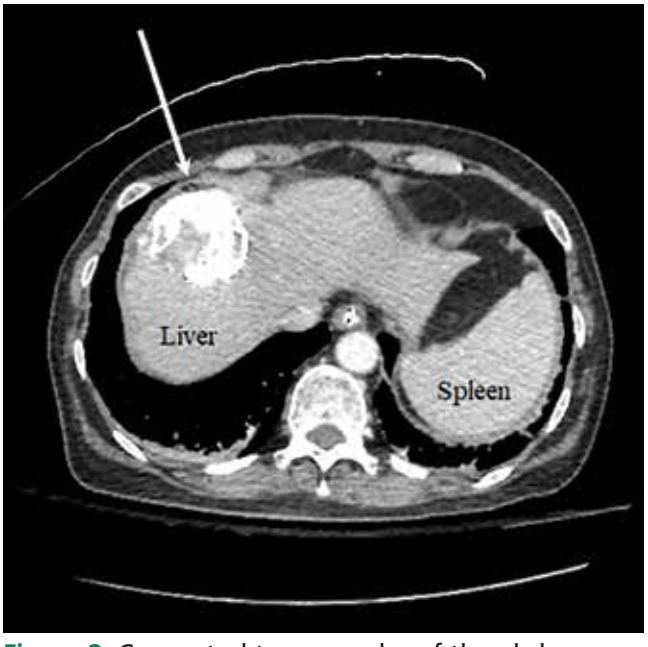

Figure 2. Computed tomography of the abdomen demonstrating a 4.7-cm lesion in the dome of the right hepatic lobe (arrow) containing hyperdense material with hypodense areas, likely related to earlier transarterial chemoembolization treatment.

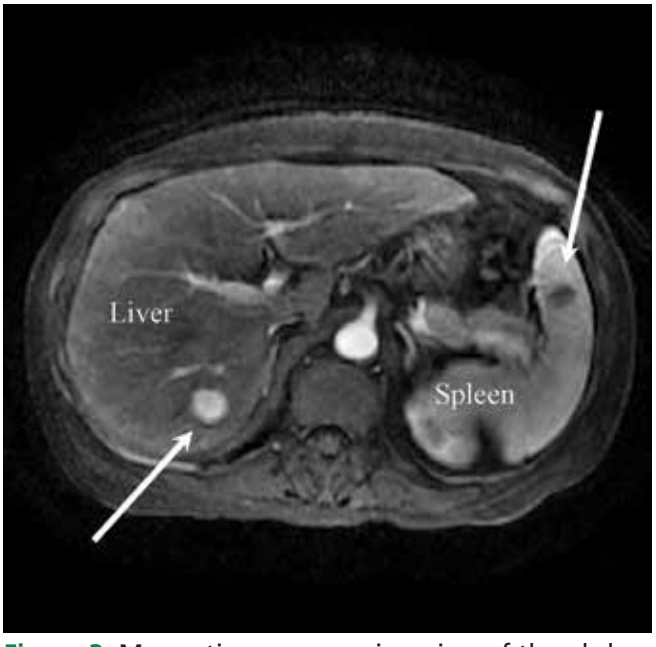

Figure 3. Magnetic resonance imaging of the abdomen reveals a 1.7-cm lesion in hepatic segment 6 (left arrow) and a 1.6-cm hypoenhancing lesion within the inferior pole of the spleen (right arrow).

- Alpha-fetoprotein level 22,728 ng/mL (< 8.8 ng/mL).

Additional radiographic imaging

CT with contrast of the abdomen and pelvis showed a 4.7-cm area within the dome of the right hepatic lobe containing hyperdense material with hypodense areas, likely related to prior transarterial chemoembolization treatment (**Figure 2**). Magnetic resonance imaging (MRI) (**Figure 3**) showed a 1.7-cm hypodense lesion within hepatic segment 6, in addition to scattered low-attenuation lesions smaller than 1 cm in the inferior right hepatic lobe and a 1.6-cm hypodense lesion within the spleen, which were worrisome for metastatic and residual disease.

Multiphase abdominal MRI showed 2 lesions in 2 different hepatic lobes, categorized as LR-5 (definitely hepatocellular carcinoma) by the diagnostic criteria of the Liver Imaging Reporting and Data System (LI-RADS).

Liver biopsy confirms the diagnosis

To obtain pathologic correlation, liver biopsy was performed. Hepatocyte paraffin-1, glypican-3, and arginase-1 were positive on immunohistochemical staining, confirming hepatocellular carcinoma. Results of the fine-needle aspiration of the mandible showed a similar patchy pattern of arginase-1 staining and shared histopathologic features with the liver sample, consistent with metastatic disease.

She had been treated for liver cancer but was not told the diagnosis

PATHOGENESIS AND DIAGNOSIS OF HEPATOCELLULAR CARCINOMA

Results of serologic tests obtained as part of an infectious disease workup initiated earlier during the hospitalization showed:

- Human immunodeficiency virus antibody negative
- Epstein-Barr virus viral load < 750 copies/mL (normal < 750)
- Hepatitis C antibody negative
- Hepatitis B surface antibody (anti-HBs) negative
- Hepatitis B surface antigen (HBsAg) positive
- Total hepatitis B core antibody (anti-HBc) positive.

TABLE 1

Interpretation of hepatitis B serologic markers

Infection phase	Serologic marker: HBsAg[a]	Total anti-HBc[b]	IgM antibody to anti-HBc[c]	Anti-HBs[d]
No current infection	Negative	Negative	Negative	Negative
Immunity due to past infection	Negative	Positive	Negative	Positive
Immunity due to vaccination	Negative	Negative	Negative	Positive
Acute infection	Positive	Positive	Positive	Negative
Chronic infection	Positive	Positive	Negative	Negative
Other [e]	Negative	Positive	Positive or negative	Negative

[a] Hepatitis B surface antigen.
[b] Total antibody to hepatitis B core antigen.
[c] Immunoglobulin M antibody to hepatitis B core antigen.
[d] Antibody to hepatitis B surface antigen.
[e] Possibilities include resolved infection (most common), resolving acute infection, "low-level" chronic infection, and no current infection due to false-positive anti-HBc.

Hepatocellular carcinoma is the most common primary malignancy of the liver

2 The results of our patient's hepatitis B serologic tests (anti-HBs negative, HBsAg positive, and anti-HBc positive) are most consistent with which of the following?

- ☐ Acute infection
- ☐ Chronic infection
- ☐ Acute or chronic infection
- ☐ Recovery from an acute infection

Hepatitis B serologic testing measures the levels and titers of several hepatitis B virus-specific antigens and antibodies, which are used to determine the phase of infection (**Table 1**).

At 4 to 10 weeks after exposure to the virus, HBsAg becomes detectable in the blood, followed by immunoglobulin M (IgM) anticore antibodies.[12] Accordingly, in the acute phase of the infection, HBsAg, total anti-HBc, and IgM anti-HBc are positive. A resolving infection is characterized by the disappearance of HBsAg and the subsequent emergence of anti-HBs within 4 to 6 months. Of note, as the appearance of anti-HBs may be delayed after HBsAg clearance, sometimes anti-HBc is the only serologic marker of hepatitis B virus infection. Since HBsAg is the antigen used to generate an immune response to the hepatitis B vaccine, the presence of anti-HBs reflects not only recovery and natural immunity but also immunity as a result of vaccination.[12]

While most individuals will clear the hepatitis B virus, an estimated 5% of immunocompetent adults progress to chronic infection.[13] In persistent infection, HBsAg will remain but at lower titers than during primary infection. As total anti-HBc indicative of previous or ongoing infection will persist for life, the presence of IgM antibodies to the hepatitis B core antigen can help to delineate acute from chronic infection.[12] Therefore, our patient's initial laboratory results were consistent with either acute or chronic infection. As IgM anti-HBc was negative, we concluded she had chronic infection.

Other serologic markers of interest are hepatitis B e antigen (HBeAg) and antibody (anti-HBe). Like the surface antigen, the e antigen indicates active viral replication, appearing during an acute infection and remaining only if the primary infection does not clear.[12] The continued presence of HBeAg and delayed seroconversion to anti-HBe reflect high levels of hepatitis B virus DNA

with chronic infection. HBeAg levels help with determining when to initiate hepatitis B virus-directed treatment, and high HBeAg levels are a significant risk factor for the development of hepatocellular carcinoma.[14] Our patient was found to be HBeAg-positive and anti-HBe-negative.

HEPATOCELLULAR CARCINOMA: EPIDEMIOLOGY, RISK FACTORS, AND DIAGNOSIS

Liver cancer is the fourth most common cause of cancer-related death worldwide and is the most common cancer type in Southeast Asia, with hepatocellular carcinoma accounting for 75% to 85% of cases.[9,15]

The incidence of hepatocellular carcinoma varies by geographic location, with 72% of cases occurring in Asia vs 5% in North America.[16] This variation is likely due to differences in exposure to risk factors, particularly hepatitis viruses. Worldwide, hepatitis B is the main cause of hepatocellular carcinoma, especially in Asia and sub-Saharan Africa due to low vaccination rates. In Western countries, hepatitis C virus is the leading cause of hepatocellular carcinoma. While cirrhosis of any etiology increases the risk of hepatocellular carcinoma, hepatitis B virus has a direct oncogenic effect regardless of the presence of underlying liver fibrosis, as seen in this patient.[17] In patients with hepatitis C, hepatocellular carcinoma occurs commonly in those who have advanced-stage fibrosis.

Other risk factors for hepatocellular carcinoma include alcohol use, tobacco exposure, nonalcoholic steatohepatitis (NASH), and co-infection with human immunodeficiency virus. Particularly in the United States, the high prevalence of NASH has raised concern. As the incidence of hepatocellular carcinoma has risen since 1999,[18] NASH has been identified as the most common underlying risk factor for it and is present in 59% of cases.[19] Like some hepatitis viruses, NASH may confer an increased risk of hepatocellular carcinoma independent of cirrhosis, and the pathogenesis of NASH-associated hepatocellular carcinoma involves immune and inflammatory responses, DNA damage, and oxidative stress.[20]

The diagnosis of hepatocellular carcinoma can be made with imaging alone, either with dynamic contrast-enhanced CT or MRI of the abdomen.[15] Lesions are scored using LI-RADS to determine the likelihood of hepatocellular carcinoma, with categories LR-4 indicating probable and hepatocellular carcinoma and LR-5 indicating definite hepatocellular carcinoma. For LR-4 lesions or other lesions with an inconclusive pattern on imaging, biopsy is usually warranted.

Patients without cirrhosis or known chronic liver disease may require additional serologic testing for hepatitis viruses and tumor markers (eg, alpha-fetoprotein), as done in this patient. Although a serum alpha-fetoprotein level higher than 400 ng/mL in a high-risk patient is more than 95% specific for hepatocellular carcinoma, fewer than one-fifth of hepatocellular carcinoma cases are associated with such high alpha-fetoprotein levels.[21] In our patient, although MRI alone was diagnostic of hepatocellular carcinoma, liver biopsy was performed owing to her unusual presentation.

CASE CONTINUED

Bone marrow biopsy was performed to evaluate the peripheral blasts and was normal. We attributed these findings to the patient's underlying disease.

Her hepatitis B serology:
Anti-HBs negative
HBsAg positive
Anti-HBc positive
HBeAg positive
Anti-HBe negative

THE CHILD-PUGH SCORE AND ITS POTENTIAL PITFALLS

To determine candidacy for treatment of her hepatocellular carcinoma, a Child-Pugh score was calculated.

3 The Child-Pugh score is based on which combination of clinical criteria?

- ☐ Total bilirubin, albumin, nutritional status, ascites, and encephalopathy
- ☐ Total bilirubin, albumin, prothrombin time (PT) and international normalized ratio (INR), ascites, and encephalopathy
- ☐ Total bilirubin, PT/INR, creatinine, sodium, and need for dialysis in the last week
- ☐ Total bilirubin and PT/INR

Introduced in 1964, the Child-Turcotte-Pugh classification is a scoring system originally used to predict operative mortality and variceal bleeding risk in cirrhotic patients under-

going portocaval shunt surgery.[22] It is based on total bilirubin, albumin, nutritional status, ascites, and encephalopathy. In 1973, the system was revised to include PT/INR instead of nutritional status.[23]

Since its inception, the Child-Pugh score has become an important tool for prognostication in patients with cirrhosis and determination of the necessity of liver transplantation. Additionally, it is used in patients with metastatic hepatocellular carcinoma to estimate severity of liver dysfunction and guide treatment options. Child-Pugh scores range from A (mild) to C (severe).

The Model for End-stage Liver Disease (MELD) score, based on total bilirubin, prothrombin time, creatinine, sodium, and need for dialysis, is another scoring system for assessing liver function and was created to predict survival in cirrhotic patients undergoing transjugular placement of intrahepatic portosystemic shunts.[24] Like the Child-Pugh score, the MELD score is also used to estimate short-term risk of death, and helps with the prioritization of liver transplants.

Unrelated to the management of cirrhosis and hepatocellular carcinoma is the Maddrey discriminant function formula, which is based only on total bilirubin and PT and predicts benefit from steroid administration in patients with alcoholic hepatitis.

The patient received radiation therapy to the jaw and started lenvatinib, but ultimately entered hospice after painful vertebral fractures

HEPATOCELLULAR CARCINOMA: STAGING, PROGNOSIS, AND TREATMENT

While the Child-Pugh score is a predictive model used most commonly in patients with cirrhosis, it is also used in patients with hepatocellular carcinoma to help determine candidacy for resection and systemic therapy in the metastatic setting.[25] Although most established clinical trials of systemic therapy for metastatic hepatocellular carcinoma have been conducted in patients with Child-Pugh grade A cirrhosis, given concern for the competing risks of mortality and poor hepatic drug clearance due to liver dysfunction,[26,27] there is a growing effort to include Child-Pugh grade B patients.[28–30] It is important to note that the use of the Child-Pugh score for assessment of liver dysfunction is clinician-dependent, whereas other tools such as the MELD score and the albumin-bilirubin grade have also been used.[15]

The Child-Pugh score is also used in the Barcelona Clinic Liver Cancer algorithm, which is the most commonly used staging system and included in the consensus guidelines for the management of hepatocellular carcinoma.[25,31] The Barcelona system categorizes patients into 1 of 5 stages, accounting for liver function (determined by the Child-Pugh score), tumor burden, and performance status.[32] Accordingly, the Barcelona stages range from stage 0 (very early disease) to stage D (end-stage disease), with stage 0 patients having preserved liver function, excellent performance status, and single lesions measuring no more than 2 cm, while terminal stage D patients have metastatic disease with poor liver function and functional status. Hepatocellular carcinoma is an aggressive tumor and is often diagnosed late in its course, with most patients having stage C and D disease and median survival ranging from 2 to 20 months after diagnosis.[33,34]

For patients who have localized and resectable disease with preserved liver function, the mainstay of therapy is surgery with curative intent. Other curative options include liver transplant and liver-directed approaches (eg, thermal ablation). Importantly, patients may even be placed on liver transplant lists on the basis of diagnostic imaging alone, provided that certain technical, protocol, and standardized reporting requirements are met. In this manner, the risk of bleeding and tumor-tract seeding seen with biopsy is minimized.[35]

Unfortunately, many patients are ineligible for transplant due to the extent of disease or severity of their underlying liver dysfunction. In such cases, noncurative treatments to slow disease progression are offered, including transarterial chemoembolization, transarterial radioembolization, stereotactic body radiation therapy, and systemic therapy.[15] Since the development of targeted therapy agents, supportive care is no longer the only option for Barcelona stage C patients. Therapies that have been approved as first-line options for nonresectable hepatocellular carcinoma include the multikinase inhibitors sorafenib and lenvatinib[25–27] as well as atezolizumab plus bevacizumab.[36] At progression, there are many

other therapeutic options including but not limited to checkpoint inhibitors, regorafenib, or cabozantinib.[37] As patients with Barcelona stage D tumors have an extremely poor prognosis, management is focused on symptom control with best supportive care.

CASE CONCLUSION

Although this patient had a normal bilirubin level and INR and no ascites or encephalopathy, she was characterized as being in Child-Pugh stage B due to her hypoalbuminemia. However, her albumin level of 2.5 g/dL was believed to be due to anorexia and poor oral intake due to her mandibular mass rather than liver dysfunction. Additionally, in this case the applicability of the Child-Pugh score was limited, as she did not have evidence of cirrhosis.

Because her functional status was otherwise good, systemic therapy with lenvatinib was started after completion of palliative radiation to her mandible for pain control. Unfortunately, 2 months into treatment, the patient developed painful vertebral fractures from her metastatic disease, and she entered hospice care.

4 If this patient's chronic hepatitis B had been diagnosed earlier, how would she have been appropriately screened for hepatocellular carcinoma?

- ☐ CT of the abdomen and pelvis with contrast every year
- ☐ CT of the abdomen and pelvis with contrast every 6 months
- ☐ Hepatic ultrasonography every year
- ☐ Hepatic ultrasonography every 6 months

HEPATOCELLULAR CARCINOMA: SURVEILLANCE

The goal of surveillance is to improve overall survival through early tumor detection in groups at risk. The definition of high-risk populations varies by societal group, but the general consensus is to screen all patients who have any of the following[25,38,39]:

- Child-Pugh A or B cirrhosis
- Child-Pugh C cirrhosis awaiting transplant
- Active hepatitis B but no cirrhosis
- A family history of hepatitis C
- African or Asian descent
- Chronic hepatitis C with advanced-stage fibrosis in the absence of cirrhosis.

The American Association for the Study of Liver Diseases recommends surveillance with ultrasonography every 6 months, with or without alpha-fetoprotein levels (threshold of 20 ng/mL). Imaging with dynamic contrast-enhanced CT or MRI of the abdomen is typically indicated only if ultrasonographic visualization is limited, or for further characterization of lesions 1 cm or larger, as these are highly suspicious for hepatocellular carcinoma. Lesions smaller than 1 cm are likely benign but are closely monitored every 3 to 6 months at the physician's discretion.[25] These screening methods allow for earlier detection of hepatocellular carcinoma, leading to a lower risk of death and more treatment options.

In summary, this case illustrates an unusual presentation of hepatocellular carcinoma, the most common primary malignancy of the liver. While metastasis usually occurs in abdominal lymph nodes, bone, adrenal glands, or lung, only a few case reports have described spread to the mandible and maxilla.[40–42] This case also demonstrates the importance of early recognition and detection of risk factors for hepatocellular carcinoma, including hepatitis B and C, particularly in diverse patient populations, as appropriate screening may lead to earlier diagnosis and better prognosis and outcome.

Earlier detection of hepatocelular carcinoma may lead to better outcomes

TAKE-HOME POINTS

- Liver cancer is the fourth most common cause of cancer-related death worldwide, and hepatocellular carcinoma accounts for 80% of cases.
- Mandibular metastases are rare and suggest aggressive, widespread underlying malignancy.
- Hepatitis B is the main cause of hepatocellular carcinoma worldwide, whereas hepatitis C is the most common cause in Western countries. While cirrhosis is generally a prerequisite for the development of hepatocellular carcinoma in patients with hepatitis C, hepatitis B can progress to hepatocellular carcinoma without cirrhosis.
- Patients at high risk for developing hepa-

tocellular carcinoma, including patients with cirrhosis from any etiology and patients with hepatitis B with or without cirrhosis, should undergo surveillance for hepatocellular carcinoma with hepatic ultrasonography every 6 months.

- The Child-Pugh score plays an important role in estimating the severity of liver dysfunction, which affects the prognosis and management of hepatocellular carcinoma. At the same time, it is important to recognize other confounding clinical variables that may affect the total score.

DISCLOSURES

Dr. Cho has disclosed consulting, teaching, and speaking for Bristol Myers Squibb and consulting for Eisai, Exelixis, and Genentech/Roche. The other authors disclose no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Evaluation and management of orthostatic hypotension: Limited data, limitless opportunity

ABSTRACT

Although orthostatic hypotension is common and can have serious consequences, recommendations about its evaluation and management are based on limited data. Here, the author outlines a systematic approach, noting the areas that pose an opportunity for improvement.

KEY POINTS

The diagnosis of orthostatic hypotension must be systematic. Do not assume causality. For example, if the patient has diabetes mellitus and orthostatic hypotension, do not assume that diabetic autonomic neuropathy is the cause of the orthostatic hypotension.

When evaluating the cause of orthostatic hypotension, consider the tempo of progression of disease and the coexistence of neurologic symptoms.

Treatment should first focus on nondrug therapy, but when adding drug therapy such as fludrocortisone and vasoconstrictors, consider volume status and the presence or absence of supine hypertension.

Supine hypertension is common in neurogenic orthostatic hypotension. It should be treated by discontinuing fludrocortisone and long-acting antihypertensives. Elevation of the head of the bed, high-carbohydrate snacks at bedtime, and short-acting antihypertensive drugs at bedtime, preferably nitrates or clonidine, can be useful.

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An 83-year-old woman was transferred from another hospital because of refractory orthostatic hypotension (OH) and recurrent syncope for the past 3 months. She had been healthy through her life other than for well-controlled hypertension and hyperlipidemia. She lived independently and was very functional. On admission, she could not stand for more than 1 to 2 minutes because of severe presyncopal dizziness. Her review of systems was otherwise negative, aside from frontal headaches that happened primarily when her blood pressure (BP) was high, and constipation, which had been worse recently.

Her medications at the time of transfer included midodrine 10 mg three times a day, fludrocortisone 0.1 mg daily, and atorvastatin.

Supine, her BP was 172/94 mm Hg and her heart rate (HR) was 64 beats per minute. Sitting, her BP dropped to 108/72 mm Hg with an HR of 76 beats per minute. After standing for 1 minute her BP dropped to 66/42 mm Hg while her HR increased only to 84 beats per minute. She immediately sat down because of presyncopal dizziness. Other findings on examination, including a complete neurologic examination by a neurologist, were unremarkable.

She had already undergone many tests with normal results. These included a complete metabolic panel; complete blood cell count; thyroid function tests; urinalysis; electrocardiography; echocardiography; chest radiography; brain magnetic resonance imaging; auto-antibody serologic testing (antinuclear antibody, Sjögren syndrome antibody A, Sjögren syndrome antibody B); tests for human immunodeficiency virus, Lyme disease, hepatitis B, and hepatitis C; vitamin B profile; vitamin D

levels; and serum protein electrophoresis and free circulating light chains.

Which is the most appropriate next diagnostic test for this patient?

- Formal autonomic nervous system testing
- Serum paraneoplastic and autoimmune neuroautoantibody panel
- Abdominal fat pad biopsy
- Electromyography and nerve conduction studies
- Skin biopsy to measure nerve fiber density.

The answer lies in an understanding of OH and key elements of the evaluation.

ORTHOSTATIC HYPOTENSION DEFINED

OH is present if the systolic BP drops by more than 20 mm Hg or the diastolic BP drops by more than 10 mm Hg.[1] The systolic BP is preferred because it has better association with cerebral blood flow and symptoms.[2,3] If the patient is hypertensive, then a systolic drop of more than 30 mm Hg is the threshold.[1]

ADAPTATION TO STANDING

When we stand up, gravitational forces lead to blood pooling in veins of the lower body, amounting to about 500 to 800 mL. About 50% of the pooling occurs in the thighs, 25% in the lower legs, and 25% in the pelvis. Given the increased venous hydrostatic pressure, plasma fluid leaks into the interstitial space, leading to a modest (10%–15%) decrease in plasma volume, decreased BP, and decreased pulse pressure (a useful marker of decreased stroke volume). These hemodynamic changes lead to decreased arterial baroreceptor firing, which in turn leads to increased sympathetic tone and decreased parasympathetic tone. This immediate response is what leads to the appropriate responses of tachycardia, arterial vasoconstriction, venoconstriction, and increased cardiac contractility. There are also increases in antidiuretic hormone and angiotensin II, but these take longer to take effect. In short, the immediate adaptations to orthostatic stress are primarily mediated by enhanced sympathetic activity.

OH develops when these compensatory measures fail. OH is very common, affecting up to 30% of ambulatory patients, especially at older age. Hospitalized patients also have high rates, particularly transient OH related to immobility and volume depletion. OH causes troublesome symptoms such as orthostatic dizziness and lightheadedness, fatigue, visual blurring, muffled hearing, pain in the neck and shoulders ("coat-hanger" symptoms), and impaired concentration, as well as syncope and falls, often with injuries. However, many patients are completely asymptomatic despite severe reductions in BP.[3] A meta-analysis of available observational cohorts showed that OH is associated with significantly increased risk of death (risk ratio 1.50), coronary disease (risk ratio 1.41), stroke (risk ratio 1.64), and heart failure (risk ratio 2.25).[4] Despite extensive observational data identifying these risks, there are no clinical trials demonstrating that this risk can be modified by therapy.

EVALUATION OF ORTHOSTATIC HYPOTENSION

Following appropriate procedure is essential for accurate identification of OH. BP and HR are measured with the patient supine after at least 5 minutes of supine rest.[1] The patient then is tilted up or, in the office, the patient stands up, and BP and HR are measured at 1 minute and 3 minutes. Seated measurements are not needed, although I often obtain them to allow patients with severe OH to adapt before standing, and knowledge of seated BP levels is important as part of monitoring patients under treatment.

About 50% of venous pooling is in the thighs, 25% in the lower legs, and 25% in the pelvis

Supine BP values are useful to identify supine hypertension (see discussion below). Standing values provide us a measure of the severity of OH. In treated patients, measurements at the peak of action of drugs assess the effectiveness of therapy. Seated values, on the other hand, serve as a marker of safety as they identify both hypotension in untreated patients and excessive BP elevation in patients with treated OH.

Is there an appropriate heart rate response?

If the patient has OH, the first and critical question is whether there is an appropriate HR response (**Figure 1**).

As BP falls, the HR should increase in response. An appropriate HR response is defined by the ratio of the change in HR to the change in systolic BP with head-up tilt or

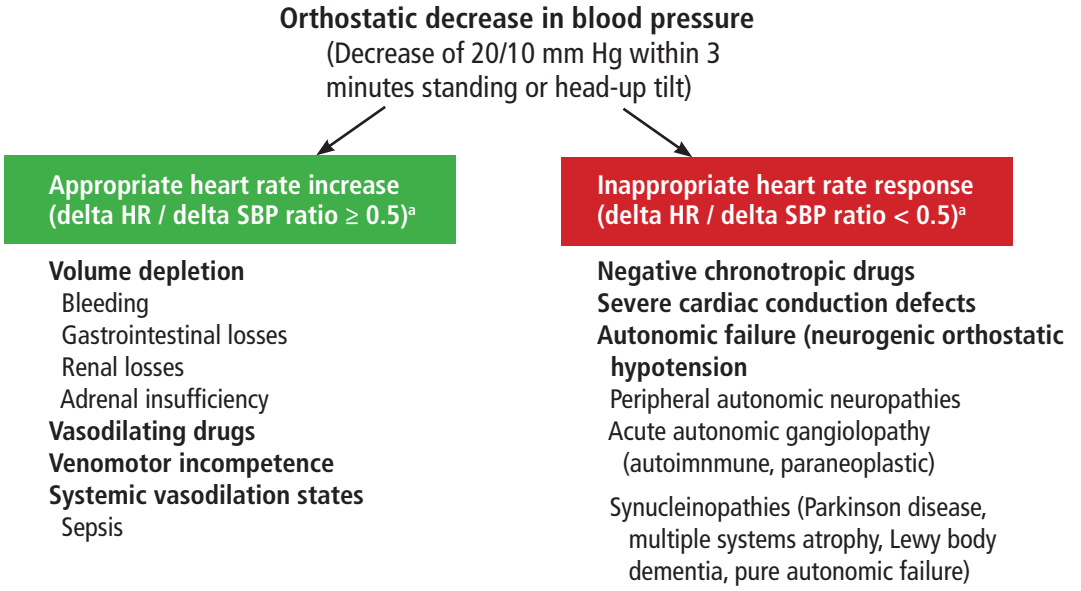

Figure 1. Diagnostic approach to orthostatic hypotension.

[a] Delta HR/delta SBP ratio is the ratio of the change in heart rate divided by the change in systolic blood pressure with standing or head-up tilt. Most patients with neurogenic orthostatic hypotension have a ratio below 0.3. Most patients with a normal autonomic response have a ratio above 1.0.

The critical diagnostic step is the heart rate response: if appropriate, think hypovolemia and medications; if inappropriate, think cardiac and neurogenic causes

standing.[5,6] In patients with intact autonomic responses, this ratio is greater than 0.5: for example, if the systolic BP falls by 40 mm Hg, a normal HR response should be an increase of greater than 20 beats per minute.[6] A ratio less than 0.5 identifies a neurogenic component with good sensitivity (91%) and specificity (88%).[6]

Use of this ratio is an important recent advance in the evaluation of OH, though a recent study corroborated its sensitivity but demonstrated very low specificity (50%).[7] Therefore, it is likely that further refinement of the procedure will be needed.

If there is an appropriate HR response, think of common causes, such as volume depletion of any cause, vasodilator drugs, venomotor incompetence (very often associated with immobility), or systemic vasodilatory states.

If the HR response is inadequate, possibilities include the use of a negative chronotropic drug (eg, beta-blocker, verapamil, diltiazem, ivabradine), the presence of a cardiac conduction defect (easily identified by an electrocardiogram and often requiring a pacemaker for effective management), or autonomic failure (neurogenic OH).

What are the neurogenic causes of orthostatic hypotension?

Autonomic neuropathy is a common cause of neurogenic OH. Possible etiologies of autonomic neuropathy are too numerous to list but include diabetes mellitus, amyloidosis, toxic neuropathies (drugs, heavy metals), infections, autoimmune diseases, hereditary conditions, paraneoplastic syndromes, and metabolic disorders. **Table 1** provides a summary of the most common causes of peripheral autonomic neuropathies to help guide further diagnostic testing based on clinical plausibility.

An approach to sorting out the neurogenic causes of OH involves considering the type of associated neurologic findings (if any) and whether the onset of the OH was acute/subacute or chronic and progressive.[8] Using this approach, the following 5 distinct categories arise:

1. **No neurologic symptoms, acute or subacute onset** (less than 3 to 6 months)**.** Consider autoimmune or paraneoplastic ganglionopathy and toxic exposures, particularly neurotoxic drugs. These cases often go undiagnosed. It is essential that these conditions be identified because

they often have specific therapy, such as immunomodulatory therapy for autonomic ganglionopathies or removal of a potentially toxic drug.

2. **No neurologic symptoms, chronic, slow progression.** Consider pure autonomic failure, a synucleinopathy that usually presents without nonautonomic features but often progresses to Parkinson disease or multiple system atrophy after prolonged follow-up.[9]
3. **Extrapyramidal or cerebellar motor features, chronic progressive course.** Consider synucleinopathies such as Parkinson disease, Lewy body dementia, and multiple system atrophy (with parkinsonian or cerebellar features).
4. **Peripheral neuropathic symptoms, acute or subacute onset.** Consider paraneoplastic syndromes, Sjögren syndrome and other connective tissue diseases, and toxic exposures.
5. **Peripheral neuropathy, chronic progressive onset.** Consider diabetes, amyloidosis, autoimmune disorders, infections, toxic exposures, and metabolic or hereditary disorders.

Diagnostic testing

A review of systems should look for causes of volume depletion, infection, and heart disease in addition to specific nonautonomic neurological symptoms (particularly extrapyramidal, cerebellar, or peripheral sensorimotor).

Vital signs should be taken in the office and at home. As part of the initial evaluation, I ask patients to keep a log of orthostatic BP at home for 1 to 2 weeks. I instruct them to measure BP at the following times:

- Upon getting up in the morning before taking any medications; this informs us of the presence and magnitude of supine hypertension and helps quantify the severity of the orthostatic hypotension
- After meals, because postprandial hypotension is common, and meal content may need to be modified (less rich in carbohydrates)
- If applicable, after vasopressor doses (1 to 2 hours after midodrine or droxidopa) to assess the effectiveness and safety of the treatment
- In the evening, to assess BP changes throughout the day. Most patients with neurogenic OH tend to have higher BP and less OH in the afternoon and evening.

Additionally, 24-hour BP monitoring can be useful to assess for nighttime supine hy-

TABLE 1

Relevant causes of peripheral autonomic neuropathies to help guide the diagnostic evaluation

Diabetes mellitus

Amyloidosis
AA (secondary) amyloidosis
AL (light chain, primary) amyloidosis
Transthyretin and other hereditary forms

Toxins
Heavy metals
Vincristine
Paclitaxel
Cisplatin
Thalidomide
Bortezomib

Infections
Human immunodeficiency virus
Chagas disease
Leprosy
Botulism
Diphtheria
Lyme disease
Syphilis

Autoimmune
Sjögren syndrome
Systemic lupus erythematosus
Mixed connective tissue disease
Sarcoidosis
Acute inflammatory demyelinating polyneuropathy
Chronic inflammatory demyelinating polyneuropathy

Hereditary
Hereditary peripheral and autonomic neuropathy
Fabry disease
Allgrove syndrome

Paraneoplastic

Metabolic
Renal failure
Hypothyroidism
Vitamin B_{12} deficiency
Porphyria

The cornerstone drugs are fludrocortisone, midodrine, and droxidopa

pertension and overall BP control. This is particularly useful in patients with significant BP changes from supine to seated to standing positions.

A detailed medication review should identify drugs that may lower BP or predispose to OH. These include antihypertensives, diuretics, anticonvulsants, antipsychotics, antidepressants, opioids, and benzodiazepines.

Testing includes electrocardiography, complete blood cell count, complete metabolic panel, thyroid function tests, and urinalysis for all patients. Patients without obvious neurologic findings often undergo further testing guided by the nature of the findings. Many patients benefit from echocardiography to rule out pericardial disease, pulmonary hypertension, severe valvular disease (especially aortic stenosis), and left ventricular dysfunction. Likewise, a cosyntropin stimulation test may be done to rule out adrenal insufficiency.

Many other tests have limited data to support them but may be used creatively in the management of complex cases. For example, I often use bioimpedance to objectively measure extracellular fluid volume when unsure of the level of volume repletion in a patient, allowing me to adjust some of the treatments that target volume expansion (salt tablets, fludrocortisone). Likewise, autonomic testing equipment with beat-to-beat BP monitoring can provide hemodynamic data (stroke volume, cardiac output, peripheral resistance) that can help guide adjustments in medications. The equipment I use for autonomic testing (Finapres NOVA) has a hemodynamics module useful in complex cases, though this approach has only been used anecdotally and has not been tested in clinical trials.

Fludrocortisone and a vasoconstrictor can be combined; if the patient is already receiving both, then pyridostigmine or atomoxetine can be added

A detailed autonomic evaluation using beat-to-beat BP and HR monitoring (during tilt and Valsalva maneuver) and quantitative sweat responses may have value. But usually, when patients present with OH due to autonomic failure, the diagnosis is obvious, and autonomic testing usually adds little.

Electromyography, nerve conduction studies, skin biopsy to quantify nerve fiber density and identify amyloid fibrils (and possibly alpha-synuclein), and targeted serologic evaluation can be of value in the evaluation of patients with peripheral neuropathic findings.

Brain imaging is always done for patients with motor findings and includes magnetic resonance imaging. Sometimes magnetic resonance or computed tomographic angiography of the head and neck may be useful to evaluate the vertebrobasilar circulation in patients who develop severe orthostatic symptoms at BP levels that are not very low (eg, systolic BP > 120 mm Hg).

A dopamine transporter scan may be of value to confirm a diagnosis of Parkinson disease, multiple system atrophy, or dementia with Lewy bodies.

Finally, cardiac ^{123}I-meta-iodobenzylguanidine scintigraphy or ^{18}F-fluorodopamine positron emission tomography may help distinguish between multiple system atrophy and Lewy body synucleinopathies (Parkinson disease and Lewy body dementia). In the former, there is preserved cardiac autonomic innervation, whereas in Parkinson and Lewy body dementia, cardiac uptake of catecholamines is decreased.[10]

MANAGEMENT OF ORTHOSTATIC HYPOTENSION

Patients with nonneurogenic causes of OH can usually be managed with treatment of underlying disorders, removal of offending agents, and volume replacement. Likewise, a pacemarker may be needed for patients with qualifying conduction defects.

Most causes of OH requiring long-term treatment are neurogenic. A consensus panel assembled by the American Autonomic Society and the National Parkinson Foundation recommends a stepwise approach to the treatment of neurogenic OH.[11]

Step 1 is a detailed medication review to identify drugs that often cause OH. Long-acting antihypertensives almost always should be stopped. When absolutely needed, administration should be at night. Antidepressants and anticonvulsants may have to be reconsidered.

Step 2 is the addition of nonpharmacologic measures. Exercise increases muscle tone and improves venomotor competence, reducing venous pooling, but should be either recumbent (eg, on a recumbent bike or rowing machine) or aquatic (swimming or pool-walk-

TABLE 2

Key drugs used in treating orthostatic hypotension

Drug	Class	Advantages	Disadvantages	Comments
Fludrocortisone	Synthetic mineralocorticoid	Increases extracellular volume and blood pressure Increases sensitivity to catecholamines	Supine hypertension Edema Long-acting (half-life 18–36 hours)	Start at 0.1 mg daily; increase to 0.2 mg after 2 weeks Onset of action is not immediate; full effect takes several days to 1 week
Midodrine	Prodrug of desglymidodrine (a direct alpha-1 agonist)	Increases arterial and venous tone and blood pressure Short-acting (half-life 3–4 hours)	Supine hypertension Urinary retention	Start with 2.5 mg three times a day (TID) (early morning, lunchtime, late afternoon); avoid doses within 4–6 hours before bedtime Increase dose by 2.5 mg TID every 3–7 days until symptoms controlled or maximum dose of 10 mg TID reached Higher doses are approved for other indications, but there is a flat dose-response curve at doses above 10 mg
Droxidopa	Precursor of norepinephrine (after conversion by dopa decarboxylase)	Increases arterial and venous tone Short-acting (half-life 2.5 hours)	Supine hypertension	Start with 100 mg TID (early morning, lunchtime, late afternoon) Avoid doses within 4–6 hours before bedtime Increase dose by 100 mg TID every 3–7 days until symptoms controlled or maximum dose of 600 mg TID reached
Pyridostigmine	Anticholinesterase	Improves standing blood pressure without change in supine blood pressure Short-acting (half-life 3–4 hours)	Wheezing Abdominal pain Diarrhea Hyperhidrosis	Useful in patients with constipation with or without urinary hesitancy Start with a 30-mg test dose; if well tolerated, give 60 mg twice a day, increasing to TID after 1–2 weeks if tolerated Seldom used at doses > 90–120 mg TID Titrations made every 1–2 weeks
Atomoxetine	Selective norepinephrine reuptake inhibitor	Increases standing blood pressure	Supine hypertension Irritability Insomnia Aggressive behavior Suicidal ideation	Used in lower doses than for attention deficit hyperactivity disorder Start at 10 mg once daily in morning, increasing to 18 mg, then 25 mg once daily Higher doses avoided, though safe to use up to 50 mg daily Titrations made every 1–2 weeks Half-life 5 hours, active metabolites 6–8 hours

ing) to maximize tolerability.

I recommend high sodium (> 150 mEq/day) and fluid (at least 2 L/day) intake to most patients. A premeal water load such as drinking 500 mL of water in about 5 minutes can be useful, especially if the patient has significant postprandial symptoms. In patients with autonomic failure, there is a significant increase in BP for 60 to 90 minutes in response to the osmosympathetic reflex whereby a decrease in osmolality of splanchnic blood results in an increase in sympathetic tone.[12]

I also recommend external venous compression to all patients. Compression stock-

ings should ideally come up to the waist to maximize the extent of compressed venous territory. Because the venous pressure at the level of the hips is about 30 mm Hg, patients should preferably wear garments that have a "30-40 gradient" (30 mm Hg at the thigh or waist and 40 mm Hg at the ankle), but some patients cannot tolerate the compression due to discomfort. In addition, some patients cannot get them on, so a compromise with lower compression garments (20-30 mm Hg or 15-20 mm Hg) is often needed. Most patients tolerate waist-high garments except for those who have urinary frequency or significant abdominal bloating or pain.

Step 3 is drug treatment. Despite the absence of high-quality evidence to support their use,[13,14] the cornerstone drugs are fludrocortisone, midodrine, and droxidopa; pyridostigmine and atomoxetine are used less often. **Table 2** summarizes relevant pharmacologic and clinical features of these agents. Only midodrine and droxidopa are approved by the US Food and Drug Administration (FDA) for use in OH. All other medications are used off-label.

Supine hypertension is a common complication of orthostatic hypotension, affecting 40% to 70% of patients

Fludrocortisone is a synthetic mineralocorticoid that increases extracellular fluid volume and increases sensitivity to catecholamines.[15] Because of its long duration of action, sustained hypertension (particularly at night) is often a problem limiting its use.

The vasoconstrictors midodrine and droxidopa are short-acting and therefore more useful for treatment during the daytime while avoiding supine hypertension at night. In one study, midodrine significantly increased the time to development of syncope or near-syncope on tilt testing by about 600 seconds, though not all patients responded.[16] Droxidopa is less potent than midodrine, but it does cause a significant increase in BP compared with placebo, along with a decrease in orthostatic symptoms.[17,18]

Midrodine and droxidopa have never been compared against each other, but individual patients respond differently. Some have a greater response to midodrine than to droxidopa, and some, the reverse. We do not yet know the reason for these differences nor can we predict how patients will respond, so in practice, if one drug does not work well, I try the other. Combining droxidopa and midodrine has not been formally tested. Anecdotal experience has been at times successful.[19]

Pyridostigmine is an acetylcholinesterase inhibitor that increases cholinergic transmission in autonomic ganglia and peripheral nerves. It has a modest and inconsistent effect on OH.[20,21] The ganglionic effect increases sympathetic tone, particularly in response to orthostatic stress, thus limiting the occurrence of supine hypertension.

Atomoxetine is a selective norepinephrine transporter inhibitor with inconsistent effects on orthostatic BP,[22] but in one recent study it was noted to improve standing BP similarly to midodrine while producing marginally larger improvements in orthostatic symptoms.[23]

Other medications used much less frequently, usually as last options when nothing else works, include octreotide, erythropoietin, desmopressin, pseudoephedrine, and ergot derivatives.[13]

My opinion-based approach to initial therapy. If the patient has no supine hypertension, I start with either a vasoconstrictor or fludrocortisone. I prefer vasoconstrictors not only because they are FDA-approved, but also because they can be used on an as-needed basis to treat intermittent symptoms, which is often the case, especially in patients with mild disease or early in the course of a progressive disease. If patients have no heart failure, edema, or hypokalemia, one can use either fludrocortisone or a vasoconstrictor, but the presence of any of these conditions argues against using fludrocortisone. I use pyridostigmine as the first choice only if a patient has mild neurogenic OH and significant constipation or gastroparesis, as it allows me to treat both the OH and the gastrointestinal hypomotility.

Step 4. Fludrocortisone and a vasoconstrictor can be combined. If the patient is already receiving both, then pyridostigmine or atomoxetine can be added.

Importantly, most of the trials to support the above treatments are small, uncontrolled observational studies. There is much need for improvement. For example, we have no drugs to specifically target the impaired venomotor tone. Perhaps a drug that blocks the natriuretic peptide receptor could cause valuable

venoconstriction—picture it as the opposite of a nitrate or nesiritide. Alternatively, noncatecholamine vasoconstrictors (vasopressin, angiotensin II) are available for intravenous use in critically ill patients, but these are not yet translated to viable oral options that could be used to treat neurogenic OH. Desmopressin is a vasopressin V2-receptor agonist with limited pressor function. Its modest favorable effects in neurogenic OH are likely related to decreased nocturnal urine output, not vasoconstriction. Terlipressin, on the other hand, is a potent vasopressin V1-receptor agonist used in patients with hepatorenal syndrome. It has a potent pressor effect in patients with neurogenic OH when given intravenously[24] but is not available in oral form. Additionally, and very importantly, we do not know the long-term impact of therapy on patient-reported outcomes, functional outcomes (injurious falls, syncope, cognition), or cardiovascular outcomes.

SUPINE HYPERTENSION

Supine hypertension is a common complication of OH, affecting 40% to 70% of patients, adding complexity to patient management. It is graded as mild if the supine BP is 140–159/90–99 mm Hg, moderate if 160–179/100–109 mm Hg, and severe if 180/100 mm Hg or higher, as measured after at least 5 minutes of supine rest.[25] I usually accept supine BPs up to 160/100 mm Hg, and depending on the severity of the OH, I may be forced to accept pressures as high as 180 mm Hg. In such cases, 24-hour BP monitoring is extremely helpful to quantify the overall BP burden.

The approach to its treatment is first nonpharmacologic. Fludrocortisone should almost always be stopped. Vasopressors should not be given within 4 to 6 hours before going to bed. Elevation of the head of the bed, typically about 8 inches, is helpful but often not well tolerated. If using an adjustable mattress, the head of the bed is elevated about 30 degrees and, if adjustable, the foot of the bed is lowered by a similar amount. Also, if the presence of diabetes or obesity does not prohibit it, I often recommend a high-carbohydrate snack at bedtime if patients have a demonstrable response to it. The typical effective dose is 200 to 400 calories (50–100 g) in the form of pure carbohydrates, eg, candy. Sensitivity varies, and many patients have a good response to smaller doses.

Pharmacologic management is often needed.[26] Because of the problem of OH during the day, long-acting agents cannot be used. Short-acting antihypertensive drugs are given at bedtime. Several agents can effectively lower BP, but my personal preference for initial use is nitrates. Most of the studies have used topical nitroglycerin,[27] though to avoid hypotension, patients have to wake up early to remove the patch and stay in bed for 30 to 60 minutes before getting up. Because of this, I prefer isosorbide dinitrate (starting dose 20 mg, titrated up to 80 mg as needed).

Clonidine (0.1 mg orally) and nitroglycerin lower nighttime BP to a similar degree, but nitroglycerin has less residual BP-lowering effect in the morning.[27] Clonidine is often helpful in patients with residual sympathetic tone, which is most commonly observed in patients with multiple system atrophy.

Other drugs tested in single-dose trials include sildenafil, captopril, losartan, nebivolol, eplerenone, minoxidil, and hydralazine, with variable results and often a "tail effect" in the morning.[26] Even though losartan is relatively long-acting, surprisingly it does not worsen morning OH, presumably due to increased angiotensin II levels.[28] It is a drug I prescribe often, particularly in patients with chronic kidney disease or heart failure with reduced ejection fraction, in whom the use of a blocker of the renin-angiotensin system has significant benefits.

Short-acting antihypertensive drugs may be needed at bedtime to treat supine hypertension

CASE CONCLUDED

In our patient, the rapid pace of development raised the concern for an acute autonomic ganglionopathy. Acute autonomic neuropathy is called ganglionopathy because the lesion is at the autonomic ganglia.[29] This is a rare disorder in which patients present with acute or subacute pandysautonomia (orthostatic hypotension, neurogenic bladder, gastrointestinal hypomotility, pupillary dysfunction, hypohidrosis) in various combinations. It is typically immune-mediated and can be transferred passively in animal models. The initial description was caused by antibodies against the

ganglionic acetylcholine alpha 3 receptor.[30] These antibodies have also been described in paraneoplastic autonomic ganglionopathy, although in that condition the most common antibody is the antineuronal nuclear antibody type 1 (ANNA-1, formerly called anti-Hu antibody).[29] These antibodies are tested using commercially available neuroautoantibody panels. Several other rare antibodies have been described, and 30% to 50% of patients presenting with the classic syndrome are seronegative. The severity of the elevation of antibody titers often correlates with the clinical presentation. It is likely that seronegative patients have antibodies against epitopes not yet identified, as many improve with immunomodulatory treatments.[31] Treatments reported include plasma exchange, intravenous immunoglobulin, and a variety of immunosuppressants.[29,32] Our protocol includes intravenous immunoglobulin with or without steroids.

Given this possibility in our patient, we obtained a neuroautoantibody panel (Mayo Clinic Laboratories). The patient had moderately high titers of antibody against the ganglionic acetylcholine receptor. Given her age, we suspected a paraneoplastic syndrome despite a lack of symptoms, but no tumor was identified on computed tomography (neck to pelvis), in addition to a normal recent colonoscopy. Sometimes the syndrome presents before a malignancy is clinically identifiable. However, in its absence, we diagnosed her as having autoimmune autonomic ganglionopathy with predominant cardiovascular involvement (and perhaps mild gastrointestinal disease, given the constipation). We treated her with intravenous immunoglobulin (2 g/kg over 5 days) and intravenous methylprednisolone (500 mg/day for 5 days). She had a positive response and was able to walk out of the hospital and to attend rehabilitation 3 weeks after treatment was started. She remained on biweekly intravenous immunoglobulin for 2 months and on monthly doses for another 4 months. She continued to have OH but regained reasonable orthostatic tolerance and returned to independent living on maintenance therapy with midodrine 5 mg 2 to 3 times daily. Her current orthostatic tolerance is in the range of 7 to 10 minutes.

As for the other possible answers to the question regarding the most appropriate test for our 83-year-old patient, autonomic testing would not have given additional information. Amyloid was not likely based on the rapid rate of progression (ie, within 3 months) and the negative screen for AL amyloid. Hereditary amyloid forms and AA amyloid were clinically improbable. Electromyography and nerve conduction studies would probably not have helped as the patient had no peripheral sensorimotor findings. Skin biopsy could be useful to identify decreased nerve fiber density as seen in small fiber neuropathies, but the presentation did not suggest this.

DISCLOSURES

Dr. Peixoto has disclosed research/independent contracting for Bayer, Boehringer-Ingelheim, Lundbeck, and Vascular Dynamics; serving as advisor or review panel participant for Ablative Solutions and Relypsa Pharmaceuticals; and serving as consultant/advisor or review panel participant for Diamedica Therapeutics. This presentation discusses off-label-use of medications: fludrocortisone, pyridostigmine, octreotide, and atomoxetine.

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Cardiac considerations in liver transplantation

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ABSTRACT

Cardiovascular events have a major impact on overall outcomes after liver transplantation. Today's transplant patients are older than those in the past and therefore are more likely to have coexisting cardiac comorbidities. In addition, pathophysiologic effects of advanced liver disease on the circulatory system pose challenges in perioperative management. This review discusses important preoperative, intraoperative, and postoperative cardiac considerations in patients undergoing liver transplant.

KEY POINTS

The average age of patients undergoing liver transplant has risen over the years, and a greater percentage than in the past now have nonalcoholic steatohepatitis as their underlying diagnosis.

Cardiac evaluation and optimization before liver transplant is crucial to avoid adverse clinical outcomes. This should ideally be done by a dedicated cardiology team with experience and expertise in managing cardiac issues pertinent to this specific population.

Outcomes after liver transplant have improved over time even though the patients are at higher risk.

The clinical outcomes of liver transplant recipients might be further improved preoperatively with standardized cardiac risk-stratification pathways, and perioperatively with evidence-based cardiac clinical care. This is an evolving field, and more research is needed to guide clinical decision-making in several important areas of clinical care.

Attention to the heart before, during, and after liver transplantation can pay off in terms of better outcomes. This, even though today's liver transplant patients are older than those in the past and more likely to have fatty liver disease as the cause of their liver failure, and even though liver failure, the transplant procedure, and the post-transplant regimen can all predispose to heart disease.

The changing demographics of patients receiving liver transplants and the unique cardiac pathophysiology of patients with advanced liver disease pose significant challenges in managing these patients perioperatively, as we will discuss in the following sections.

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OLDER PATIENTS, MORE FATTY LIVER DISEASE

Liver transplant is currently the second most common organ transplant in the United States, after kidney transplant. The number of liver transplants per year has increased greatly over time, from 1,713 in 1988 to 8,906 in 2020.[1]

At the same time the age of patients receiving transplants has also increased. For instance, 476 (28%) of the 1,713 liver transplant recipients in 1988 were age 50 or older, increasing to 6,497 (73%) of 8,906 in 2020.[1] Survival rates are lower in older patients: 75.0% at 5 years in those age 35 to 49, 70.9% in those age 50 to 64, but only 65.9% in those 65 and older,[1] likely due to more comorbidities such as coronary artery disease in the older patients.

Another important change in patients receiving liver transplants has been an increase in those with nonalcoholic steatohepatitis as the underlying diagnosis. In 2013, nonalcoholic steatohepatitis was the second most common cause of liver failure in new wait-list registrants for liver transplant, after hepatitis C cirrhosis.[2]

Patients with nonalcoholic steatohepatitis typically have traditional risk factors for coronary artery disease such as diabetes mellitus, obesity, hypertension, and hyperlipidemia,[3] and thus have a higher risk of coronary artery disease.[4] After liver transplant, cardiovascular events are much more common in patients with nonalcoholic steatohepatitis than in those with other causes of liver failure.[5]

HEART DISEASE IN LIVER TRANSPLANT RECIPIENTS

Liver transplant recipients have a higher prevalence of coronary artery disease than in the general population. Other important cardiac conditions to recognize and manage include cirrhotic cardiomyopathy, portopulmonary hypertension, heart failure, and thromboembolism.

Coronary artery disease

In various studies,[6–8] the prevalence of coronary artery disease in patients with end-stage liver disease has ranged from 16.2% to 27%, which is higher than in the general population (6%)[9] and similar to that in patients with diabetes. A recent study found an even higher number (32.5%), reflecting the changing profile of patients undergoing liver transplant, with the increasingly older patient population.[10]

The risk of coronary artery disease is particularly high in patients over age 50 and those with coronary risk factors such as diabetes mellitus.[7] Other important risk factors include hypertension, existing cardiovascular disease, hyperlipidemia, and smoking. Having 3 or more of these risk factors is associated with higher risks of severe coronary artery disease, major adverse cardiovascular events, and death after transplant.[11] Thus, patients who have multiple risk factors should be thoroughly evaluated for severe coronary artery disease, even if they have no coronary symptoms.[12]

Moreover, older patients currently undergoing liver transplant are also more likely to have concomitant valve disease, which adds further complexity to the management of coronary artery disease in these patients.

Heart failure

Patients with liver disease can develop both cardiac systolic and diastolic dysfunction over time. Other changes in cardiovascular physiology in end-stage liver disease are listed in **Figure 1**. These patients also have splanchnic and marked peripheral vasodilation with activation of the renin-angiotensin-aldosterone axis. This results in volume overload and elevated pressures in the right ventricle, pulmonary arteries, and left atrium.

Signs and symptoms of heart failure may be masked in patients with cirrhosis

Signs and symptoms of heart failure may be masked in patients with cirrhosis, owing to chronic vasodilation, which reduces cardiac afterload, allowing patients to compensate under resting conditions. However, this cirrhotic cardiomyopathy may be unmasked during conditions of cardiovascular stress, such as during liver transplant. Also, after liver transplant, vascular tone promptly returns to normal, with an ensuing increase in venous return, which can further elevate right-sided pressures and precipitate acute heart failure.[13] In particular, patients with elevated pulmonary arterial pressure (including those with portopulmonary hypertension), diastolic dysfunction,[14] and older age are more likely to develop heart failure after transplant.[15]

Thus, it is crucial to carefully optimize he-

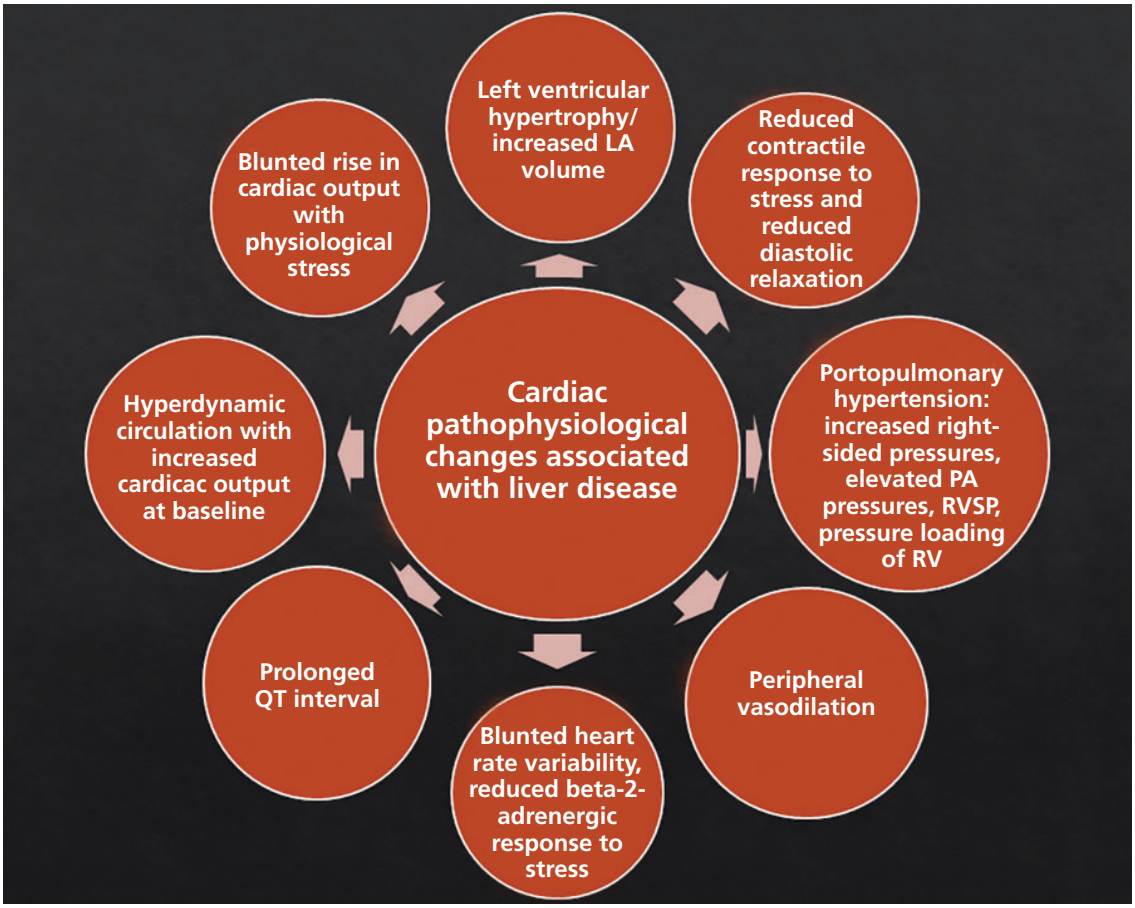

Figure 1. Cardiovascular pathology in end-stage liver disease.

LA = left atrial; PA = pulmonary artery; RV = right ventricle; RVSP = right ventricular systolic pressure

Reducing cardiovascular risk remains one of the most crucial aspects of the pretransplant workup

modynamic variables in the perioperative period, particularly preventing volume overload through careful perioperative fluid management and judicious use of diuretics as needed. Of note, however, cirrhotic cardiomyopathy is reversible, and liver transplant can improve left ventricular thickness, diastolic function, and cardiac systolic response to stress over time.[16]

Other cardiovascular events

Other cardiovascular events such as perioperative arrhythmias and stroke are also common in liver transplant recipients and contribute to higher morbidity and mortality rates after the procedure.[17] As a result, liver transplant recipients face a greater risk of cardiovascular events perioperatively, and cardiovascular events are a leading cause of death after liver transplant.[18] Thus, reducing cardiovascular risk remains a crucial part of the pretransplant workup in patients with end-stage liver disease.[10,17,19] These aspects of perioperative management in liver transplant recipients are discussed further in subsequent sections of this review.

PREOPERATIVE SCREENING FOR HEART DISEASE

History and physical examination

The joint 2012 American College of Cardiology and American Heart Association (ACC/AHA) guidelines for evaluation of cardiac disease in kidney and liver transplant recommend a complete history and physical examination as the first step in evaluating cardiac risk.[12] This should focus on any active symptoms of heart disease, risk factors for coronary artery disease, and preexisting coronary or cardiovascular conditions.

Echocardiography for pulmonary hypertension

The 2012 ACC/AHA guidelines note that it is reasonable for patients to undergo echocardiography to look for pulmonary hypertension and intrapulmonary arteriovenous shunting,[12] while the 2014 guidelines from the American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation (AST) note that it should be done routinely.[20] Portopulmonary hypertension (concomitant portal and pulmonary hypertension) is found in 5% to 10% of patients with chronic liver disease.[21] Unless patients undergo liver transplant or start on appropriate medical therapy, portopulmonary hypertension carries a very poor prognosis, with 5-year survival rates as low as 14%.[21,22]

Right heart catheterization

Right heart catheterization should be performed in patients who have evidence of portopulmonary hypertension on echocardiography, to accurately evaluate the severity and etiology of the pulmonary hypertension (defined as mean pulmonary artery pressure ≥ 25 mm Hg, pulmonary capillary wedge pressure ≤ 15 mm Hg, and pulmonary vascular resistance > 3 Wood units on right heart catheterization).[12,20] Furthermore, the guidelines recommend consulting a specialist in pulmonary arterial hypertension and considering vasodilator therapy to manage pulmonary hypertension when appropriate if there is no clear secondary cause such as obstructive sleep apnea or left heart disease.

Liver transplant can be offered to patients with portopulmonary hypertension who respond to medical therapy and have a mean pulmonary artery pressure no greater than 35 mm Hg.[20]

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing and a 6- or 3-minute walk test can provide additional useful prognostic information.[20–23] In addition, patients being evaluated for liver transplant should have a cardiac workup to see if they may be at increased risk of myocardial ischemia and infarction perioperatively, so that their risk can be optimized.

Cardiac single-photon emission computed tomography

Cardiac single-photon emission computed tomography (SPECT) has traditionally been a popular choice for the noninvasive ischemic evaluation of patients with a low to moderate risk of cardiovascular events in noncardiac surgery. However, due to the underlying vasodilated state in patients with end-stage liver disease, SPECT can have low sensitivity and specificity as a screening test for coronary artery disease in candidates for liver transplant.[12,24,25]

Stress echocardiography

The 2013 AASLD/AST guidelines strongly recommend stress echocardiography for cardiac evaluation in liver transplant candidates.[20] Recognizing that patients with advanced liver disease are less likely to achieve their target heart rate with exercise, the AASLD/AST guidelines recommend pharmacologic stress echocardiography with a vasodilatory agent such as adenosine, dipyridamole, or dobutamine. Cardiac catheterization in cases in which coronary artery disease cannot be excluded confidently with stress testing.[20]

Similarly, the 2012 ACC/AHA statement advocates noninvasive testing for coronary artery disease in candidates for liver or kidney transplant being evaluated for coronary artery disease but does not endorse one particular test.[12]

Dobutamine stress echocardiography remains a commonly used noninvasive tool for preoperative screening for coronary artery disease in liver transplant patients.[20] However, it has variable sensitivity in these patients and limited ability to identify those at high risk of cardiovascular events and poor outcomes after transplant.[25–27] In view of its limitations, other imaging modalities such as coronary artery calcium scoring and computed tomographic coronary angiography are being investigated for their utility in the cardiovascular evaluation of liver transplant patients, though their exact role is currently less well defined.[28–31]

Coronary angiography

Coronary angiography is increasingly being used to screen for cardiovascular disease in liver transplant candidates, particularly in those over age 50 and those who have either known coronary disease or risk factors for it.

Cardiac evaluation and optimization should ideally be done by a dedicated cardiology team

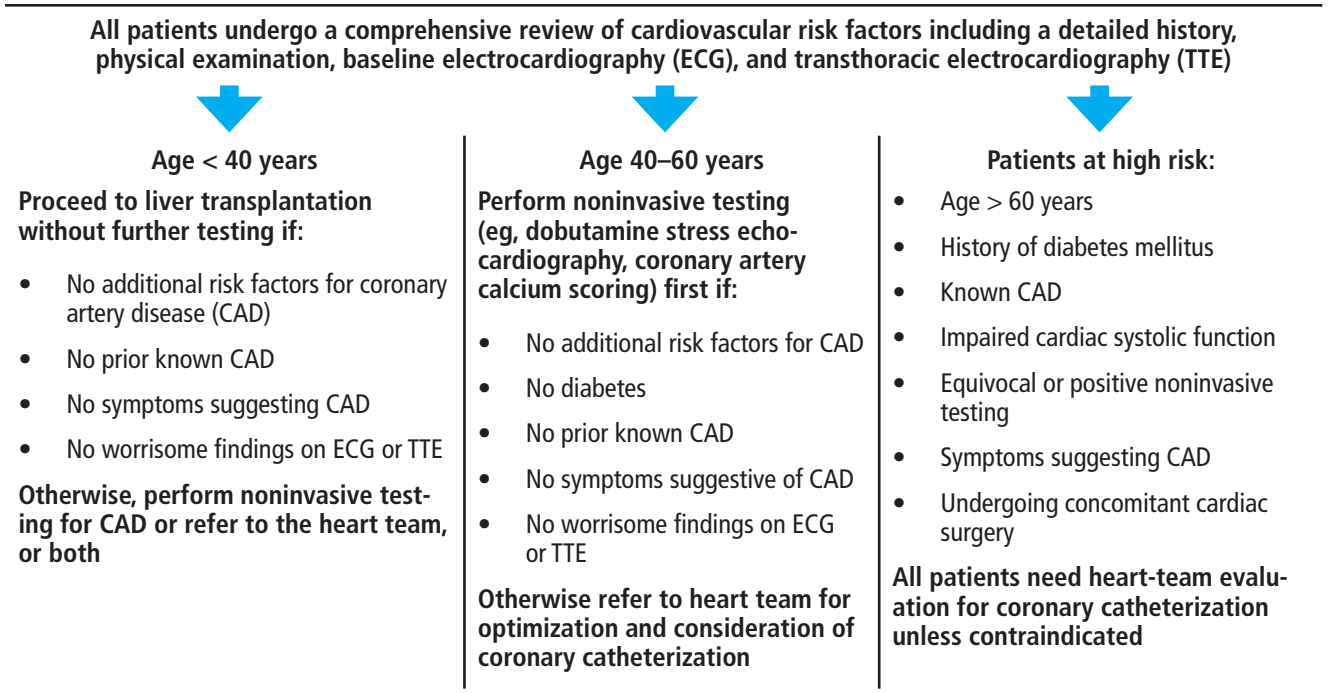

Figure 2. Protocol for cardiac evaluation before liver transplantation at Cleveland Clinic.

A dilemma: dual antiplatelet therapy after stenting may delay transplant

Other patients who need an invasive assessment for coronary artery disease include those undergoing concomitant cardiac surgery (such as valve surgery) to accurately study the coronary anatomy so that the need for simultaneous coronary artery bypass grafting can be addressed.

Coronary angiography has become safer for patients undergoing evaluation for liver transplant, especially with increasing use of an approach through the radial artery instead of the femoral artery. This approach greatly reduces the risk of vascular complications. Strict emphasis on minimizing dye load and other precautions such as the use of biplane coronary angiography have also reduced the risk of contrast nephropathy.

Team approach

Cardiac evaluation and optimization should ideally be done by a dedicated cardiology team with experience and expertise in managing cardiac issues pertinent to this population,[12] particularly to address the need for coronary revascularization and to optimize cirrhotic cardiomyopathy or any coexisting valve disease before liver transplant and to manage cardiovascular events afterward. **Figure 2** summarizes the Cleveland Clinic protocol for pretransplant cardiovascular evaluation of patients with advanced liver disease.

CORONARY REVASCULARIZATION BEFORE LIVER TRANSPLANT

Patients with preexisting coronary artery disease have a higher risk of perioperative death and postoperative morbidity after liver transplant, and cardiac events are associated with lower survival rates, particularly in older patients.[12] Yet evidence is still currently lacking regarding which patients would benefit from coronary revascularization before liver transplant.

The 2012 ACC/AHA guidelines state that it is reasonable to consider revascularization for patients who have medically refractory angina before liver transplant, while acknowledging the lack of evidence to support this approach.[12] Specific indications for revascularization in those without symptoms remain to be established.

Currently, due to the lack of standardized national or international guidelines, the decision about the need for revascularization must

TABLE 1

Inclusion and exclusion criteria for combined cardiac surgery and liver transplantation at Cleveland Clinic

Inclusion criteria
Severe or complex coronary artery or valve disease not amenable to percutaneous intervention
Contraindication to dual antiplatelet therapy such as need for repeated paracentesis or a noncardiac intervention, or chronic thrombocytopenia
Child-Pugh score > 8, needing cardiac surgery for cardiovascular optimization but otherwise a candidate for liver transplantation
Patients with a very high Model for End-stage Liver Disease score who cannot wait to complete at least 3 months of dual antiplatelet therapy after a percutaneous intervention before proceeding with liver transplantation
Left ventricular ejection fraction > 55%
Exclusion criteria
Left ventricular dysfunction
Advanced chronic kidney disease
Unsuitable coronary anatomy
Active infection
Extrahepatic malignancy
Other contraindications to liver transplantation itself, such as evidence of substance abuse, history of nonadherence, and poor social resources

be individualized and based on the experience and prevailing practice in each center. More research and clinical trials are critically needed to guide decision-making in this regard.

In patients who undergo percutaneous coronary intervention before liver transplant, the need for dual antiplatelet therapy necessitates delaying the transplant procedure for at least 3 months.[12] Further, patients with liver cirrhosis have a higher risk of bleeding complications during dual antiplatelet therapy after percutaneous coronary intervention. However, newer-generation drug-eluting stents may allow for a shorter duration of dual antiplatelet therapy,[32,33] thereby allowing earlier transplant and reducing bleeding complications after the coronary intervention.[34] Recent studies have shown that with optimal management of coronary artery disease, clinical outcomes can be similar to those in patients without coronary disease.[35]

VALVE REPAIR BEFORE LIVER TRANSPLANT

Patients with heart valve abnormalities also need careful hemodynamic optimization perioperatively, and those with severe valve disease may need valve surgery (if the operative risk is not otherwise prohibitive) or transcatheter intervention as appropriate. Improvements in transcatheter valve therapy in recent years have expanded the indications for these interventions, and outcomes of transcatheter valve therapy are now comparable to those of surgical valve interventions.

COMBINED HEART SURGERY AND LIVER TRANSPLANT

In some patients, the bleeding risk associated with dual antiplatelet therapy may rule out percutaneous coronary intervention before liver transplant. Furthermore, the coronary anatomy in some patients may be unsuitable for percutaneous intervention, or the coronary disease may be diffuse and therefore impossible to treat with percutaneous intervention.

In addition, some patients may also have coexisting severe valve disease that can only be addressed with cardiac surgery. Such patients have a high risk of perioperative mor-

Liver disease can cause vasodilation, low systemic vascular resistance, and an impaired response to vasoconstrictors

tality and morbidity if they undergo cardiac surgery or liver transplant alone. For instance, patients with a Child-Pugh score higher than 8 are deemed to have a very high risk of perioperative complications if they undergo cardiac surgery before liver transplant.[36]

In such patients, concomitant cardiac surgery (or cardiac transplant if appropriate and feasible) and liver transplant can be offered, though the risk of adverse events associated with these procedures is higher in patients with advanced liver disease (Child-Pugh class B and C).[12,36] Patients with a high Model for End-stage Liver Disease score or with a short predicted wait-time for transplant cannot wait to undergo at least 3 months of dual antiplatelet therapy after percutaneous coronary intervention. These patients can be offered simultaneous liver transplant and cardiac surgery, provided they do not have specific contraindications, such as left ventricular dysfunction.[36]

Important contraindications to this combined surgical approach include advanced chronic kidney disease, unfavorable coronary anatomy, active infection, extrahepatic malignancy, evidence of substance abuse, history of nonadherence, and poor social resources.

Acute left ventricular dysfunction can develop after liver transplant

There are relatively few data in the literature on patients who have undergone simultaneous liver transplant and cardiac surgery.[36,37] However, we anticipate that with the increasing age at presentation of patients undergoing liver transplant, such combined procedures may become more common.

Table 1 lists the criteria for combined liver and cardiac surgery at Cleveland Clinic.

INTRAOPERATIVE CARDIAC CONSIDERATIONS

Liver transplant is one of the most demanding surgical procedures and is associated with a significant risk of intraoperative cardiovascular complications and therefore poses intraoperative challenges.

Hemodynamic instability

A significant number of patients presenting for liver transplant carry hemodynamic sequelae of end-stage liver disease including generalized vasodilation, low systemic vascular resistance, and an impaired vasoconstrictive response to both endogenous and exogenous vasoconstrictors. Cirrhotic cardiomyopathy has been noted in as many as 60% of patients with cirrhosis.[38] These patients also have simultaneous central hypovolemia with splanchnic hypervolemia. The combination of acute blood loss, large fluid shifts, and manipulation of the inferior vena cava during surgery can put a significant stress on the cardiovascular system.

Because of these factors, intraoperative hemodynamic instability is common during the dissection phase (due to blood loss) and the hepatic phase (due to obstruction of the inferior vena cava) of liver transplant.

Postreperfusion syndrome

Immediately after reperfusion of the graft, many patients experience postreperfusion syndrome, defined as a decrease in mean arterial pressure of more than 30% below the baseline value, lasting at least 1 minute, during the first 5 minutes after reperfusion of the graft.[39] The reported incidence of postreperfusion syndrome varies widely, ranging from 12% to 77%.[40] Up to 5% of patients may experience postreperfusion cardiac arrest.[41]

Other intraoperative cardiovascular complications

Acute heart failure. Intraoperative heart failure has been reported to occur in up to 3% of liver transplant procedures,[42] but that may be an underestimation due to underutilization of intraoperative transesophageal echocardiography.[42] Transesophageal echocardiography can be safe and useful for intraoperative monitoring of major life-threatening cardiovascular complications during liver transplant surgery, after carefully reviewing the risks and benefits in each patient.[43]

Dynamic left ventricular outflow obstruction can develop intraoperatively due to a combination of decreased venous return (due to bleeding, vena cava obstruction, or volume loss due to the drainage of a large amount of ascites) and hyperdynamic left ventricular function. If untreated, it can lead to severe hypotension and hemodynamic instability.[44]

Takotsubo cardiomyopathy. Stress-induced cardiomyopathy, commonly referred to as takotsubo cardiomyopathy, has been reported perioperatively in the setting of liver trans-

plant and is most commonly seen in female patients. Risk factors for developing stress-induced cardiomyopathy are poorly understood. Management is similar to that for acute heart failure from other causes, with recovery of systolic function expected in a significant percentage of patients.[45]

Thromboembolism. Right-sided intracardiac thrombosis and pulmonary embolism are other serious thrombotic complications seen during liver transplant and have high mortality rates. Their incidence ranges from 1% to 6%.[41,46] Awareness of these common complications during surgery can lead to their prompt recognition, allowing the anesthesiologist to intervene early and prevent a poor outcome.

CARDIAC CONSIDERATIONS AFTER LIVER TRANSPLANT

Acute left ventricular dysfunction can develop after liver transplant, particularly if there is evidence of diastolic dysfunction before transplant.[14] Patients who develop acute left ventricular failure after transplant have a high risk of death and graft failure within the first year. Some patients may recover left ventricular function after liver transplant, though recovery is less likely if they have preexisting diastolic dysfunction.[14]

Heart failure. Patients with evidence of diastolic dysfunction or reduced systolic function before transplant need close postoperative surveillance for signs and symptoms of heart failure. Patients with suspected heart failure or volume overload after transplant should be evaluated with echocardiography, and the cardiology team should be involved early to help manage it.

New coronary artery disease. Liver transplant recipients have an increased risk of developing metabolic syndrome and coronary artery disease after transplant, in particular as a side effect of immunosuppressive regimens.[47] For instance, steroids, calcineurin inhibitors, and inhibitors of mammalian target of rapamycin are associated with hyperlipidemia, hypertension, obesity, and diabetes, whereas mycophenolate mofetil and azathioprine appear to have no effect on the risk profile for coronary artery disease.[17]

Thus, it is important to focus on preventing coronary artery disease after liver transplant in these patients, aggressively modifying risk factors and carefully selecting the immunosuppressive regimen, especially in those who had a moderate to high risk of coronary artery disease before transplant.[19] Statins are safe in this patient population. They significantly reduce mortality risk and decrease the risk of graft rejection, yet they remain widely underutilized.[48]

FUTURE DIRECTIONS

Outcomes after liver transplant, particularly patient and graft survival, have improved with time[1] despite a higher risk profile in current patients, who are older and have more cardiac comorbidities than those in the past. Considering the major impact that perioperative cardiovascular events have on outcomes, effective cardiac risk stratification and optimization using standardized and evidence-based protocols could further improve the clinical outcomes of liver transplant.

We anticipate that the use of imaging modalities such as computed tomographic coronary calcium scoring and computed tomographic angiography will expand, in addition to the already rising use of coronary angiography and transcatheter valve interventions in high-risk patients.

Outcomes after liver transplant have improved despite the higher risk profile of current patients

Next-generation drug-eluting stents and greater use of transcatheter valve interventions may allow for further improvement in the range of options for cardiovascular optimization before transplant.

Growing knowledge about the risk factors for development and progression of heart failure and coronary artery disease after transplant has also clarified the need for thorough clinical monitoring and effective preventive strategies after liver transplant.

More research is needed into these aspects of cardiovascular care, including screening for heart disease and optimizing cardiovascular health before transplant, managing cardiovascular complications during transplant, and preventing cardiovascular disease afterward.

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Dr. Eghtesad has disclosed work as advisor or review panel participant and principal or co-investigator of funded research for Genzyme/Sanofi. Dr. Tong has disclosed consulting, teaching, and speaking for Abbott and Abiomed. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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