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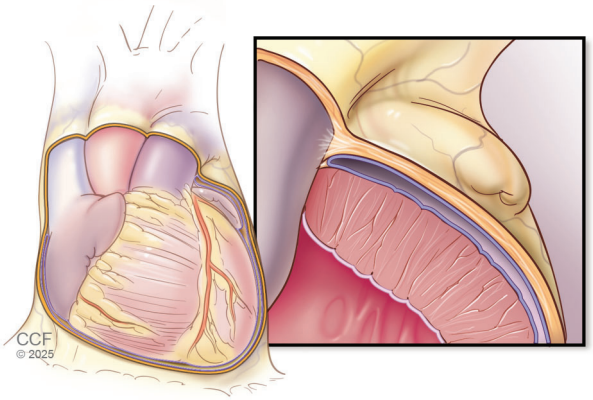

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Treating the thyroid: Trust the feedback loop

The mechanisms for cellular effects of thyroid hormones on target tissues in the periphery and on the pituitary gland for negative feedback control of thyroid-stimulating hormone (TSH) release are complex.[1] Interaction with genomic receptors directly affects transcriptional elements, other effects are mediated via interactions with the plasma membrane, and some hypermetabolic effects result from direct interaction of thyroid hormones with mitochondria. The systemic clinical effects are myriad. In addition to effects on the basal metabolic rate, thyroid hormones increase expression of beta-adrenergic receptors on the surface of cardiac myocytes[2] and decrease the level of circulating low-density lipoprotein (LDL) cholesterol by both stimulating the conversion of hepatocyte cholesterol to bile acids and reducing the level of proprotein convertase subtilisin/kexin type 9,[3] an enzyme that degrades hepatic LDL receptors, resulting in increased clearance of circulating LDL cholesterol by the liver. Many factors external to the thyroid gland can modulate these diverse effects, making it difficult to assess the thyroid status of patients solely on clinical grounds.

I contrast the complexity of thyroid hormone functions with the relative simplicity and reliability of the pituitary-thyroid axis that dictates hormone output by the functioning thyroid gland. It is sufficiently straightforward that a thermostat and furnace analogy works reasonably well for almost all patients, and can help guide our clinical reasoning. Measurement of the TSH alone (the thermostat setting) is sufficient for initial screening and follow-up for most patients with suspected or known thyroid disease, yet multiple studies have demonstrated that we order more free thyroxine (T4) and triiodothyronine (T3) levels than are necessary.[4] While there are always exceptional situations, we should apparently trust the TSH feedback loop more than we do.

In this issue of the *Journal*, Bodnar and Saberi[5] discuss a patient with apparent hyperthyroidism, which was suspected based on an abnormally low TSH level. In their Symptoms to Diagnosis article, the authors work through with the reader the patient's clinical course after the initial diagnosis.

But I want to discuss briefly an alternative scenario in which a patient is found to have a slightly *elevated* TSH. Once the abnormal TSH level is detected (but not before), it is appropriate to check a free T4 level to distinguish the patient with true primary hypothyroidism from the rarer scenario of inappropriate secretion of TSH from the pituitary (or another site). Although routine testing of TSH in asymptomatic patients has been strongly discouraged,[6] the symptoms consistent with mild hypothyroidism are diverse and nonspecific enough that testing is often warranted.

Not infrequently, mild elevations in TSH are accompanied by a free T4 level in the normal range. The TSH, when rechecked (as it should be), may be back in the normal range, since low-level TSH elevations may physiologically fluctuate by as much as 40%,[7] while free T4 levels may vary by 15%. But the persistent demonstration of what is usually a minimal elevation of TSH with a normal free T4 defines subclinical *hypo*thyroidism.

Many patients with subclinical hypothyroidism can be observed off treatment, with scheduled rechecking of TSH and free T4, because some patients will develop clinical hypothyroidism. The highest estimate of progression of patients to overt hypothyroidism that I found in the literature was 58% over 10 years, but, importantly, this was in patients who all had antiperoxidase thyroid antibodies,[8] the major measurable factor predicting ultimate thyroid failure. Other factors that

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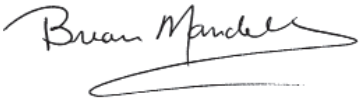
increase the risk of progression include being female, having a higher TSH level (> 10 mIU/L), having heterogeneous thyroid tissue on ultrasonography examination, or having a very low normal T4. But without the presence of antiperoxidase antibodies, the risk of progression is low. In the absence of changing clinical symptoms or otherwise unexplained laboratory findings such as rising LDL cholesterol, repeat measurement of TSH and free T4 every 12 months, or every 6 months in the presence of antiperoxidase antibodies, seems reasonable. There is no need to recheck antibody titers or to check reverse T3 levels.[9] Evaluating and following patients with subclinical *hyper*thyroidism is different, and checking the free T3 level is also important, especially in patients who may have Graves disease.[10] Letting trust in the reliability of the physiology dictate our thyroid testing makes good clinical sense, and is cost-effective.



Brian F. Mandell, MD, PhD
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2025

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Department of Dermatovenereology, Chengdu Second People's Hospital, Chengdu, Sichuan, China

Peimei Zhou, MD, PhD
Department of Dermatovenereology, Chengdu Second People's Hospital, Chengdu, Sichuan, China

Tao Chen, MD, PhD
Department of Dermatovenereology, Chengdu Second People's Hospital, Chengdu, Sichuan, China

Vesicular pityriasis rosea

A 37-year-old man presented to the dermatology clinic with a 9-day history of disseminated pruritic rash on his trunk and extremities. The patient was previously healthy, denied the use of any medication, and affirmed that no family member had similar eruptive lesions.

Physical examination revealed erythematous papulosquamous eruptions primarily localized on the trunk and extremities (**Figure 1**). Individual lesions exhibited an oval shape and marginal scale attachment, with their long axes parallel to the lines of skin cleavage. Notably, a sizable oval scaly patch on the left chest was first noticed by the patient several days before the appearance of the disseminated lesions. Vesicles were observed on the anterior forearm surface (**Figure 1**) and the thighs. Lymphadenopathy or lesions on the mucous membranes were not observed.

Laboratory tests, including antinuclear antibody and antistreptolysin O titers, fluorescent treponemal antibody absorption test, and fungal microscopy, all yielded normal results. Skin biopsy of a vesicular lesion on the abdomen revealed acute dermatitis with epidermal hyperkeratosis accompanied by parakeratosis, intracorneal blister formation, spongiosis, and focal basal cell vacuolar degeneration. Direct immunofluorescence of the vesicular lesion was negative for immunoglobulin A, G, and M; complement component 3; and fibrinogen.

Vesicular pityriasis rosea was diagnosed based mainly on the clinical features of the rash, including erythematous papulosquamous lesions aligning with dermoid lines and a herald patch on the trunk, both typical of pityriasis rosea, and the presence of vesicular lesions. The results of the histopathologic examination were also consistent with pityriasis rosea, and laboratory testing helped exclude other possible diagnoses.

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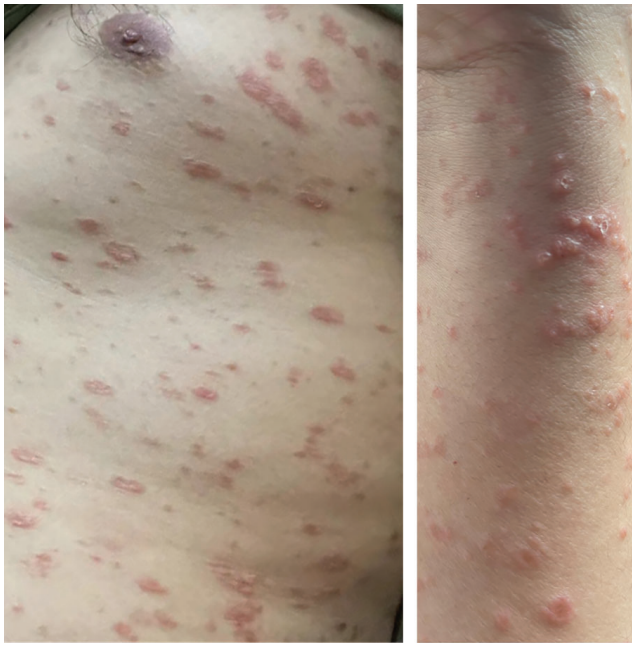

Figure 1. Left, typical papulosquamous lesions of pityriasis rosea on the trunk. Right, vesicular lesions on the anterior forearm.

VESICULAR PITYRIASIS ROSEA

Our patient exhibited the characteristic features of typical pityriasis rosea, including erythematous, oval-shaped, marginally scaly plaques with their long axes parallel to the lines of skin cleavage and a herald patch on the left chest.[1] The presence of vesicles surrounding the lesions pointed to a diagnosis of vesicular pityriasis rosea, an atypical variant of pityriasis rosea.

Pityriasis rosea is a self-limited acute or subacute inflammatory dermatosis characterized by erythematous papulosquamous eruptions predominantly found on the trunk and proximal extremities.[2] The lesions typically resolve over a span of 2 to 10 weeks without treatment. Vesicular pityriasis rosea accounts for only

0.5% of reported cases.[2] This subtype is more frequently observed among children and young adults.

Glucocorticoids can be used for treatment, while dapsone and oral erythromycin have also been shown to be effective.[2,3]

Differential diagnosis

The differential diagnosis includes tinea corporis, secondary syphilis, guttate psoriasis, and autoimmune bullous diseases.[1]

Tinea corporis, a skin infection primarily caused by dermatophyte fungi, typically presents as a red circular rash with a slightly raised border and a clearer center, resembling a ring.[4] There may be scaling or vesicles at the edges, and the lesions can be itchy or mildly irritated. The rash is usually localized in the infected area but can spread over time if not treated. A positive fungal microscopy examination is fundamental for diagnosis. In our patient, fungal microscopy examination was negative, ruling out tinea coproris.

Secondary syphilis diagnosis requires an etiologic examination. However, syphilis can be difficult to diagnose due to its diverse manifestations. The presence of nonpruritic red or reddish-brown papulosquamous eruptions on any part of the body, including the palms and soles, along with the presence of plasma cells on histopathologic examination, is indicative of secondary syphilis.[5] Negative results on fluorescent treponemal antibody absorption testing ruled out secondary syphilis in our patient.

Guttate psoriasis is a relatively rare variant of psoriasis characterized by an abrupt onset of small, diffuse, salmon-colored papulosquamous papules with silver scales.[5] Tiny points of blood are visible when the scales are rubbed or picked off. Guttate psoriasis exhibits a predilection for children and youth and is frequently associated with streptococcal infections. It has characteristic histologic features of psoriasis, including mild epidermal hyperplasia, focal spongiosis, disappearance of the granular layer, and migration of neutrophils into the epidermis to produce epidermal or subcorneal collections.[5,6] Histopathologic examination in our patient revealed no evidence of guttate psoriasis or an acantholytic process.

Autoimmune bullous diseases such as pemphigus, bullous pemphigoid, and dermatitis herpetiformis are a group of rare skin disorders characterized by widespread erythema and blisters. They occur due to autoantibodies disrupting the junction between the dermis and epidermis.[7] Diagnosis of these disorders involves comprehensive evaluations, including clinical features, histologic examination, and immunohistologic assessment. In our patient, autoimmune diseases were ruled out based on a normal result on antinuclear antibody testing, the absence of associated symptoms, and negative direct immunofluorescence studies of the biopsy sample.

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DISCLOSURES

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Address: *Tao Chen, MD, PhD, Department of Dermatovenereology, Chengdu Second People's Hospital, 165 Caoshi Street, Chengdu 610017, Sichuan, China; 13980427003@163.com*

Brittany Jackson, MD
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Mary S. Hedges, MD
Department of Internal Medicine, Mayo Clinic, Jacksonville, FL

ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Which patients with presumed acute infectious diarrhea in an outpatient setting should undergo gastrointestinal pathogen panel testing?

A 65-year-old man presents to the clinic with a 7-day history of diarrhea. His medical history is significant for psoriasis treated with abatacept, hypertension, and gastroesophageal reflux disease. A polymerase chain reaction (PCR) gastrointestinal pathogen panel was ordered, which returned positive results for Salmonella.

A: Advances in multiplex PCR assays have significantly improved the diagnosis of diarrhea in patients in whom testing is appropriate. These assays enable simultaneous detection of multiple pathogens from a single stool sample, including bacteria, viruses, and parasites, in as little as 1 hour. Most cases of acute diarrhea are mild and self-resolving. Conditions that warrant gastrointestinal pathogen panel testing include fever, visible blood in the stool, sepsis, severe abdominal pain, hospitalization, persistent diarrhea (≥ 7 days), advanced age, and immunocompromise.[1–3] Inflammatory bowel disease should be considered in patients with persistent diarrhea who have negative results on testing.[1,2]

ACUTE DIARRHEA DEFINED

Diarrhea occurs when the normal physiologic processes of the small and large intestines are disrupted. These organs typically absorb ions, substrates, and water. Diarrhea results from either reduced water absorption or increased water secretion in the intestines, leading to excessive fluid in the stool.

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The American College of Gastroenterology[1] describes acute diarrhea as passage of unformed, loose, or watery stool for a duration of less than 2 weeks. In contrast, chronic diarrhea lasts more than 4 weeks. Acute diarrhea is often caused by viruses, bacteria, or parasites.[2]

Chronic diarrhea is less likely to be infectious but may be related to parasitic infections.[1] Distinguishing between infectious and noninfectious causes of diarrhea is crucial for guiding the clinical approach and determining appropriate management strategies.

WHAT ARE COMMON INFECTIOUS CAUSES OF ACUTE DIARRHEA?

Common bacterial causes of acute diarrhea include *Salmonella*, *Campylobacter*, *Escherichia coli*, *Shigella*, and *Clostridioides difficile*. Bacterial infections are associated with travel, food ingestion, and antibiotic use.[3] A specific cause can often be found based on the exposure history.

Common viral causes include norovirus and rotavirus. Norovirus causes acute diarrhea outbreaks worldwide, often in close-containment settings such as dormitories, nursing facilities, cruise ships, and hospitals. Rotavirus is commonly found in children younger than 5 years. However, cases have decreased in high-income countries due to increased rotavirus vaccination rates.[2]

TABLE 1
Organisms detected on multiplex gastrointestinal molecular panels

	Panels					
	Verigene system[a]	xTAG panel[b]	Biofire panel[c]	BD Max assays[d,e]	BioCode panel[f]	QIAstat-Dx panel[g]
Bacteria and bacterial toxins						
Campylobacter species	X	X	X	X	X	X
Clostridioides difficile toxins A and B		X	X		X	
Plesiomonas shigelloides			X	X		X
Salmonella species	X	X	X	X	X	X
Yersinia enterocolitica	X		X	X	X	X
Vibrio cholerae	X	X	X	X		
Vibrio parahaemolyticus	X		X	X	X	
Vibrio vulnificus			X	X		
Enteroaggregative *Escherichia coli*			X		X	
Enteropathogenic *E coli*			X			X
Enterotoxigenic *E coli*		X	X	X	X	X
Shiga-like toxin–producing *E coli*	X	X	X	X	X	X
E coli O157		X	X		X	X
Shigella and enteroinvasive *E coli*	X	X	X	X	X	X
Parasites						
Cryptosporidium species		X	X	X	X	X
Cyclospora cayetanensis			X			X
Entamoeba histolytica		X	X	X	X	X
Giardia duodenalis[h]		X	X	X	X	X
Viruses						
Adenovirus 40/41		X	X	X	X	X
Astrovirus			X			X
Norovirus genogroups I and II	X	X	X	X	X	X
Rotavirus	X	X	X	X	X	X
Sapovirus			X	X		

[a]Diasorin. Verigene enteric pathogens test. https://us.diasorin.com/en/molecular-diagnostics/kits-reagents/verigene-enteric-pathogens-test. Accessed January 16, 2025.
[b]Diasorin. xTAG gastrointestinal pathogen panel. https://us.diasorin.com/en/molecular-diagnostics/kits-reagents/xtag-gastrointestinal-pathogen-panel-gpp. Accessed January 16, 2025.
[c]Biomeriéux. Biofire Filmarray gastrointestinal panel. www.biomerieux.com/us/en/our-offer/clinical-products/biofire-gastrointestinal-panel.html. Accessed January 16, 2025.
[d]The BD Max Enteric assays include an enteric bacterial panel, extended enteric bacterial panel, enteric parasite panel, enteric viral panel, and an enteric viral panel that tests for only norovirus and rotavirus.
[e]BD. Gastrointestinal infections portfolio. www.bd.com/en-no/products-and-solutions/solutions/gastrointestinal-infections-portfolio. Accessed January 16, 2025.
[f]Applied BioCode. Gastrointestinal pathogen panel. www.apbiocode.com/products/assays/gi-panel/. Accessed January 16, 2025.
[g]Quiagen. Syndromic testing for GI infections with QIAstat Dx. www.qiagen.com/us/applications/syndromic-testing/syndromic-testing-benefits/diagnosing-gastrointestinal-infections-with-qiastat-dx. Accessed January 16, 2025.
[h]Also known as *G lamblia* or *G intestinalis*.

Based on information from assay manufacturer websites[a–c,e–g] and reference 6.

Parasitic and protozoal causes of acute diarrhea are typically acquired through ingesting contaminated water or food or person-to-person transmission. Parasites and protozoans are a significant cause of morbidity and mortality, specifically in low-income countries. Common organisms in the United States include *Giardia duodenalis* (also known as *G lamblia* or *G intestinalis*), *Cryptosporidium* species, *Cyclospora*, and *Entamoeba histolytica*.[2]

Gastrointestinal infections in immunocompromised persons

Acute diarrhea is prevalent among all individuals but poses a significant risk among those with a compromised immune system, often leading to considerable morbidity. The etiologic agents that cause diarrhea in immunocompromised persons may be the same as those in immunocompetent persons, but, due to impaired

immunity, the former are more susceptible to infection and may not recover as quickly.

C *difficile* is the most common cause of antibiotic-associated diarrhea.[4] In the community or healthcare setting, it can cause severe colitis in both immunocompetent and immunocompromised patients. *Salmonella* species, *Cryptosporidium* species, and *Cyclospora cayetanensis* cause severe diarrhea, particularly in patients with immunocompromised states.[5] Cryptosporidiosis is self-limited in immune-competent individuals but causes severe, prolonged diarrhea in immunocompromised patients, especially those with impaired cell-mediated immunity.[5]

CONSIDERATIONS WHEN ORDERING A GASTROINTESTINAL PATHOGEN PANEL

Six multiplex PCR gastrointestinal pathogen panels are approved by the US Food and Drug Administration (**Table 1**).[6] These panels test for up to 22 enteropathogens (bacteria, viruses, parasites) and, compared with traditional culture methods, have increased sensitivity of organism detection as well as a faster turnaround time.[7] The ability to detect a broad range of pathogens helps clinicians tailor treatment more effectively, particularly in patients with complex clinical presentations.[1,7]

Considerations when ordering a multiplex panel include clinical history and presentation, the type and number of organisms to be tested for, treatment implications based on diagnostic results, test cost for the patient, and the patient population tested. Although recommendations from the Centers for Medicare & Medicaid Services generally guide insurance providers, some insurance plans may limit coverage to panels with fewer than 5 targets.[8] The lack of consistency across insurance plans accentuates the need for clinicians to be aware of limitations in coverage when recommending diagnostic tests.

Also, multiplex pathogen panels detect the toxin genes in C *difficile*, a result that needs to be correlated clinically and confirmed by an additional test such as the antigen test for C *difficile* toxin.[2] When bacterial pathogens are detected, bacterial culture may be needed for susceptibility testing and to fulfill public health reporting requirements and provide epidemiologic data.[6]

Gastrointestinal pathogen panels play an essential role in public health surveillance. They also can improve clinical management and reduce healthcare costs.[6] A retrospective observational study assessed diagnostic methods for acute infectious gastroenteritis using data from 36,787 outpatients with this diagnosis who had a traditional workup (eg, bacterial culture, antigen testing, microscopy), multiplex PCR panel testing with less than 12 target pathogens, or multiplex PCR panel testing with 12 or more target pathogens.[9] This study supported the cost-effectiveness and clinical utility of large multiplex PCR panels (> 12 targets) in diagnosing acute infectious gastroenteritis, finding that such panels were associated with greater diagnostic yield, lower 30-day follow-up cost, and reduced hospitalization risk compared with a traditional workup.

In the case example, multiplex testing for 22 enteropathogens was positive for *Salmonella* species. The patient was immunocompromised and was successfully treated with antibiotics. The possible source of his diarrheal illness was cucumbers that had been recalled due to *Salmonella* contamination.[10]

THE BOTTOM LINE

Timely diagnosis and treatment of diarrhea are essential in specific patient populations, including those who are immunocompromised and are at increased risk of complications. Testing using multiplex gastrointestinal pathogen panels, available in most microbiology laboratories, provides accurate detection of a broad range of pathogens in a timely, cost-effective manner and can improve patient outcomes.

DISCLOSURES

Dr. Hata has disclosed serving as a research principal investigator for Roche Molecular and teaching and speaking for Seegene. 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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Address: *Brittany Jackson, MD, Department of Internal Medicine, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32257; Jackson.Brittany3@mayo.edu*

GREGORY W. RUTECKI, MD, Section Editor

Timothy W. Bodnar, MD
Assistant Chief, Section of Endocrinology & Metabolism, Medicine Service, VA Ann Arbor Healthcare System, Ann Arbor, MI; Clinical Assistant Professor, Department of Internal Medicine, Division of Metabolism, Endocrinology & Diabetes, Michigan Medicine, Ann Arbor, MI

Sima Saberi, MD
Clinical Assistant Professor, Department of Internal Medicine, Division of Metabolism, Endocrinology & Diabetes, Michigan Medicine, Ann Arbor, MI

Thyroid obstacle course: Many challenges from a single gland

A man in his 30s presented to his primary care clinician for new irritability, anxiety, and insomnia, without suicidal ideation. Symptoms began after an increase in job-related stress and the anniversary of his mother's death.

His medical history included obesity, depression, attention-deficit hyperactivity disorder, irritable bowel syndrome, and erectile dysfunction. He was a lifelong nonsmoker and did not use illicit drugs. Current medications were vitamin D and sildenafil. In addition, he had been treated with chemotherapy (unknown regimen; no radiation) at age 3 years for acute lymphoblastic leukemia.

INITIAL EVALUATION AND MANAGEMENT

At the primary care visit, his temperature was 36.7°C (98°F), heart rate 90 beats per minute, and blood pressure 119/81 mm Hg. Physical examination was unremarkable, with normal heart, lung, abdomen, skin, and neurologic evaluations, including absence of murmur, tremor, or edema.

The differential diagnosis for generalized anxiety is broad and includes cardiac disorders (eg, arrythmia or heart failure), endocrine disorders (eg, hyperthyroidism or hypoglycemia), and psychiatric disorders (eg, anxiety).[1] His primary care clinician favored anxiety and recommended behavioral counseling along with sertraline 50 mg daily. Given his acute lymphoblastic leukemia history and the development of new symptoms (by their mid-40s, approximately 95% of those who survived childhood cancer will have a health problem related to the cancer diagnosis or treatment[2]), laboratory tests were also ordered.

Initial laboratory tests showed no evidence of anemia, electrolyte disturbance, hypoglycemia, kidney failure, or liver failure (**Table 1**) but revealed a thyroid-stimulating hormone (TSH) level of 0.025 mIU/L (reference range 0.350–4.920 mIU/L). Repeat thyroid function tests 1 month later showed a similarly low TSH level of 0.019 mIU/L but a normal free thyroxine (T4) level of 1.01 ng/dL (0.70–1.48 ng/dL). Due to persistently low TSH, he was referred to endocrinology.

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ENDOCRINOLOGY EVALUATION

Two weeks later at the endocrinology visit, he reported worsening anxiety despite ongoing use of sertraline 50 mg daily. He denied heat intolerance, tremors, eye pain, vision changes, or neck discomfort. His weight was stable and had not varied by more than 3 pounds during the previous 6 months.

He had no recent history of iodinated contrast or infections and was not taking iodine supplements. There was no family history of thyroid disease, but his sister was thought to have ulcerative colitis. Although childhood cancer survivors, like this patient, have higher rates of hyperthyroidism, it is typically linked to radiation treatment rather than to chemotherapy or the cancer diagnosis.[3] Interestingly, he had been in Japan near the tsunami-related nuclear power plant disaster in 2011.

Physical examination revealed mild thyromegaly without a discrete nodule, tremors, proptosis, or lid lag. His temperature was 36.1°C (97°F), heart rate 74 beats per minute, and blood pressure 122/70 mm Hg. Heart sounds were regular without murmurs. Breathing was nonlabored with no adventitious sounds. No rash, edema, ataxia, or other abnormality was noted.

Neck ultrasonography was ordered because of the goiter, and results of laboratory testing that day showed the following:

- TSH 0.021 mIU/L
- Free T4 1.02 ng/dL

TABLE 1
Initial laboratory results

Test	Result (reference range)[a]
White blood cell count	9.42 × 10^9/L (4.0–11.0)
Hemoglobin	16.9 g/dL (12.1–17.2)
Hematocrit	49.2% (38–51)
Mean corpuscular volume	85.4 fL (80–100)
Platelet count	252 × 10^9/L (130–400)
Sodium	141 mmol/L (137–145)
Potassium	4.0 mmol/L (3.5–5.0)
Chloride	106 mmol/L (98–107)
Carbon dioxide	25 mmol/L (24–34)
Urea nitrogen	15 mg/dL (8–26)
Creatinine	1.1 mg/dL (0.57–1.25)
Glucose	87 mg/dL (73–115)
Calcium	10.2 mg/dL (8.4–10.2)
Proteins, total	8.0 g/dL (6.0–8.3)
Albumin	4.5 g/dL (3.5–5.0)
Bilirubin, total	0.6 mg/dL (0.1–1.1)
Aspartate aminotransferase	23 U/L (12–50)
Alanine aminotransferase	46 U/L (21–72)
Alkaline phosphatase	72 U/L (40–150)
Thyroid-stimulating hormone	**0.025 mIU/L** (0.350–4.920)
Hemoglobin A1c	5.2% (4.2–5.8)

[a]Result outside of reference range is in bold.

- Free triiodothyronine (T3) 3.53 pg/mL (1.71–3.71 pg/mL)
- Thyroid-stimulating immunoglobulin 0.42 IU/L (≤ 0.54 IU/L).

DIFFERENTIAL DIAGNOSIS

1 Which of the following is the most likely diagnosis based on results of his thyroid function tests?

☐ Central hypothyroidism
☐ Euthyroid sick syndrome (nonthyroidal illness)
☐ Drug-mediated suppression of TSH
☐ Subclinical hyperthyroidism due to Graves disease or autonomous nodules

The differential diagnosis of low TSH includes causes of overt or subclinical hyperthyroidism, thyroiditis, hypothalamic or pituitary disease, euthyroid sick syndrome, and drug-mediated suppression (**Table 2**). A thorough history and physical examination can narrow the differential.

TABLE 2
Differential diagnosis of low thyroid-stimulating hormone level

Endogenous thyrotoxicosis due to single or multiple autonomously functioning or hot nodules and Graves disease
Thyroiditis, in which preformed hormone is released from an inflamed thyroid
Hypothalamic or pituitary disease (central hypothyroidism), resulting in low production of thyroid-stimulating hormone
Euthyroid sick syndrome (nonthyroidal illness)
Medication effects from glucocorticoids, exogenous thyroid hormone, lithium, amiodarone, and interferon

The patient's potential radiation exposure while he was in Japan could have increased the risk of a thyroid nodule, and a goiter was felt on examination. He had no neck discomfort, iodine exposure, or recent infection, making thyroiditis less likely. His free T4 level was in the mid-normal range, which ruled out hypothalamic or pituitary disease because a lower T4 level is expected in central hypothyroidism. He had no other acute or subacute illness, so euthyroid sick syndrome, which results in a transient reduction in TSH, was unlikely. He also was not taking medications that would affect thyroid function. While the underlying cause was unknown, the most correct endocrine diagnosis at this point was subclinical hyperthyroidism.

Subclinical hyperthyroidism is defined as low or undetectable TSH with normal T3 and free T4 levels.[4] Overt hyperthyroidism is defined as TSH below the lower limit of normal with an elevated level of T3 (either free or total), free T4, or both. Obtaining a T3 level is important because some patients, especially those with Graves disease, present with T3 thyrotoxicosis with low TSH, normal free T4, and elevated T3 levels.[4] Subclinical hyperthyroidism typically has fewer or no symptoms compared with overt hyperthyroidism (**Table 3**).[4]

Overt hyperthyroidism requires treatment; subclinical hyperthyroidism requires treatment only in select patients. A TSH level less than 0.10 mIU/L has been associated with an increased risk of atrial fibrillation, decreased bone density in postmenopausal women, and a higher likelihood of progression to overt hyperthyroidism.[5] The American Thyroid Association recommends considering TSH level, age, comorbidities,

TABLE 3
Hyperthyroidism signs and symptoms

Common findings	Less-common findings
Palpitations, atrial fibrillation	Elevated alkaline phosphatase, elevated aminotransferases, or both
Weight loss, often despite increased appetite	Syncope or presyncope
Anxiety	Periodic paralysis
Heat intolerance	Thymus enlargement
Tremor	Normochromic normocytic anemia
Increased frequency of bowel movements	Pretibial myxedema
Shortness of breath	
Lighter menstrual periods	
Erectile dysfunction, decreased libido	
Hair loss (scalp and lateral eyebrows)	
Proptosis, lid lag, chemosis	

Based on information from reference 4.

and risks when deciding whether to treat subclinical hyperthyroidism (**Table 4**).[6]

CASE CONTINUED: FINDINGS ON IMAGING, SUBSEQUENT FINE-NEEDLE ASPIRATION

A week later, neck ultrasonography showed a mildly enlarged thyroid. The thyroid had heterogeneous echotexture and normal vascularity. There was a solid hypoechoic nodule on the right middle pole that measured 4 mm anteroposteriorly and was scored on the Thyroid Imaging, Reporting and Data System[7] (TI-RADS) scale as TR4 (see below for more about TI-RADS scoring). There was also a nodule on the left middle pole that measured 0.9 × 1.4 × 0.9 cm, was noted as taller-than-wide (**Figure 1**), and was scored TR5 on the TI-RADS scale.

Given the patient's thyroid nodules and low TSH level, a radioactive iodine uptake and scan was obtained. After oral administration of 10.2 µCi iodine-131, 24-hour iodine uptake was 16% (7%–30%) with heterogenous distribution of the radiotracer throughout the thyroid gland. Thus, a diagnosis of subclinical hyperthyroidism due to toxic multinodular goiter was made.

The imaging was reviewed by a radiologist, who could not definitively categorize the 1.4-cm middle-pole nodule on the left as hot (tracer uptake is greater in the nodule than in the surrounding healthy thyroid tissue, indicating the nodule has an extremely low risk of malignancy[8]) or cold (less tracer uptake in the nodule than in the surrounding thyroid) but favored cold.

Because this nodule was scored as TR5 (highest risk category for cancer) and was larger than 1 cm, thyroid fine-needle aspiration (FNA) was indicated and performed. Initial cytology was nondiagnostic (Bethesda category 1) due to scant cellularity. An FNA was repeated 8 weeks later, and the cytology was atypia of undetermined significance (Bethesda category 3).

Although very rarely documented in the literature, performing an FNA can trigger worsening of thyrotoxicosis, including thyroid storm.[9] Thus, the recommendation is to avoid FNA in overt hyperthyroidism; however, because our patient had subclinical hyperthyroidism, FNA was justified.

MANAGEMENT OF ATYPIA IN THYROID CYTOLOGY

2 What are the options for management of thyroid nodules with indeterminate cytology (Bethesda category 3 or 4)?

- ☐ Diagnostic hemithyroidectomy
- ☐ Repeat thyroid FNA
- ☐ Radioactive iodine ablation
- ☐ Molecular diagnostic testing

Thyroid nodules are very common—more than half the general population may have at least 1.[10] Most are benign and nonfunctional; approximately 10% are cancerous.[11] An ongoing challenge is determining which nodules are clinically significant thyroid cancer that, left untreated, would lead to morbidity or mortality.

TI-RADS scoring

Previous studies have shown papillary carcinomas that would not result in mortality or symptoms if left alone

TABLE 4
Summary of American Thyroid Association recommendations for treatment of subclinical hyperthyroidism

	Thyroid-stimulating hormone persistently < 0.10 mIU/L	Thyroid-stimulating hormone between 0.10 mIU/L and lower limit of normal
Any symptoms, age ≥ 65, cardiovascular disease, osteoporosis, postmenopausal and not on estrogen or osteoporosis treatment	Treatment is recommended	Consider treatment
None of the above	Consider treatment	Observation is recommended

Based on information from reference 6.

are overdiagnosed.[12] Because of this overdiagnosis, in 2017 the American College of Radiology published the TI-RADS system to identify thyroid nodules that warrant FNA based on a reasonable likelihood of clinically significant cancer.[7] Points are assigned based on a rubric covering 5 categories: nodule composition (ie, cystic vs solid), echogenicity, shape (ie, wider-than-tall vs taller-than-wide on transverse view), margins, and echogenic foci. Points are then totaled to determine a TI-RADS score or risk level. The risk level—TR1 to TR5—is then combined with nodule size to guide FNA decision-making. For example, a TR4 nodule has an aggregate risk of malignancy of 9.1% and a TR5 nodule has an aggregate risk of malignancy of 35%.[13] Thus, patients with TR4 nodules undergo FNA when the nodules are 1.5 cm or larger and patients with TR5 nodules when the nodules are 1 cm or larger.

Bethesda system

The Bethesda System for Reporting Thyroid Cytology, which has been in widespread use for more than a decade, offers a standardized approach to describing and categorizing thyroid specimens from FNA.[10]

- Bethesda category 1 (nondiagnostic) thyroid nodules are typically biopsied again[14]
- Bethesda category 2 thyroid nodules have benign cytology
- Bethesda category 3 or 4 (indeterminate cytology) is common and carries an intermediate risk of malignancy; management strategies include repeat FNA, use of additional molecular testing to stratify the nodule risk based on genetic profile, and diagnostic lobectomy or thyroidectomy
- Bethesda 5 (suspicious for cancer) or 6 (consistent with cancer) nodules are typically managed with referral to a thyroid surgeon for hemithyroidectomy or total thyroidectomy.

CASE CONTINUED: MULTIDISCIPLINARY DISCUSSION

The patient was informed of the indeterminate cytology, and details of his case were discussed with the multidisciplinary endocrine tumor board, which included endocrinologists, otolaryngologists, and nuclear-medicine specialists. Because the patient strongly desired definitive therapy for all thyroid diseases, the consensus recommendation was thyroidectomy.

THYROIDECTOMY IN SUBCLINICAL HYPERTHYROIDISM

Thyroidectomy is not the typical first-line treatment of subclinical hyperthyroidism,[6] nor is it the only option for thyroid nodules with indeterminate cytology,[14] as reviewed above. However, radioactive iodine ablation was not considered given the patient's personal history of acute lymphoblastic leukemia and because of the indeterminate thyroid cytology, as a potential thyroid cancer cannot be fully ablated without first performing a thyroidectomy. Medical treatment of subclinical hyperthyroidism with methimazole would not have addressed the indeterminate cytology, and the healthcare system where the patient was receiving care did not have access at that time to reliable molecular testing for indeterminate thyroid nodules.

Therefore, total or near-total thyroidectomy is a reasonable approach for multiple scenarios that apply to our patient: treatment of hyperthyroidism when there is coexisting structural disease and indeterminate cytology of the thyroid nodules. Referral to a high-volume thyroid surgeon is preferred. High-volume surgeons, described as performing more than 25 thyroid surgeries per year, have better clinical and cost patient outcomes than low-volume surgeons, who have 51% higher complication rates.[15] Those complications can

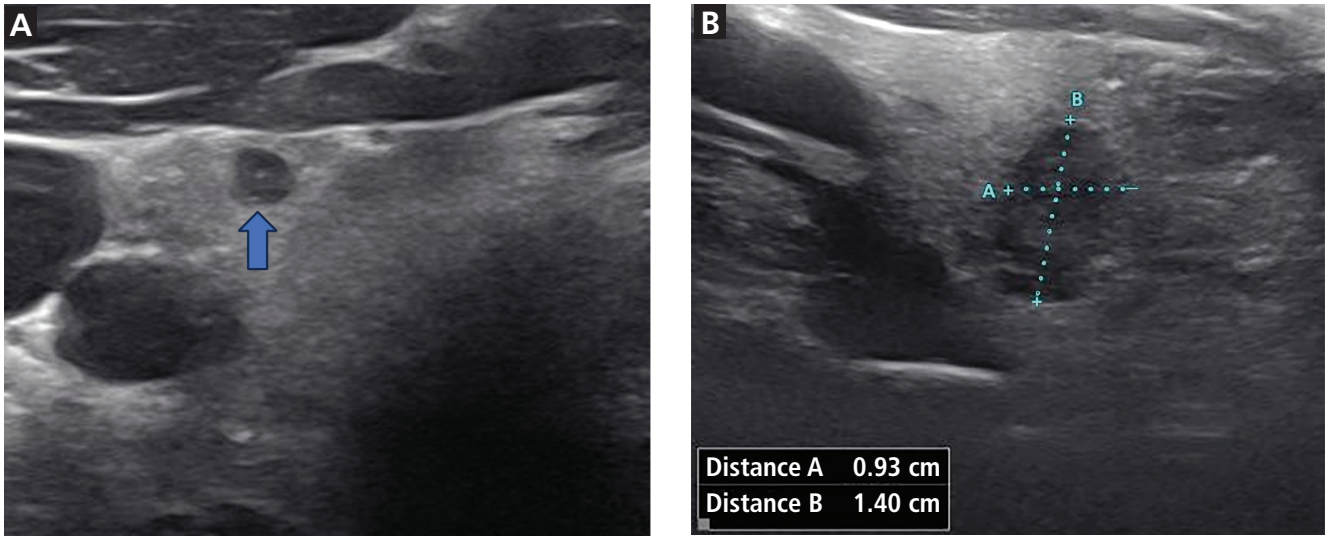

Figure 1. Thyroid ultrasonography images. (A) Transverse view of the right thyroid lobe showing a 4-mm nodule (blue arrow). (B) Transverse view of the left thyroid lobe showing a solid hypoechoic nodule that is taller-than-wide (see calipers and measurements).

include postsurgical hypoparathyroidism and recurrent laryngeal nerve injury.

CASE CONTINUED: THYROIDECTOMY

Total thyroidectomy was performed 6 weeks later (approximately 5 months after initial presentation). Thyroid function was similar at the time of surgery: TSH 0.019 mIU/L and free T4 0.98 ng/dL.

The surgical pathology report indicated a small (< 1 mm) microscopic focus of nonencapsulated papillary thyroid carcinoma. The remaining background thyroid was reported as "no significant pathologic findings." Two healthy parathyroid glands were removed and reimplanted in the neck. Small samples of each gland were sent to pathology, and the results were reported as "cellular parathyroid tissue" with "no evidence of malignancy."

The patient was discharged home after the thyroidectomy on levothyroxine 200 µg daily based on his weight of 135 kg. Subsequently, he has had no clinical or biochemical evidence of hypoparathyroidism.

YET ANOTHER THYROID DIAGNOSIS

3 What is the next step in management given the finding on surgical pathology of papillary thyroid microcarcinoma?

- ☐ Radioactive iodine ablation
- ☐ Reoperation with lymph node dissection
- ☐ Chemotherapy
- ☐ No additional treatment

Even when thyroid surgery is explicitly performed for presumed benign thyroid disease, incidental papillary thyroid microcarcinoma is common and accounts for nearly 10% of cases.[16] As both active surveillance and surgical excision are now considered reasonable strategies for papillary thyroid microcarcinoma (< 1 cm), the thyroidectomy that discovered the microcarcinoma is considered sufficient treatment.[17] Such patients are not treated more aggressively (eg, radioactive iodine ablation, chemotherapy, or lymph node dissection) because papillary thyroid microcarcinomas generally have an excellent prognosis[16] with low risk of structural recurrence.[8]

CASE CONTINUED: EYE SYMPTOMS DEVELOP

While awaiting thyroidectomy, the patient had developed periorbital edema on his right side. At that time, he had no blurry or double vision, excessive dryness, or tearing of the eyes. Thyroid eye disease (TED) was suspected. Results from repeat laboratory testing showed that his thyroid-stimulating immunoglobulin level was mildly elevated at 0.77 IU/L.

4 Which of the following are management options for TED?

- ☐ Smoking cessation and avoidance of secondhand smoke
- ☐ Lubricating eye drops
- ☐ Avoidance of hypothyroidism
- ☐ Radioactive iodine treatment of hyperthyroidism

THYROID EYE DISEASE

TED is associated with antibodies that bind the TSH receptor (eg, thyroid-stimulating immunoglobulin and thyrotropin receptor antibodies), which is present in orbital fibroblasts and forms a complex with the insulin-like growth factor 1 receptor.[18] This process is not fully understood, but it seems to result in the activation of orbital fibroblasts and deposition of glycosaminoglycans in the extracellular matrix, causing swelling.[19] Risk factors for TED include age 40 to 60 years, cigarette smoking, high thyroid-stimulating immunoglobulin or thyrotropin receptor antibody titers, and uncontrolled hyper- or hypothyroidism.

Radioactive iodine therapy may exacerbate TED, so it is typically avoided.[19] Thionamides and thyroidectomy have not been shown to affect the course of TED. Mild-to-moderate TED is typically managed with local supportive measures, such as lubricating eye drops, and careful maintenance of a euthyroid state. Intravenous glucocorticoids have historically been used for moderate-to-severe active TED.

Teprotumumab, an insulin-like growth factor 1–receptor inhibitor, was approved by the US Food and Drug Administration in 2020 for moderate-to-severe active orbitopathy.[20] Adverse effects of teprotumumab, which occur in 10% to 30% of patients, include sensorineural hearing loss, infusion reactions, and hyperglycemia.[21] Hyperglycemia is more common in patients with preexisting diabetes mellitus and can persist after teprotumumab cessation.[22]

Orbital decompressive surgery is considered either emergently for vision-threatening manifestations of TED, such as optic neuropathy, or nonemergently to correct the sequelae of TED, such as severe proptosis with exposure keratopathy or strabismus.[19]

CASE CONTINUED: LONGITUDINAL MANAGEMENT

In the months after his thyroidectomy, the patient's levothyroxine dose required frequent adjustment because he continued to have low TSH values on repeat testing. His TSH level did not normalize until 13 months after the thyroidectomy, when it was 0.384 mIU/L on levothyroxine 125 µg daily. However, his TSH levels rose as high as 14.516 mIU/L in the ensuing months, despite careful dose adjustment, patient adherence to proper administration, and frequent follow-up. His levothyroxine dose was titrated up by endocrinology, and he ultimately reached euthyroidism at 137 µg daily. However, this was accompanied by worsening TED symptoms, with an increase in pressure sensation, greater proptosis, and blurry vision in his left eye.

When his TSH level reached 14.516 mIU/L, the patient was evaluated by an oculoplastic surgeon, who did not find any optic nerve compromise and found normal visual acuity. Treatment included artificial tears, warm compresses, and vitamin D supplementation.

Teprotumumab continues to be considered; however, 2 years after the patient's thyroidectomy, it has not yet been started because it is believed that the risks clearly outweigh the benefits for the patient.

CONCLUSION

This case shows how a patient can present with symptomatic subclinical hyperthyroidism but have several thyroid-related diagnoses, including thyroid nodules, incidental papillary thyroid microcarcinoma, and TED. Thyroid care is complex, especially when extrathyroidal manifestations of thyroid disease are present. Patients may require a team of specialists comprising endocrinologists, thyroid surgeons, nuclear medicine physicians, ophthalmologists, and oculoplastic surgeons.

TAKE-HOME POINTS

- Subclinical hyperthyroidism (low TSH with normal T4 and T3) should be treated when symptomatic; when TSH is persistently less than 0.10 mIU/L in patients 65 or older; in patients with cardiac risk factors, heart disease, or osteoporosis; and in postmenopausal women who are not on estrogen or osteoporosis treatment.[6]
- Thyroid nodules are best visualized by ultrasonography. If TSH is low, a radioactive iodine uptake and scan is also indicated to determine whether the nodule is hot, because those nodules are more likely benign.[8]
- The TI-RADS scoring system, combined with nodule size, helps determine which nodules can be assessed by FNA.[7]
- Papillary thyroid microcarcinomas (< 1 cm) are considered fully treated by hemithyroidectomy or thyroidectomy.[17]
- TED is a common extrathyroidal manifestation of thyroid disease. It can threaten sight, so a high level of suspicion is required, with involvement of specialists as needed.

DISCLOSURES

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Address: *Timothy W. Bodnar, MD, Section of Endocrinology & Metabolism, Medicine Service, VA Ann Arbor Healthcare System, 2215 Fuller Road, Mail Code 111e, Ann Arbor, MI 48105; timothy.bodnar@va.gov*

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COMMENTARY

Pooja Cerrato, PharmD, BCPS
Medical Operations, Inpatient Pharmacy, Cleveland Clinic, Cleveland, OH

Steven Mawhorter, MD, DTM&H
Infectious Disease Department, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Respiratory virus season: Strategies for successful navigation

"Everything should be made as simple as possible, but not simpler." — Paraphrased from Albert Einstein

Helping our patients stay healthy during respiratory virus season requires a comprehensive approach, with preventive measures, vaccination, efficient diagnostic tests, and targeted medications—and we need to communicate clearly with our patients what we want to do, and why.

Here, we review the burden, prevention, diagnosis, and treatment of 3 important respiratory viral illnesses: respiratory syncytial virus (RSV) infection, COVID-19, and influenza. Acknowledging the pressure that the respiratory virus season places on frontline clinicians and their practices, we offer an analogy-driven narrative for patient communication.

AN ANALOGY TO MOTOR-VEHICLE ACCIDENTS

When talking to patients about ways to avoid respiratory infections, we find it useful to use the analogy of avoiding motor-vehicle accidents:

First, avoid exposure to infections as much as possible. Use handwashing and mask-wearing as appropriate, and limit crowd contact. This is analogous to defensive driving.

Second, vaccinate against infectious diseases, especially when it is difficult to limit exposure. This is analogous to wearing seat belts.

Third, use symptom-triggered medication if a patient is allergic to vaccines, refuses to be vaccinated, or has a breakthrough infection. Analogy: air bags.

Influenza, COVID-19, and RSV infections can be compared to a car running through a stop sign—an event beyond our control. While seat belts (vaccines) and air bags (medications) cannot prevent accidents (illnesses), having them in place significantly reduces the severity of the outcomes. Vaccines prime our immune system for a swift and effective response. Using all 3 elements together—avoidance, vaccination, and treatment—ensures an optimal outcome, embracing a "both/and" approach rather than an "either/or" mindset. This analogy helps some vaccine-hesitant patients to agree to vaccination by explaining its role in understandable terms.

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BENEFITS OF DISTANCING AND VACCINATION

The early COVID-19 lockdown and the widespread adoption of physical distancing, mask-wearing, and enhanced hand hygiene helped limit the spread of not only COVID but other respiratory viruses as well. For example, only 1,899 (0.2%) of more than 1 million clinical samples tested positive for influenza A or B during the 2020 to 2021 period.[1]

Vaccines also play a crucial role. Shattock et al[2] estimate that since 1974, childhood vaccination has prevented 150 million deaths, including 140 million among children under 5 and 100 million among children younger than 1 year. On average, for every life saved, 66 years of full health were gained, totaling approximately 10.2 billion years of health. The investigators estimate that vaccination contributed to 40% of the observed decline in global infant mortality, and 52% in Africa. Thanks to vaccination, in 2024, a child under 10 years old is 40% more likely to survive to their next birthday than they would be if vaccines had never been invented. This increased survival benefit extends into late adulthood as well.

The topic of vaccine hesitancy and how to deal with it has been recently covered in 2 excellent articles in this journal.[3,4]

HIGH COST OF ILLNESS

Respiratory viruses cause significant morbidity and death. The Centers for Disease Control and Prevention

TABLE 1
Some representative influenza vaccines

Brand name (vaccine form)	Approved ages	Dose
Fluzone (inactivated, egg-based)	6–35 months	0.25 mL
Fluzone (inactivated, egg-based)	≥ 3 years	0.5 mL
Fluzone High-Dose (inactivated, egg-based)	≥ 65 years	0.5 mL
FluBlok (recombinant, egg-free)	≥ 18 years	0.5 mL
FluMist (live attenuated, egg-based)	2–49 years	0.1 mL in each nostril (0.2-mL prefilled single-use intranasal sprayer)
Fluad (inactivated adjuvanted, egg-based)	> 65 years	0.5 mL

Information from reference 7.

estimates that, between 2010 and 2023, influenza caused 9.3 to 41 million illnesses, 100,000 to 710,000 hospitalizations, and 4,900 to 51,000 deaths each year.[5]

They also impose a significant economic burden on individuals and society. Molinari et al[6] estimate that seasonal influenza costs the US economy nearly $90 billion each year in the form of medical expenses, lost workdays due to illness, and deaths. They suggest that interventions targeting the elderly could offer the greatest economic benefit, as this group bears 64% of the total economic burden, including 36,000 deaths annually.

VACCINE FORMULATIONS AND RECOMMENDATIONS

Vaccination reduces illness severity and saves lives. Here are the current formulations and their indications.

Influenza vaccines are now trivalent

The 2024–2025 seasonal influenza vaccine in the United States is trivalent, containing hemagglutinin from 3 strains[7]:

- Influenza A/Victoria/4897/2022 (H1N1) or influenza A/Wisconsin/67/2022 (H1N1)
- Influenza A/Thailand/8/2022 (H3N2) or influenza A/Massachusetts/18/2022 (H3N2)
- Influenza B/Austria/1359417/2021 (Victoria lineage).

In past years, the US seasonal influenza vaccine was quadrivalent. However, this year, the vaccine no longer contains the B/Yamagata strain, which has not been detected globally since March 2020.

Three types of influenza vaccines are available: inactivated (which are egg-based), recombinant (which are not egg-based), and a live attenuated formulation (which, unlike the others, is inhaled rather than injected) (**Table 1**).[7]

Who should be vaccinated? Influenza vaccine is recommended for all persons age 6 months and older, but certain groups may be at higher risk of medical complications attributable to severe influenza and therefore should be prioritized for vaccination[7]:

- Children age 6 through 59 months
- Adults age 50 years or older
- Adults and children who have chronic disorders—pulmonary (including asthma), cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic (including diabetes mellitus)
- Persons who are immunocompromised due to any cause
- Persons who are or will be pregnant during the influenza season
- Children and adolescents through 18 years who are receiving aspirin- or salicylate-containing medications and who might be at risk of Reye syndrome after influenza virus infection
- Residents of nursing homes and other long-term care facilities
- American Indian or Alaska Native persons
- Persons who are extremely obese (body mass index ≥ 40 kg/m^2 for adults).

Ideally, influenza vaccine should be offered in September or October, according to the Advisory Committee on Immunization Practices (ACIP). However, vaccination efforts should continue as long as the influenza virus is circulating.

All persons should receive a vaccine that is appropriate for their age. Adults age 65 and older should receive an enhanced influenza vaccine (ie, either a high-dose formulation of inactivated or recombinant influenza vaccine, or adjuvanted influenza vaccine), if these are available. Live attenuated influenza vaccine is not recommended in pregnancy or for immunocompromised persons.[7]

Persons with egg allergies may receive egg-based vaccines and are not at increased risk for adverse events in doing so.[8] In most cases, no additional safety measures are needed when giving egg-based influenza vaccines to egg-allergic individuals.

COVID-19 vaccination is still needed

There are 2 types of COVID-19 vaccines: messenger RNA (mRNA)–based and protein subunit (spike)–based. The US Food and Drug Administration has approved the 2024–2025 COVID-19 mRNA vaccines by Moderna (Spikevax) and Pfizer-BioNTech (Comirnaty) for persons 12 years and older. These vaccines are also approved for children age 6 months to 11 years under emergency use authorization. The 2024–2025 COVID-19 adjuvanted protein subunit vaccine by Novavax (Nuvaxovid, Covovax) is also approved under emergency use authorization for persons 12 years and older.

The approved vaccines are monovalent and protect against the currently circulating JN.1 variant of COVID-19.[9,10]

The ACIP recommends a US Food and Drug Administration–approved 2024–2025 COVID-19 vaccine for all persons age 6 months and older.

Why do we still need COVID-19 vaccinations? Although hospitalization and death rates are much lower now than at the height of the pandemic, COVID-19 infection remains an ongoing public health concern. During the 2023–2024 season, by age group, the COVID-19–associated hospitalization rate was highest in those age 75 and older, in whom it peaked at 207 cases per 100,000 people in December 2023.[11] However, in the same month, hospitalization rates were also high in adults 65 through 74 years old (63 cases per 100,000 people) and infants younger than 6 months (75 cases per 100,000 people).[11] COVID-19–associated death rates were also highest in those 75 and older (peak of 46 deaths per 100,000 people in January 2024).[11]

Data from the 2023–2024 bivalent COVID-19 vaccine were reviewed in the approval process for the updated vaccines.[12] Vaccine effectiveness, a comparison of the frequency of disease in vaccinated and unvaccinated people in real-world conditions, was evaluated for various end points in adults and adolescents: medically attended emergency department and urgent care visits due to COVID-19 (pooled vaccine effectiveness 43%), hospitalization due to COVID-19 (pooled vaccine effectiveness 44%), and prevention of death due to COVID-19 (pooled vaccine effectiveness 23%).

A vaccine effectiveness of 23% means that vaccination reduces the risk of death by 23%. This might seem like a modest reduction, but remember that the most vulnerable individuals have already been affected by the disease, and over time population immunity—due to vaccination and previous infections—continues to increase. In infants and children, the vaccine effectiveness in terms of medically attended emergency department and urgent care visits was 80%.[12]

Regarding safety, investigations are ongoing regarding possible associations between Guillain-Barré syndrome and Pfizer-BioNTech COVID-19 vaccine among people 65 years and older, ischemic stroke and Moderna COVID-19 vaccine in the same age group, and ischemic stroke and the Pfizer-BioNTech vaccine among adults age 50 to 64 years. However, at this time, no direct link to vaccination has been established.[12]

In August 2021, 69% of adults reported being up to date on COVID-19 vaccines. This had dropped to 28% in February 2024.[12] The 2024–2025 COVID-19 vaccines can provide protection against currently circulating variants and reduce rates of COVID-19–associated hospitalization and death.[12]

Respiratory syncytial virus vaccination

Three RSV vaccines are available from GSK, Moderna, and Pfizer. The GSK and Pfizer RSV vaccines are protein subunit products, while the Moderna RSV vaccine is an unadjuvanted mRNA-based product (**Table 2**).[13–16] Overall, the Pfizer RSV vaccine demonstrated strong efficacy that was maintained over 2 seasons, and it was well tolerated by patients.[15]

Revised recommendation. In June 2024, the ACIP[13] revised its recommendation on RSV vaccination. Previously, it said that adults age 60 years and older *may* receive a single dose of RSV vaccine; now, it says that all adults age 75 years and older *should* receive it, as should those age 60 through 74 years who are at higher risk for severe RSV disease, including, for example, those with any of the following:

- Chronic cardiovascular disease
- Chronic lung or respiratory disease
- End-stage renal disease
- Diabetes mellitus with complications or taking insulin, a sodium-glucose cotransporter 2 inhibitor, or both
- Neurologic or neuromuscular conditions causing impaired airway clearance or respiratory muscle weakness
- Chronic liver disease
- Chronic hematologic conditions
- Severe obesity (body mass index ≥ 40 kg/m^2)
- Moderate or severe immune compromise
- Residence in a nursing home
- Other high-risk factors at the discretion of the clinician.

Pregnant women should also be vaccinated, which is beneficial both for their own protection and for passing on immunity to their babies. Only the Pfizer RSV vaccine is approved to be given in pregnancy.[14,15]

TABLE 2
Respiratory syncytial virus vaccines

Brand name (vaccine form)	Approved ages[a]	Dose	Efficacy, %[b]	Side-effect rates, %
Arexvy (inactivated protein subunit, adjuvanted)[15]	≥ 75 years 60–74 years with high-risk factor	0.5 mL	Season 1: 94.1 Season 2: 84.6	Severe reactogenicity events 3.8 (vs 0.9 with placebo) Pain 60.9 Fatigue 33.6 Myalgia 28.9 Headache 27.2
Abrysvo (inactivated protein subunit, nonadjuvanted)[14,15]	≥ 75 years 60–74 years with high-risk factor Pregnant at 32–36 weeks' gestation	0.5 mL	Season 1: 88.9 Season 2: 78.6	Severe reactogenicity events 1.0% (vs 0.7% with placebo) Pain 10.5 Fatigue 15.5 Myalgia 10.1 Headache 12.8
mResvia (inactivated messenger RNA encoding the respiratory syncytial virus F glycoprotein)[13,16]	≥ 75 years 60–74 years with high-risk factor	0.5 mL	Season 1: 80.9 Season 2: 61.1	Severe reactogenicity events 6.1 (vs 4.0 with placebo) Pain 55.9 Fatigue 30.8 Myalgia 25.6 Headache 26.7

[a]This table does not include maternal indication data.
[b]Efficacy in preventing symptomatic, laboratory-confirmed respiratory syncytial virus–associated lower respiratory tract disease with at least 3 lower respiratory signs.

VIRAL TESTING WITH REVERSE-TRANSCRIPTION POLYMERASE CHAIN REACTION TESTS

It can be hard to tell which virus a patient has solely on the basis of signs and symptoms. Multiple respiratory viruses are often circulating simultaneously and producing similar clinical signs. Perhaps the distinction did not matter so much in the past, when we could just say "the patient has a virus." But now we have specific drugs for some viruses, and moreover, the drugs need to be started as soon as possible after the onset of symptoms. Thus, the need for laboratory tests to identify the pathogen—and quickly! Delays in obtaining precise and timely results can compromise patient care.[17]

Triple reverse-transcription polymerase chain reaction (RT-PCR) tests can simultaneously detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, which causes COVID-19), influenza, and RSV from a nasopharyngeal swab, and their use can accelerate the process from sampling to diagnosis to treatment. As COVID-19 and influenza have specific antiviral treatments, testing for them conserves resources, especially when timely treatment prevents severe illness or hospitalization. Multiplex assays such as these also have the potential to enhance and expand surveillance systems, leveraging the capabilities developed during the COVID-19 pandemic to improve epidemic and pandemic preparedness, prevention, and response.[17]

Using RT-PCR rather than rapid antigen tests may seem counterintuitive, since the latter are, well, rapid, and patients can do them themselves in the comfort and privacy of their own homes. However, PCR is more sensitive than rapid antigen testing and thus gives fewer false-negative results. Also, testing for 3 viruses at once is an advantage, and if we get organized and set up our practices to obtain and process RT-PCR tests quickly, the time and convenience factors can be overcome.

In a study in 263 children, the sensitivity of a triple RT-PCR test was 88.9% (95% confidence interval [CI] 51.8%–99.7%) for SARS-CoV-2, 91.6% (95% CI 84.1%–96.3%) for influenza, and 79.1% (95% CI 64.0%–90.0%) for RSV.[18] Specificity was 100% for each virus.

We encourage both patients and clinicians to prioritize early testing, ideally using nasopharyngeal swab PCR platforms rather than home antigen tests. In a study in Florida, state organizations provided PCR testing for individuals who tested positive on the home antigen tests, showed symptoms, or requested PCR testing.[19] Of 18,457 individuals tested, 3,153 (17.1%)

TABLE 3
COVID-19 outpatient treatments

Treatments	Who[a]	When	How	Clinical considerations
Molnupiravir	Adults	Start as soon as possible; must begin within 5 days of symptom onset	Taken at home orally	Not recommended in pregnant or lactating women No renal or hepatic adjustment
Nirmatrelvir-ritonavir	Adults; children ages 12 years and older	Start as soon as possible; must begin within 5 days of symptom onset	Taken at home orally	Renal dosing if estimated glomerular filtration rate is 30–59 mL/min, and not recommended if < 30 mL/min Review drug-drug interactions
Remdesivir	Adults and children	Start as soon as possible; must begin within 7 days of symptom onset	Intravenous infusions at a healthcare facility for 3 consecutive days	Consider stopping if patient develops alanine aminotransferase (ALT) elevation ≥ 10 times the upper limit of normal during treatment Discontinue if ALT elevation is accompanied by signs or symptoms of liver inflammation

[a]Age ≥ 65 years and those with certain underlying medical conditions including: asthma, cancer (hematologic malignancy), cerebrovascular disease, chronic kidney disease (people receiving dialysis), chronic lung diseases (bronchiectasis, chronic obstructive pulmonary disease, interstitial lung disease, pulmonary embolism, pulmonary hypertension), chronic liver diseases (cirrhosis, nonalcoholic fatty liver disease, alcoholic fatty liver disease, autoimmune hepatitis), cystic fibrosis, diabetes mellitus type 1 and 2, disabilities including Down syndrome, heart disease (heart failure, coronary artery disease, cardiomyopathies), human immunodeficiency virus, mental health conditions (mood disorders, schizophrenia), neurologic conditions (dementia), obesity, physical inactivity, recent or current pregnancy, primary immunodeficiencies, current or former smoking, transplantation, tuberculosis, and use of corticosteroids or immunosuppressive medications.

Information from references 20 and 21.

TABLE 4
Anti-influenza outpatient treatments

Treatments	Who	When	How	Clinical considerations
Influenza treatment: oseltamivir	Adults and children from birth	As soon as possible; ideally begin within 2 days of symptom onset	Taken at home orally	For persons at high risk of complications,[a] initiate as soon as possible, even if > 2 days since symptom onset Renal dosing if creatinine clearance is < 60 mL/min
Influenza prevention after exposure[b]: oseltamivir	Adults and children from 3 months of age at very high risk for influenza complications[a]	Start as soon as possible after exposure	Taken at home orally	Prophylaxis and treatment dosing differ—refer to your institutional guideline Renal dosing if creatinine clearance is < 60 mL/min

[a]Adults ≥ 65 years, people who are pregnant or post partum (within 2 weeks after delivery), residents of long-term care facilities, non-Hispanic Black persons, Hispanic or Latino persons, American Indians and Alaska natives, persons with body mass index ≥ 40 kg/m^2, and individuals with certain chronic medical conditions (eg, pulmonary, cardiovascular, endocrine [eg, diabetes mellitus], renal, hepatic, hematologic, metabolic, neurologic, human immunodeficiency virus, malignancy), or those receiving immunosuppressive medications.

[b]Contact within the past 48 hours with a confirmed or suspected case.

Information from reference 22.

Cleveland Clinic

Caregiver Instructions

Nasopharyngeal Swab Collection for Respiratory Virus Testing

These instructions illustrate how to correctly use a swab to collect a specimen for respiratory virus testing.

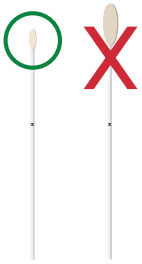
1. Don the appropriate PPE. Refer to the Standard Precautions Policy.

2. Document the collection in Epic, print the label, and place the label on the UTM tube. Verify patient identifiers on the label with the patient before collecting the specimen.

3. Obtain a **UTM, Nasopharyngeal Swab** with a flexible shaft for specimen collection.

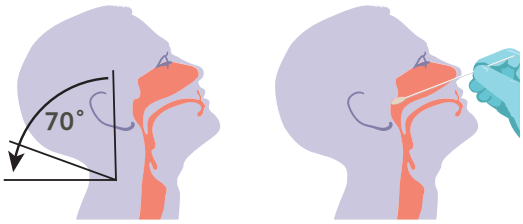
Small swab, flexible shaft = Nasopharynx

Large swab, rigid shaft = Nasal/Nares



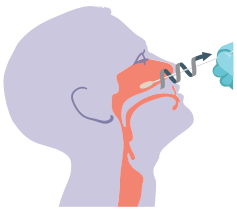
4. Tilt the patient's head back 70 degrees. Gently and slowly insert the mini-tip swab through the nostril parallel to the palate (not upward) until you encounter resistance or the distance is equivalent to that from the patient's ear to the nostril, indicating contact with the nasopharynx.

Gently rub and roll the swab. Leave the swab in place for several seconds to absorb secretions.

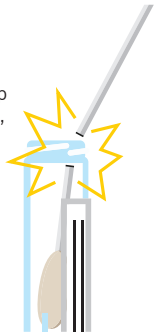


5. Slowly remove the swab while rotating it.

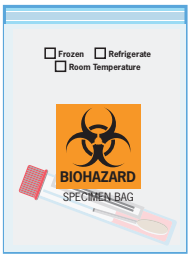
If the swab is saturated or a nostril is blocked, collection from one nostril is adequate."



6. Place the swab, tip first, into the transport tube provided. Break the swab shaft at the score line, discard the top portion of the stem, and close the cap.



7. Place the UTM into a biohazard bag and walk or send it via the tube system to the lab.



Specimens will be rejected if there is more than one swab in transport media, no swabs in the transport media, dry swabs without transport media, or if they are inappropriately labeled.

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Figure 1. Nasopharyngeal swab collection for respiratory virus testing.

PPE = personal protective equipment

were PCR-positive. The positive percent agreement of the antigen test compared with PCR was 49.2% overall and 51.9% for people with symptoms. The study found that the antigen test's performance was lower than previously reported. Without amplification and with the potential for incomplete sample collection when conducted at home rather than by healthcare professionals, real-world antigen testing is expected to be less accurate than PCR testing. Additionally, a negative result from a home antigen test—especially early in the course of illness—should be repeated in 2 to 3 days, when viral load is typically higher, often leading to a positive result at that time.[19]

Starting antiviral medications early is important—within 2 days for oseltamivir and 5 days for nirmatrelvir-ritonavir, molnupiravir, and remdesivir for patients with intact immune systems—emphasizing the importance of prompt testing. Patients on steroids, other immunosuppressant medications, or periodic infusions (eg, adalimumab, ocrelizumab) should start oseltamivir with a confirmed influenza diagnosis regardless of duration of symptoms (**Table 3**,[20,21] **Table 4**[22]).

GETTING READY

Every year, the respiratory viral season puts a strain on the entire medical system, from clinician offices to diagnostic laboratories to hospitals. Before the onset of the season, it is helpful to establish clear and straightforward procedures in the office for ordering PCR nasopharyngeal swabs when symptoms arise (**Figure 1**). Training office staff, and possibly yourself, in the correct technique for specimen collection is essential, as accurate results depend on obtaining cells from the swab. Viruses are obligate intracellular pathogens and, therefore, you must get cells on the swab. Don't be too gentle, as this can affect test accuracy.

Additionally, practices need to develop treatment protocols and possibly template prescriptions to facilitate timely issuance of medications (**Table 3**,[20,21] **Table 4**[22]). Pay particular attention to nirmatrelvir-ritonavir due to its potential for drug-drug interactions.

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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Address: *Pooja Cerrato, PharmD, BCPS, Medical Operations, Inpatient Pharmacy, HB110, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; cerratp@ccf.org*

REVIEW

CME MOC

Anira Iqbal, MD
Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, Cleveland, OH

Vinni Makin, MBBS, MD
Department of Endocrinology, Diabetes and Metabolism, Cleveland Clinic, Cleveland, OH; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Hypoglycemia after bariatric surgery: Management updates

ABSTRACT

Bariatric procedures have been shown to decrease mortality in patients with obesity and even induce remission of type 2 diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea. One common complication of bariatric surgery is hypoglycemia, which can be observed months to years later and can significantly impact patient lifestyle. No medications are currently approved for this indication. In this article, we discuss the treatment options available and being studied for post–bariatric surgery hypoglycemia (PBH).

KEY POINTS

- PBH typically occurs more than 12 months after bariatric surgery, with symptoms presenting 1 to 3 hours after eating. Symptoms that occur in a fasting state, nocturnal hypoglycemia, or exercise-induced hypoglycemia are less likely to be PBH.
- Use of continuous glucose monitors and a food diary while tracking symptoms may assist in diagnosis, although the limitations of false lows and variable sensitivity should be considered when evaluating data from continuous glucose monitors.
- Off-label medications to treat PBH are currently widely available (acarbose, diazoxide, nifedipine, verapamil), with other agents on the horizon, including glucagon pumps, avexitide, and insulin receptor antibodies.
- Surgical intervention by reversal of gastric bypass or with gastric pouch restriction is considered a last resort.

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Bariatric procedures decrease long-term mortality in patients with obesity and even induce remission of type 2 diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea.[1–3] Given these benefits, more patients are choosing to undergo bariatric procedures to lose weight, and clinicians now encounter an increasing number of patients, both inpatient and outpatient, with a history of bariatric surgery. Hypoglycemia is a common complication of bariatric surgery that can be observed months to years after surgery.[4–10] Up to one-third of patients who underwent bariatric surgery reported symptoms of hypoglycemia during mixed meal challenges, while oral glucose tolerance testing has detected a variable incidence of 9.1% to 32.8%.[4–6]

A recently published meta-analysis of data from studies that assessed post–bariatric surgery hypoglycemia (PBH) by continuous glucose monitoring showed that more than 50% of individuals who had undergone bariatric surgery exhibited hypoglycemia.[7] Although these data may overestimate the rate of PBH, given the frequent false lows documented with use of continuous glucose monitors (CGMs), they underscore the high burden of hypoglycemia in this population. Hypoglycemia can be debilitating when symptomatic and has unknown consequences when asymptomatic. With the increased frequency of patients presenting with reported hypoglycemia, especially as continuous glucose monitoring becomes more common, diagnosing hypoglycemia, determining its cause, and knowing the available treatment options are imperative to tailor therapy and improve patient lifestyle.

The approach to PBH was thoroughly outlined in the review by Millstein and Lawler[8] in 2017. In this article, we discuss advances made since then and briefly summarize treatment options that are currently available as well as those being studied.

DIAGNOSIS

The diagnosis of hypoglycemia is based on the Whipple triad, which consists of the following[8]:

- Low glucose measured in a blood sample
- Concurrent symptoms of hypoglycemia (palpitations, shakiness, sweating, anxiety, irritability, dizziness, hunger)
- Reversal of symptoms when low blood glucose is corrected.

PBH typically occurs more than 1 year after bariatric surgery and is more severe in patients undergoing Roux-en-Y gastric bypass (RYGB) surgery compared with sleeve gastrectomy, although the incidence remains similar.[4,9,10] Risk factors for PBH other than the RYGB procedure include female sex, lower preoperative body mass index and hemoglobin A1c, lower fasting glucose, lower glucose during the oral glucose tolerance test, and greater weight loss at 6 months.[9] The symptoms of PBH typically occur 1 to 3 hours after eating, and neuroglycopenic symptoms (behavioral changes, confusion, impaired cognitive function, seizure, loss of consciousness) are seen in severe hypoglycemia.

Symptoms that occur less than 6 to 12 months after surgery, in the fasting state, or less than 1 hour or more than 4 hours after eating are less likely to be PBH. In patients who report any of these, other causes for hypoglycemia should be explored through complete history, physical examination, and laboratory testing.[9] Differentials include dumping syndrome, side effects from medications (sulfonylureas, meglitinides, insulin use), hypothyroidism, hypoglycemia due to malnutrition, adrenal insufficiency, liver dysfunction, insulinoma, and insulin antibody syndrome, among others.

Dumping syndrome is quite common after bariatric surgery and typically occurs soon after surgery, while the onset of PBH can take years.[11] The symptoms of the 2 conditions are similar, but dumping syndrome occurs within 1 hour after eating vs 1 to 3 hours after eating with PBH.[11] It has been postulated that dumping syndrome and PBH are part of the same spectrum, known as early and late dumping syndrome, respectively.

Patients should be encouraged to check their fingerstick glucose at home during episodes before self-treating and to keep a food diary to document the timing of hypoglycemia in relation to food intake. An oral glucose tolerance test may provoke symptoms of severe dumping syndrome and should not be used. The mixed meal tolerance test is a more natural and helpful diagnostic tool but is laborious and can precipitate symptoms.[9]

CONTINUOUS GLUCOSE MONITORING

A healthy person typically spends less than 1.1% of their time in a state of hypoglycemia (glucose < 70 mg/dL).[12] Continuous glucose monitoring for diagnosis of hypoglycemia in patients without diabetes has not been approved and should be used cautiously because CGMs have poor specificity for low interstitial glucose, leading to high false-positive rates, which can promote anxiety. Inaccurate readings can result from calibration errors, error margin (mean absolute relative difference), the position of sensors, interference from certain medications, humidity and extreme temperature, skin changes, and compression of sensors (if the patient lies on the site of the sensor).[13]

CGMs can assess the timing of symptoms in relation to interstitial glucose levels (with a typical lag time of some minutes) and association with food and can unveil asymptomatic or nocturnal hypoglycemia. The newer CGMs (eg, Dexcom G6 or G7, Freestyle Libre 3) are more accurate than those of previous generations. CGMs have greater sensitivity and specificity in diagnosing PBH than the mixed meal tolerance test, but a study comparing CGMs and fingerstick glucose monitoring has not been done.[14,15] Continuous glucose monitoring has been associated with reductions in both hypoglycemia and hyperglycemia in the PBH population, likely because it helps patients detect glycemic variability, allowing dietary modification and self-treatment to avoid hypoglycemia.[16]

Recently, the Dexcom Stelo was approved by the US Food and Drug Administration as the first over-the-counter CGM for patients without diabetes, followed by Abbott's Lingo, although cost and insurance coverage may remain a barrier.[17,18]

PATHOPHYSIOLOGY

Meal-induced gut factors (glucose-dependent insulinotropic polypeptide, glucagon-like peptide [GLP] 1, direct neural factors, and nutrient factors) regulate glucose homeostasis after food intake. Secretion of gut factors after a meal induces a robust pancreatic beta-cell secretory response.[19] Alterations in the anatomy of patients following bariatric surgery leads to accelerated emptying of nutrients into the intestine, bypassing the stomach and allowing for earlier, more rapid absorption of glucose, which causes an earlier and

TABLE 1
Medications for managing post–bariatric surgery hypoglycemia: Mechanisms of action

Medication	Mechanism of action
Acarbose[8,23,25,26]	Inhibits intestinal alpha-glucosidase—delays absorption of glucose from the intestine, decreases postprandial glycemic and insulinemic peaks
Diazoxide[26–28]	Reduces insulin secretion by inhibition of beta-cell adenosine triphosphate–sensitive potassium channels, induces hepatic gluconeogenesis
Octreotide, pasireotide[25,26,29]	Somatostatin analogs delay gastric emptying, reduce insulin and GLP-1 secretion
Nifedipine or verapamil[25,30]	Inhibits insulin release by inhibiting calcium channels in pancreatic beta cells
GLP-1 analogs[25,26,31]	Decreases variability in GLP release, which causes synchronous insulin and glucose peaks, delays gastric emptying, decreases appetite, stimulates glucagon secretion
Dipeptidyl peptidase 4 inhibitors[25,26]	Reduces the degradation of GLP-1 and glucose-dependent insulinotropic polypeptide and raises their levels
GLP-1 antagonist[32–34]	Prevents surges in GLP-1 and insulin, increases glucagon secretion
SGLT-2 inhibitors[35,36]	Reduces carbohydrate absorption by inhibiting intestinal SGLT-1 and increasing hepatic glucose production
Interleukin 1 beta antagonist (anakinra)[37]	Decreases dysregulated proinflammatory signaling, which can cause excessive insulin response
Glucagon[38,39]	Glucagon receptor agonist, stimulates glycogenolysis and hepatic gluconeogenesis
Insulin receptor antibody (XOMA 358)[40,41]	Reverses insulin-induced hypoglycemia by significantly decreasing insulin sensitivity and increasing hepatic glucose output

GLP = glucagon-like peptide; SGLT = sodium-glucose cotransporter

greater rise in peak postprandial glucose. This results in increased GLP-1 release from the intestine, which induces increased insulin release from the pancreas and a subsequent drop in blood glucose.[8,9]

Thus, postprandial hypoglycemia after RYGB is typically attributed to the combined effects of more rapid nutrient transit from the gastric pouch to the gut and the enhanced incretin effect. Salehi et al[20] reported that continuous infusion of the GLP-1 receptor antagonist avexitide (exendin 9-39) reduced the meal-induced insulin response in patients without diabetes who had undergone RYGB compared with patients who did not undergo surgery.

Other factors that may impact PBH are a decreased glucagon response to hypoglycemia, postoperative increased insulin sensitivity, and decreased insulin clearance.[19] An increase in beta-cell mass after surgery (nesidioblastosis) was initially thought to contribute, but a subsequent analysis revealed no difference in overall beta-cell mass in patients with PBH compared with autopsy samples from obese and lean individuals.[21] Moreover, pancreatectomy has not been found to always be curative.

Use of alcohol or medications such as beta-blockers, some fluoroquinolones, nonsteroidal anti-inflammatory drugs, and sulfonylureas has been documented to worsen hypoglycemia.[22]

MEDICAL MANAGEMENT

Dietary modifications are the cornerstone of PBH management. Frequent small, nutrient-dense meals rich in protein and low-glycemic foods and low in carbohydrates (15–30 g per meal) are recommended.[8] Healthy fats should be included to compensate for the lower carbohydrate content. Pure carbohydrates

TABLE 2
Medications for managing post–bariatric surgery hypoglycemia: Dosages and side effects

Medication	Dosage	Side effects	Notes
Acarbose[8,23,25,26]	25 mg with 1 meal per day, slowly titrate up to 100 mg at every meal daily	Bloating, abdominal cramping, diarrhea	Used as first line because it's affordable and available Not recommended in significant renal impairment If hypoglycemia occurs, correct with simple carbohydrates (glucose, dextrose, honey)—complex carbohydrates (table sugar, juice, soft drink, candy) will not be effective
Diazoxide[26–28]	50–100 mg twice daily to start	Fluid retention, edema, nausea, hypotension, hirsutism, headache	Consider dose reduction with renal impairment Typically used for hypoglycemia from insulinomas Affordability and insurance coverage are barriers
Octreotide, pasireotide[25,26,29]	Octreotide 25–100 µg SC before meals Octreotide long-acting repeatable 20-mg intramuscular injection monthly Pasireotide 50–300 µg SC before meals or 300 µg SC daily	Diarrhea, steatorrhea, cholelithiasis, hyperglycemia (more with pasireotide), QT prolongation	Safe to use in renal impairment Expensive Screening abdominal ultrasonography and electrocardiogram required Pasireotide is longer acting than octreotide and is available for compassionate use in severe PBH Oral octreotide is available but has not been used for this indication
Nifedipine or verapamil[25,30]	Verapamil 40 mg 3 times daily Nifedipine 30–60 mg daily	Hypotension, edema	Safe to use in renal impairment
GLP-1 analogs[25,26,31]	Liraglutide 0.6 mg titrated to 1.2 mg SC daily, up to 1.8 mg daily	Nausea, constipation	Contraindicated in patients with family or personal history of medullary thyroid carcinoma Use with caution in patients with history of pancreatitis Safe to use in renal impairment but avoid dehydration Expensive
Dipeptidyl peptidase 4 inhibitors[25,26]	Sitagliptin 100 mg once daily	Nausea, constipation	Inconclusive results—not recommended
GLP-1 antagonist[32–34]	Avexitide 30 mg SC twice daily	Headache, nausea, injection-site reaction	Recently granted breakthrough therapy designation by the US Food and Drug Administration for treating PBH and congenital hyperinsulinism, currently in phase 3 trial
SGLT-2 inhibitors[35,36]	Canagliflozin 100 or 300 mg daily Empagliflozin 10–25 mg daily	Dehydration, urinary tract and genital mycotic infections, euglycemic diabetic ketoacidosis	Dosage adjustment required in renal impairment Canagliflozin and empagliflozin shown to improve glycemic response to oral glucose tolerance and mixed meal tolerance tests, respectively, in patients with PBH
Interleukin 1 beta antagonist[37]	Anakinra 100 mg SC daily		Anakinra and SGLT-2 inhibitor empagliflozin reduced the number of hypoglycemic events during a liquid mixed meal test
Glucagon[38,39]	Dasiglucagon 80 or 120 µg SC injection as needed for hypoglycemia	Nausea, vomiting, hyperglycemia, reduced appetite	Still under clinical investigation, use of glucagon in an insulin pump has shown satisfactory results May be used for treatment of acute severe hypoglycemia
Insulin receptor antibody[40,41]	XOMA 358 3–9 mg/kg daily	Headache, hyperhidrosis	Results from phase 2 trial not announced yet

GLP = glucagon-like peptide; SC = subcutaneous; PBH = post–bariatric surgery hypoglycemia; SGLT = sodium-glucose cotransporter

without protein or fat should be avoided as this can precipitate severe hyperglycemia.[23] Avoiding excessive caffeine and alcohol, which can cause hypoglycemia via inhibition of hepatic glucose release, is also important. Commercial products containing uncooked cornstarch, which degrades slowly in the intestines and is absorbed slowly, are reported to be helpful.[24] However, sustaining strict dietary modifications can be difficult for patients.

Patients with PBH should treat their hypoglycemia with a simple carbohydrate combined with protein or fat, as they will often have recurrent hypoglycemia if a simple carbohydrate is used alone.

No medications are currently approved for management of refractory PBH, but several medications are used off-label (**Table 1** and **Table 2**).[8,23,25-41] In a comparative study on the effect of acarbose, sitagliptin, verapamil, liraglutide, and pasireotide on PBH after RYGB, acarbose and pasireotide reduced postprandial hypoglycemia in persons with PBH.[25] Acarbose appeared to have a glucose-stabilizing effect, reducing peak postprandial hyperglycemia. Glucocorticoids have been used off-label to prevent hypoglycemia, but because of the possibility of causing iatrogenic Cushing syndrome, use for this indication is not recommended.[8]

SURGICAL OPTIONS

In cases of nutrition- and medication-refractory severe hypoglycemia or complicated malnutrition management, enteral nutrition through a gastrostomy tube placed into the remnant stomach or jejunum should be considered.[42]

Surgical options, considered a last alternative due to risks and complications, include RYGB reversal, RYGB conversion to sleeve gastrectomy, and gastric pouch restriction.[43] If gastric bypass reversal is being considered, a trial of solely remnant stomach tube feeds (with no oral intake) should be pursued first. If this ameliorates hypoglycemia, then gastric bypass reversal may be of benefit.[8] Partial or complete pancreatectomy has been performed for this indication, but owing to a high rate of hypoglycemia recurrence and poor success rate, it is no longer recommended.[44,45]

CONCLUSION

While bariatric surgery is an excellent treatment for obesity and its complications, the long-term repercussions of recurrent hypoglycemia may lead to impaired quality of life, motor-vehicle accidents, cardiovascular events, and regain of body weight (due to overcompensation by overeating). Thus, it is important to treat PBH with currently available agents concomitantly with dietary changes. CGM use should be considered in these patients as a mode of intervention, when possible, although it is important to consider the limitations of false measured lows.

Medications currently widely available to use off-label include acarbose, diazoxide, nifedipine, and verapamil. Other medications such as GLP-1 agonists, sodium-glucose cotransporter 2 inhibitors, dasiglucagon, octreotide, and pasireotide can be used off-label when available. Agents on the horizon include glucagon pumps, avexitide, and insulin-receptor antibodies. Surgical intervention by reversal of gastric bypass or with gastric pouch restriction is considered a last alternative.

DISCLOSURES

Dr. Makin has disclosed teaching and speaking for Bayer. Dr. Iqbal reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Address: *Anira Iqbal, MD, Department of Endocrinology, Diabetes and Metabolism, F20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; aniraiqbal93@gmail.com*

William A. Schiavone, DO
Cardiologist, retired from Sydell and Arnold Miller Family Heart, Vascular, and Thoracic Institute, Cleveland Clinic, Cleveland, OH

David S. Majdalany, MD
Assistant Professor, Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, and Scottsdale, AZ

Don't judge a book by its cover: Unusual presentations of pericardial disease

ABSTRACT

The presentation of pericardial disease can be unusual, and what is assumed to be pericardial disease may not be. Knowing pericardial and mediastinal anatomy is vital for understanding these unusual presentations. This review focuses on the history, physical examination, and fundamental diagnostic testing, integrated with pericardial and mediastinal anatomy and pathophysiology.

KEY POINTS

The pericardial effusion from hypothyroidism in an elderly patient accumulates slowly and can be suspected from its classic signs and symptoms. Recognizing the radiographic appearance of a large pericardial effusion can help make the diagnosis.

When chest pain symptoms are accompanied by subcutaneous emphysema and follow prolonged Valsalva strain, pneumomediastinum should be suspected and can be confirmed by posteroanterior and lateral chest radiographs.

Because hemoglobin can, in the presence of hydrogen peroxide, act as a peroxidase, one should never use hydrogen peroxide to cleanse a draining sternotomy, which should be assumed to connect to a closed pericardial space containing blood. The result can be abrupt-onset cardiac tamponade from pneumopericardium.

Unrelenting cough can be the sole presentation of a moderate pericardial effusion.

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PERICARDIAL DISEASE can come on suddenly or gradually. Acute pericarditis, most commonly idiopathic, presents suddenly with substernal chest pain that is worse when lying supine and with deep inspiration. In contrast, constrictive pericarditis, the result of previous acute pericarditis or another form of trauma to the pericardium (eg, violent injury, surgery, or radiation), presents gradually with dyspnea on exertion and edema.

Because the pericardium surrounds the heart, it is in the cardiologist's bailiwick. However, the internist and the emergency physician are likely to be the first to encounter patients with pericardial disease.

A timely diagnosis can be lifesaving. When pericardial disease is suspected, the physical examination must include inspection of neck veins, palpation of the pulse, measurement of blood pressure during inspiration and expiration, auscultation of the heart and lungs, and inspection and palpation of the abdomen and lower extremities. As with all cases of chest pain and dyspnea, an electrocardiogram and a chest radiograph are necessary. When jugular venous distension, hypotension, or pulsus paradoxus is present, a significant pericardial effusion should be suspected, assessed by echocardiography, and addressed promptly.

Knowledge of pericardial and mediastinal anatomy is essential. The pericardium consists of a visceral layer and a parietal layer. The visceral layer is a single serous layer that covers the surface of the heart and proximal great vessels

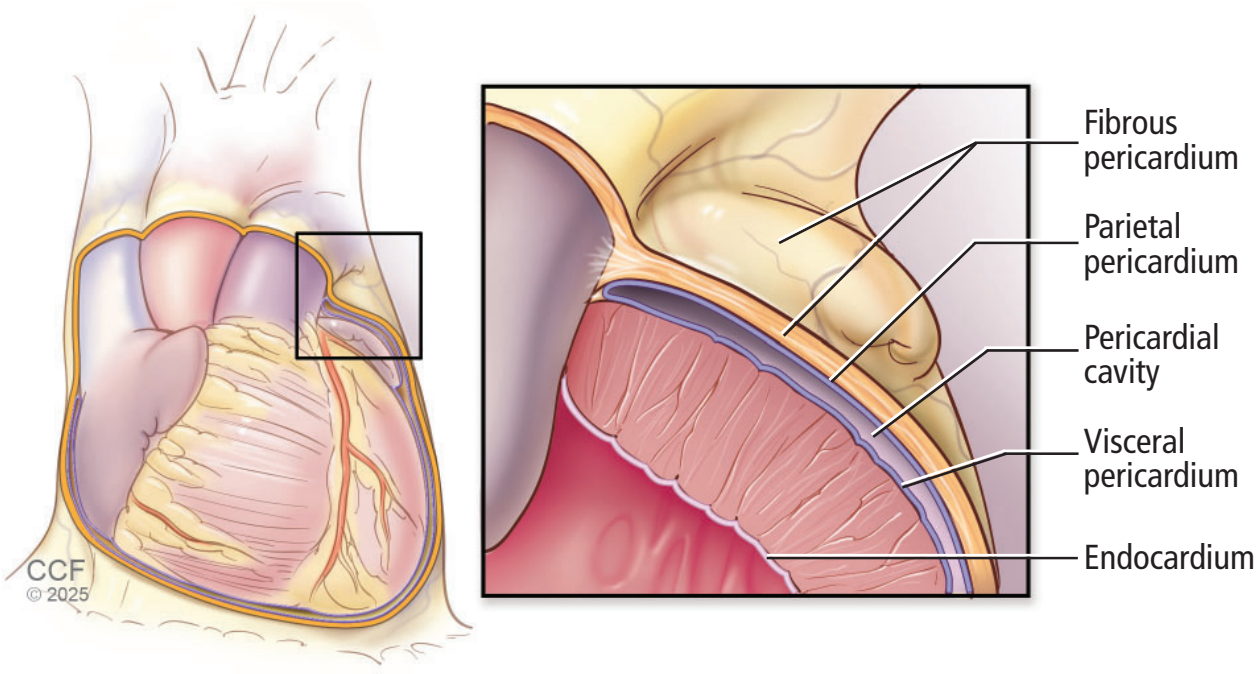

Figure 1. Artist's drawing of the reflections of the anterior parietal pericardium clockwise on the superior vena cava, ascending aorta, pulmonary trunk, and diaphragm.

(**Figure 1**), while the parietal pericardium consists of an inner serous layer, a fibrous middle layer, and the outer epicardial collagenous connective tissue (**Figure 2**). The pericardial space, which typically contains 15 to 50 cc of fluid, is the space between the visceral serous and parietal serous layers.[1]

One must learn the spectrum of pericardial disease and its mimics to formulate a differential diagnosis. You also need good physical examination skills and the ability to read a chest radiograph of the pericardium and the mediastinum.

This review presents 4 cases that can hone these diagnostic skills. Understanding the pathophysiology of each case can make the unusual more routine.

CASE 1: A 70-YEAR-OLD MAN WITH EDEMA AND FATIGUE

A 70-year-old man who had been treated by his internist with lisinopril for hypertension presented for a semiannual checkup. He complained of edema and fatigue.

On examination, his pulse was 65 per minute and regular, blood pressure 130/90 mm Hg, and weight 200 pounds (91 kg), up 10 pounds from his last visit. His arterial oxygen saturation was 95% while breathing ambient air. His voice was hoarse. His jugular veins were distended when he was sitting upright. The heart sounds were normal but distant. The right lung was clear to auscultation, but there were tubular (bronchial) breath sounds and egophony below the angle of the left scapula. There was 2+ nonpitting edema in the lower extremities. His Achilles reflexes had delayed relaxation.

The electrocardiogram showed sinus rhythm with low QRS voltage and was otherwise normal. A posteroanterior chest radiograph (**Figure 3**) showed an enlarged cardiac silhouette with a broad base and a conspicuously enlarged azygos vein. There was no pleural effusion.

An enlarged cardiac silhouette with a broad base is characteristic of a large pericardial effusion. Moreover, bronchial breath sounds and egophony audible beneath the left scapula, which this patient had, can be caused by a large pericardial effusion compressing the left bronchus, a phenomenon known as the Ewart sign.[2] In addition, he had jugular venous distension and enlargement of the azygos vein; the azygos vein drains into the superior vena cava, and the increase in superior vena cava pressure from a large pericardial effusion can be responsible for enlargement of the azygos vein.

The results of the chest radiograph, together with the presenting symptoms and signs, prompted the internist to look for cardiac tamponade by manually checking the blood pressure during inspiration and expiration (measuring pulsus paradoxus). The systolic blood pres-

sure during inspiration was 5 mm Hg lower than during expiration. Pulsus paradoxus less than 10 mm Hg is normal.[3] Therefore, cardiac tamponade was not present.

An echocardiogram was ordered. In addition, in view of the patient's relative bradycardia, jugular venous distension, edema, hoarseness, and Achilles reflexes, the internist ordered thyroid function tests, which confirmed the suspicion of hypothyroidism.

A cardiologist who was consulted interpreted the echocardiogram, which revealed a large pericardial effusion without signs of cardiac tamponade. As there were no signs of infection or malignancy, the internist and cardiologist agreed to treat the patient with a small oral dose of thyroid hormone (12.5 µg per day), gradually increasing the dose by 12.5 µg every 4 weeks.

With close follow-up, the patient steadily improved. The hoarse voice, the jugular venous distension, the Ewart sign, and the edema resolved. A chest radiograph 2 months after initiation of thyroid hormone replacement showed a decrease in cardiac silhouette and disappearance of the azygos vein (**Figure 4**).

Discussion: Pericardial effusion due to hypothyroidism

In hypothyroidism, the pericardial capillaries are more permeable to albumin, and less albumin drains into the lymphatic vessels. This increases pericardial colloidal pressure and reduces the colloid osmotic pressure gradient between the pericardium and the pericardial space, which can result in fluid accumulating in the pericardial space.[4]

In various case series, 3% to 37% of patients with hypothyroidism developed pericardial effusions, more commonly when the hypothyroidism was severe.[4,5] However, hypothyroidism is rarely the cause of pericardial effusion requiring pericardiocentesis. In 2 series of patients who underwent pericardiocentesis, hypothyroidism was the cause of the effusion in only 7 of 140 and 0 of 269 patients, respectively.[6,7] In a series of 3 patients with hypothyroidism-induced pericardial effusion who underwent pericardiocentesis,[5] the indication for the pericardiocentesis was hypotension—systolic blood pressure uniformly 90 mm Hg or less. The European Society of Cardiology recommends ruling out more common causes of pericardial effusion such as malignancy and bacterial infections and checking inflammatory markers.[8]

Pericardial effusion from hypothyroidism responds to thyroid hormone replacement, which is usually the only treatment needed.[4] Of note, patients with hypothyroidism often have hypercholesterolemia, which fosters atherosclerosis. If this atherosclerosis involves the coronary arteries, it can remain silent (ie, not cause angina pectoris) because hypothyroidism slows the heart and decreases the metabolic rate. Thyroid hormone replacement therapy can unmask this hidden coronary artery disease, and for this reason, elderly patients with hypothyroidism must be initially treated with small daily oral doses of thyroid hormone and followed closely.

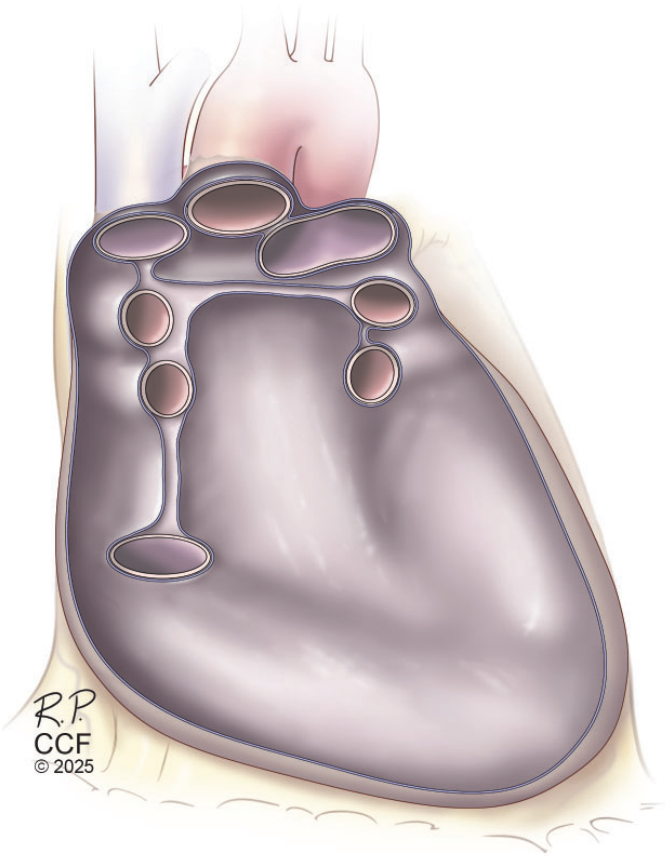

Figure 2. Artist's drawing of posterior parietal pericardial reflections on the superior vena cava, ascending aorta, pulmonary trunk, pulmonary veins, diaphragm, and inferior vena cava.

CASE 2: A YOUNG MAN WITH ACUTE-ONSET PLEURITIC CHEST PAIN

A 19-year-old man presented to the emergency department with severe pleuritic chest pain that started a few hours before his arrival. He was accompanied by his girlfriend, who was feeling well.

The patient grimaced with each shallow inspiration and was breathing rapidly at 20 respirations per minute. His blood pressure was 110/80 mm Hg, and his pulse was 105 per minute and regular. His arterial oxygen saturation was 98% while breathing ambient

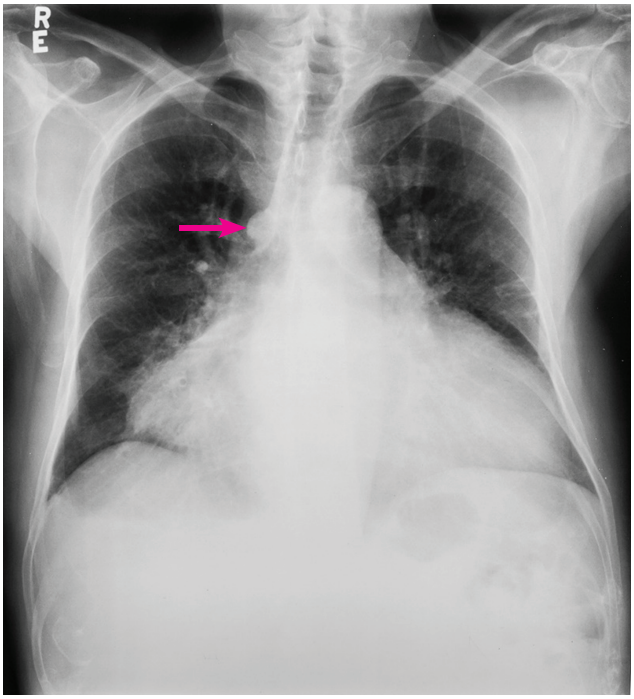

Figure 3. Posteroanterior chest radiograph in a hypothyroid patient with a large pericardial effusion and prominent azygos vein (arrow).

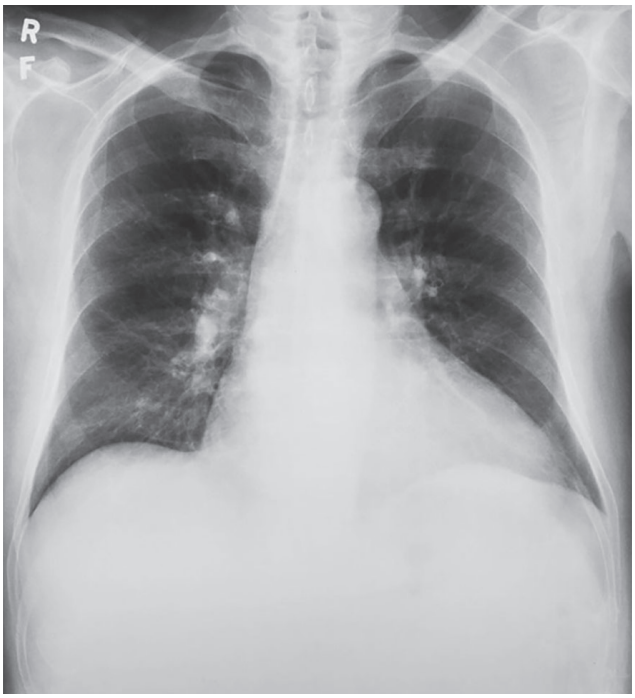

Figure 4. Posteroanterior chest radiograph of the same patient after 2 months of thyroid hormone replacement therapy.

air. Auscultating the anterior chest revealed a coarse scratching sound synchronous with the heartbeat and louder during inspiration.

A presumptive diagnosis of acute pericarditis was made, and an electrocardiogram and a chest radiograph were ordered. The electrocardiogram showed sinus tachycardia and was otherwise normal. There was no ST-segment elevation.

A posteroanterior chest radiograph (**Figure 5**) showed a normal cardiothoracic ratio (the width of the heart divided by the width of the chest is less than about 0.5), clear lungs, and no pleural effusion. Along the left heart border was a thin serosal surface separated from the heart by air. In the left supraclavicular space, there was subcutaneous emphysema. The lateral chest radiograph (**Figure 6**) showed air in the anterior mediastinum just behind the sternum. It was clear that there was no air surrounding the heart because the air extended well above the superior reflections of the parietal pericardium on the ascending aorta and the superior vena cava.

The patient was treated with nonnarcotic analgesics and was closely observed. The symptoms gradually resolved, and he was discharged 2 days after admission.

Discussion: Pneumomediastinum from smoking crack cocaine

The coarse sound we heard in the anterior chest is called the Hamman sign, first described by Louis Hamman in 1939.[9] It sounds like 2 inflated rubber balloons rubbing against each other.

This young man developed these symptoms from mediastinal emphysema (pneumomediastinum) after he and his girlfriend were smoking crack cocaine. Trying to augment the drug's effect, he (but not his girlfriend) performed a Valsalva strain maneuver (forced expiration against a closed glottis) after inhaling the drug.

Spontaneous pneumothorax, pneumomediastinum, and subcutaneous emphysema have been reported in patients who had been sniffing, smoking, or inhaling cocaine, heroin, 3,4-methylenedioxymethamphetamine (Ecstasy), or marijuana.[10]

In a series of 43 cases of cocaine-induced pneumomediastinum compiled by Alnas et al,[11] 93% of the patients had chest pain and 64% had subcutaneous emphysema. Symptoms subsided after a median of 24 hours, and radiologic abnormalities abated after 2

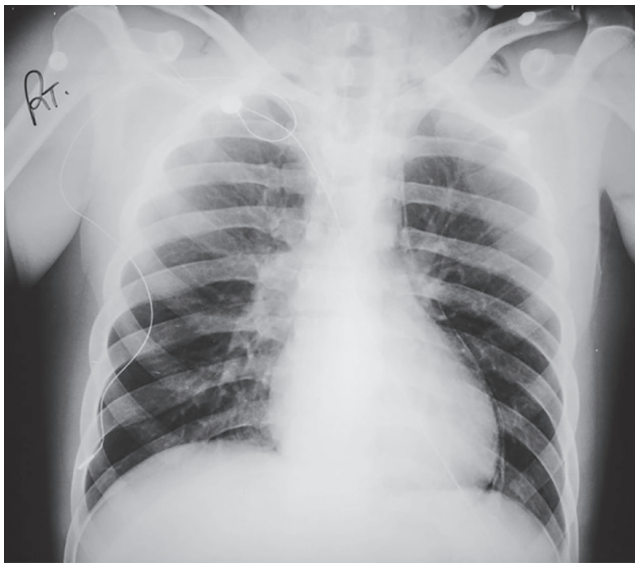

Figure 5. Posteroanterior chest radiograph of a 19-year-old patient with mediastinal emphysema and subcutaneous emphysema.

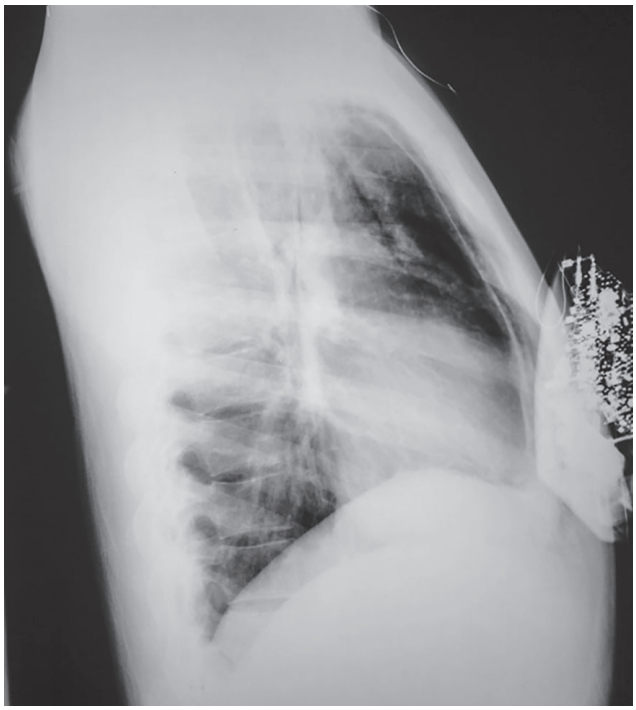

Figure 6. Lateral chest radiograph of same 19-year-old patient showing anterior pneumomediastinum.

to 30 days (median of 4.5 days). Pneumothorax was present in 8 (19%) of the patients, but only 1 required a chest tube. The authors concluded that cocaine-induced pneumomediastinum is a benign condition.

Although pneumomediastinum can be spontaneous, one should identify any precipitating events like trauma, surgery, or medical procedures (eg, instrumentation) that involve the esophagus and bronchial tree. Nearly every woman performs the Valsalva maneuver during vaginal delivery, and rarely, pneumomediastinum and subcutaneous emphysema have been reported post partum.[12] When a pleural effusion accompanies pneumomediastinum, mediastinal organ injury should be suspected and further evaluated.[13]

It is believed that pneumomediastinum results from alveolar rupture. The air tracks along the bronchovascular connective tissue planes into the mediastinum and hilum. Mediastinal air escapes into the subcutaneous tissue, resulting in subcutaneous emphysema. A prolonged Valsalva maneuver increases intra-alveolar pressure and is more likely to result in alveolar rupture.

CASE 3: A 60-YEAR-OLD MAN NEAR DEATH AFTER HEART SURGERY

A cardiologist was urgently consulted to see a 60-year-old man who was in extremis on a telemetry floor.

The patient was sitting erect and struggling to breathe. He had marked jugular venous distension, and his face was plethoric and cyanotic. The heart monitor at his bedside showed sinus tachycardia at 125 beats per minute. His fingertips were pale, and the oxygen saturation monitor would not register. His systolic blood pressure was 80 mm Hg during expiration, and Korotkoff sounds disappeared with inspiration all the way down to 0 mm Hg.

This was overt cardiac tamponade. A chest radiograph was ordered, a history was obtained, and a pericardiocentesis tray was sent for urgently.

The patient had been admitted to a local hospital because of a sternal wound infection with purulent drainage 1 week after he underwent saphenous vein graft aortocoronary bypass surgery at a referral center, with a median sternotomy. He became ill shortly after the nurse treated the sternotomy infection with topical hydrogen peroxide.

The chest radiograph showed pneumopericardium, with gas surrounding the heart in the pericardial space. **Figure 7** shows a different patient with a similar problem in whom, because of pneumopericardium, the normal pericardium is less than 2 mm in

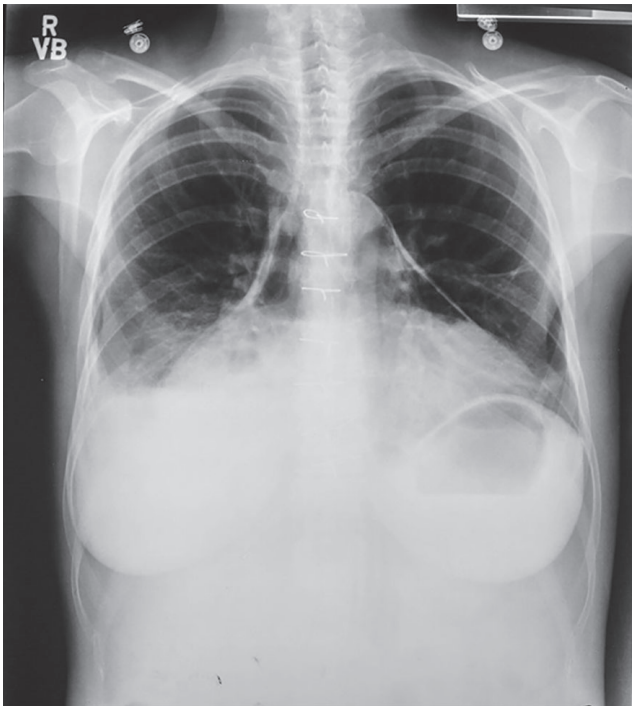

Figure 7. Anteroposterior chest radiograph of a female patient with pneumopericardium that demonstrates the same pericardial disease as that of the patient presented in Case 3. Because of pneumopericardium, the normal pericardium is less than 2 mm in thickness and the superior reflections of the parietal pericardium are within 2 to 3 cm from where the ascending aorta leaves and the superior vena cava enters the heart.

thickness and the superior reflections of the parietal pericardium are within 2 to 3 cm from where the ascending aorta leaves and the superior vena cava enters the heart.

Using sterile technique that included povidone-iodine, the cardiologist prepped the sternotomy and inserted a 16-gauge needle without a syringe 3 cm into the anterior pericardium through a rent in the sternotomy. The response was dramatic, with the sound of gas rushing through the needle and the resultant relief of symptoms. A guidewire was inserted through the needle, followed by a temporary drainage catheter.

Discussion: Oxypericardium from hydrogen peroxide

How did this gas accumulate so fast? Remember the foaming response when applying hydrogen peroxide to a bleeding skin abrasion? Hemoglobin can, in the presence of hydrogen peroxide, act as a peroxidase.[14] Blood was present postoperatively in this patient's pericardial space. The hemoglobin acted as a peroxidase with the hydrogen peroxide to release water and oxygen. The released oxygen collected in the pericardium, causing "oxypericardium," and its sudden accumulation resulted in cardiac tamponade. The rapid accumulation of gas raised the pericardial pressure so that it exceeded central venous pressure.

Take-home point: *Never cleanse a draining sternotomy with hydrogen peroxide, as it should be assumed it connects to the pericardial space, which can contain blood.*

Hydrogen peroxide has been used as an antiseptic for more than 100 years. Today, it is used less often than povidone-iodine and chlorhexidine, but it is still widely available and cheap. Because it effervesces when applied to wounds, which can aid in wound debridement, hydrogen peroxide has been considered for use together with povidone-iodine and chlorhexidine for wound irrigation in orthopedic surgery.[15] *Due to the potential for oxygen gas formation, hydrogen peroxide should not be used in cases of dural compromise, when pressurizing medullary canals, or when irrigating smaller closed spaces, to avoid the possibility of air embolism.*

CASE 4: A 67-YEAR-OLD MAN WITH COUGH

A 67-year-old man was readmitted to the hospital because of an incessant nonproductive cough 5 days after being discharged from the same hospital after saphenous vein graft aortocoronary bypass surgery and a 5-day postoperative stay. He had left the hospital with an intermittent cough and in sinus rhythm while taking aspirin, metoprolol, and a statin. He was not taking any anticoagulants. He had been prescribed these same medications without a cough for years before this operation.

A chest radiograph had been done before discharge and showed sternal wires and a small left pleural effusion, as are seen after heart surgery. However, the cardiothoracic ratio was elevated (> 0.5), and therefore an echocardiogram was ordered. This showed a small-to-moderate posterior pericardial effusion without signs of cardiac tamponade.

Now, his cough was worse. A new chest radiograph showed no change in the left pleural effusion, but the cardiothoracic ratio was further increased. A complete blood count, blood chemistries, and blood coagulation studies were normal or as expected 10 days after heart surgery. Echocardiography showed the pericardial effusion had increased to moderate in size, but again

without signs of cardiac tamponade. He was afebrile, and his blood pressure was 125/80 mm Hg with less than 10 mm Hg of pulsus paradoxus. The pulse rate was 95 per minute, and he was in sinus rhythm.

Because the pericardial effusion had enlarged and the cough was worse, his physicians decided to perform a pericardiocentesis. With echocardiographic guidance the pericardial effusion was drained percutaneously, yielding 300 mL of serosanguinous fluid. Pericardial fluid analysis revealed no sign of infection or malignancy. The cough resolved.

Discussion: Cough due to pericardial effusion

Cough ascribed to a pericardial effusion was first reported by Hancock in 1983.[16] Hancock's patient's pericardial effusion was due to idiopathic acute pericarditis. A case of cough due to a pericardial effusion resulting from radiofrequency catheter ablation for atrial fibrillation was reported by Fong et al[17] in 2018. When this pericardial effusion was drained, the cough resolved.

Perhaps in cases like these the cough is due to the enlarged heart from the pericardial effusion extrinsically compressing the left bronchus—an extreme example of Ewart sign that might result in left lung collapse.[18]

Imazio and Adler[19] note that classic symptoms of pericardial effusion include dyspnea on exertion progressing to orthopnea, chest pain, and fullness. Additional occasional symptoms due to local compression may include nausea (from compression of the diaphragm), dysphagia (from a compressed esophagus), hoarseness (from a compressed recurrent laryngeal nerve), and hiccups (from a compressed phrenic nerve). Nonspecific symptoms also include cough, weakness, fatigue, anorexia, and palpitations and reflect the compressive effect of the pericardial fluid on contiguous anatomic structures or reduced blood pressure and secondary sinus tachycardia. When pericardial effusion drainage eliminates left bronchial compression, this explanation for resolution of the cough is plausible.

Of note, pericardial effusion and cough can present as cough syncope. Saseedharan et al[20] described the case of a 64-year-old man with a large malignant pericardial effusion who had subclinical cardiac tamponade that manifested as cough syncope. Pericardial drainage resulted in complete cessation of cough and resultant syncope. The exaggerated and prolonged increase in intrathoracic pressure during coughing and elevated intrapericardial pressure due to the large pericardial effusion combined to decrease cardiac filling and cardiac output sufficient to cause syncope.

NARROWING THE DIFFERENTIAL DIAGNOSIS

In the first 3 of our cases, the differential diagnosis could be narrowed to pericardial or mediastinal disease from the history and physical examination. Specifically, in **Case 1**, pericardial effusion from hypothyroidism presented with jugular venous distension; in **Case 2**, pneumomediastinum from smoking crack cocaine presented with pleuritic chest pain and the Hamman sound; and in **Case 3**, pneumopericardium from the use of hydrogen peroxide as a disinfectant in a closed space that contained blood presented with overt cardiac tamponade.

Each case was further defined by the results of an electrocardiogram and a chest radiograph. **Case 4** presented with a cough that worsened and initially was suspected to be due to pulmonary disease. Although there was a small left pleural effusion and an increased cardiothoracic ratio by chest radiography, it was cardiac ultrasonography that was most helpful in quantifying the pericardial effusion, and it was the knowledge that a pericardial effusion can compress the left bronchus and cause a relentless cough that led to a therapeutic pericardiocentesis.

Echocardiography is the best technique to diagnose pericardial effusion. It was helpful in **Case 1** and **Case 4**. Unfortunately, it takes time to perform and interpret. Point-of-care ultrasonography is an attractive diagnostic tool that has the potential to decrease length of hospital stay.[21] The device can be carried in the pocket and, if the results were properly interpreted, they might have hastened the diagnosis and quantification of pericardial effusion in **Case 1** and **Case 4**. Because ultrasound waves do not travel well through air (waves are reflected rather than transmitted), neither formal echocardiography nor point-of-care ultrasonography would have been beneficial in **Case 2** or **Case 3**. Time spent by the physician performing promptly available point-of-care ultrasonography would have been time wasted.

Taking a good history, performing a good physical examination, and knowing how to read an electrocardiogram and a chest radiograph are the best starting points for diagnosing pericardial and mediastinal disease. Knowing the natural history of the disease and its pathophysiology and integrating it with the signs, symptoms, electrocardiogram, and chest radiograph allow the physician to see through the cover to the text of the book.

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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Address: William A. Schiavone, DO, Cardiologist, J2-4, retired from Sydell and Arnold Miller Family Heart, Vascular, and Thoracic Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; CCJM@ccf.org

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REVIEW

Masihullah Barat, MD
Clinical Fellow, Department of Cardiovascular Medicine, University of California San Diego, San Diego, CA

David Torres Barba, MD, PhD
Assistant Professor, Department of Cardiovascular Medicine, University of California San Diego, San Diego, CA

Gordon Ho, MD
Associate Professor, Department of Cardiovascular Medicine, University of California San Diego, San Diego, CA

Wolff-Parkinson-White syndrome: Diagnostic and management strategies

ABSTRACT

An unknown number of people are born with single or multiple accessory electrical pathways between the atria and the ventricles. Although most people who have an accessory pathway never experience any problems, some show characteristic abnormalities on surface electrocardiography (the Wolff-Parkinson-White [WPW] pattern), and a minority of those with the WPW pattern experience symptoms such as palpitations, dizziness, shortness of breath, and presyncope—the WPW syndrome. The latter has the potential to lead to malignant tachyarrhythmias and even sudden cardiac death. Thus, it is imperative to detect the WPW electrocardiographic pattern, diagnose WPW syndrome early, and adequately risk stratify those at risk for serious complications.

KEY POINTS

Noninvasive tests—cardiac event monitoring, echocardiography, and exercise stress testing—can help identify those at highest risk, for whom an ablation procedure can be considered.

Electrophysiologic studies are invasive, but advances in technology have made them less risky, and many cardiologists now perform an electrophysiologic study and consider accessory pathway ablation in patients who would previously have been managed conservatively.

The management challenge lies in those with WPW pattern but no symptoms.

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Tachyarrhythmias and syncope are among the most frequently evaluated problems in primary, urgent, and emergency care settings. Although their etiology is often benign, they require a thorough evaluation to assess for potentially malignant causes such as Wolff-Parkinson-White (WPW) syndrome.

WPW syndrome is a rare congenital cardiac condition in which the patient has single or multiple accessory pathways along the atrioventricular border that predispose them to potentially malignant tachyarrhythmias. It often presents with symptoms such as palpitations, dizziness, shortness of breath, presyncope, and syncope (often the symptom that prompts patients to seek medical attention), but in rare cases, the first sign or symptom is sudden cardiac death due to a malignant tachyarrhythmia.

Here we describe the pathogenesis, diagnostic strategies, general treatment guidelines, and active controversies surrounding management of WPW syndrome.

ACCESSORY PATHWAYS CAN LEAD TO MALIGNANT ARRHYTHMIAS

In a normal heart, electrical impulses are generated by the sinoatrial node and travel through the atrioventricular node and then down the bundle of His and the left and right bundle branches, triggering both ventricles to contract (**Figure 1**). The atrioventricular node is important as an electrical gatekeeper: it delays the electrical impulse long enough for the atria to contract and empty their blood into the ventricles, facilitating proper ventricular

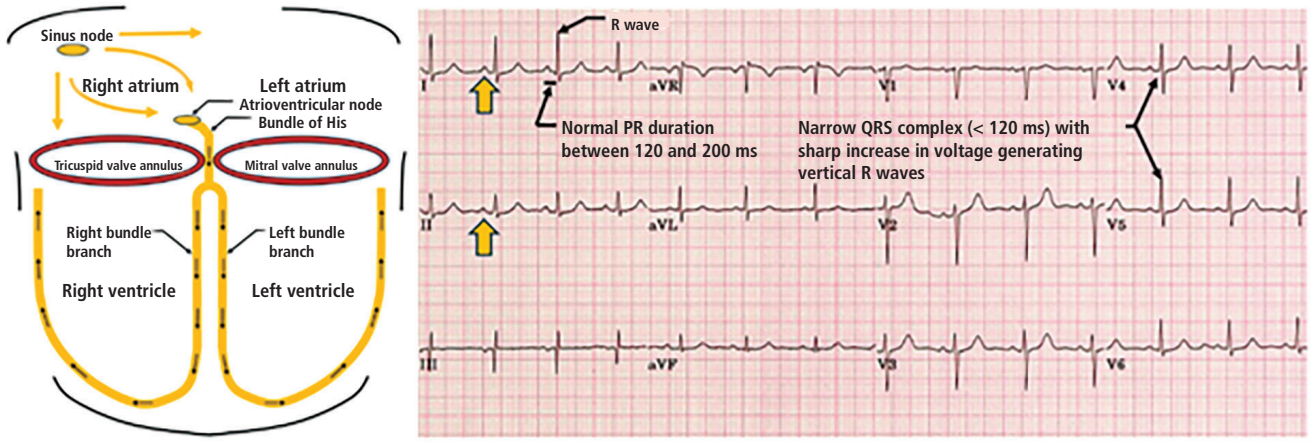

Figure 1. Left, normal conduction pathway with normal sinus rhythm generated by the sinus node and conducted through the atrioventricular node, bundle of His, and subsequently through the left and right bundle branches, leading to normal PR duration (120–200 ms), normal QRS duration (< 120 ms), and no pre-excitation. Right, normal electrocardiogram with clear upright P waves (yellow arrow), normal PR interval, and narrow QRS pattern.

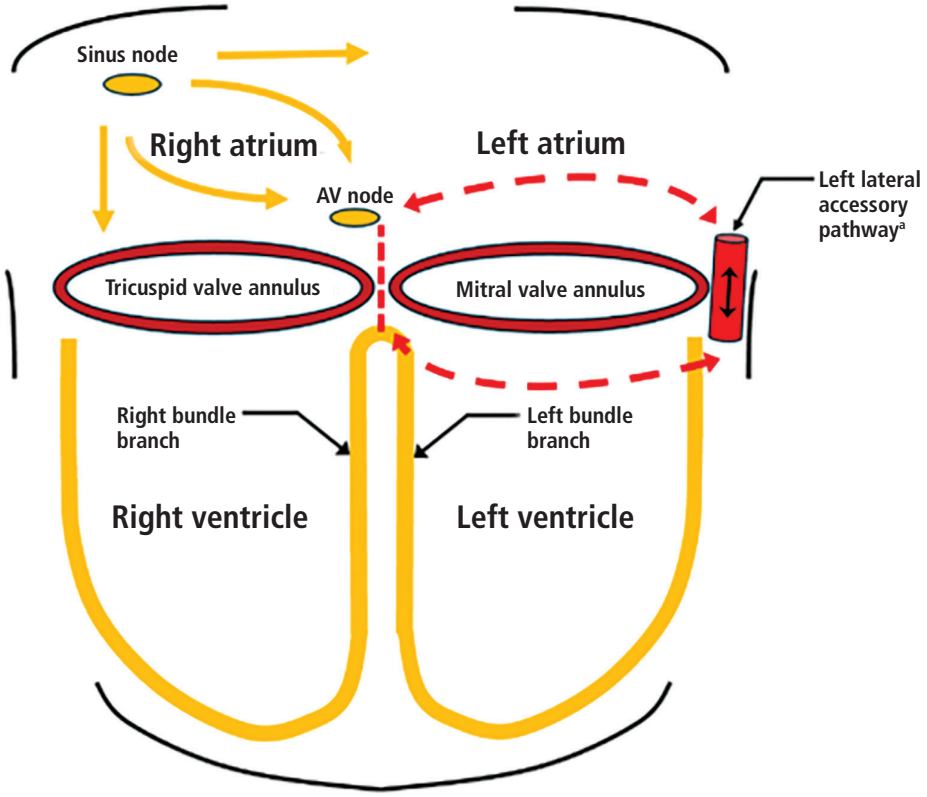

Figure 2. Electrical conduction system with a left lateral accessory pathway. An accessory pathway provides an alternate atrioventricular (AV) conduction pathway, bypassing both the atrioventricular node and the His-Purkinje system, predisposing to malignant tachyarrhythmias. A left lateral accessory pathway leads to the characteristic type A Wolff-Parkinson-White pattern on electrocardiography (**Figure 3**).

[a]Accessory pathways are capable of bidirectional flow, predisposing to retrograde conduction (conduction from ventricular to atrial tissue).

TABLE 1
Type A vs type B Wolff-Parkinson-White patterns

Type A (associated with left-sided accessory pathway)	Type B (associated with right-sided accessory pathway)
Short PR interval (< 120 ms)	Short PR interval (< 120 ms)
Delta wave: broad QRS complex with slurred R wave	Delta wave: broad QRS complex with slurred S wave
May mimic right bundle branch block	May mimic left bundle branch block
Dominant R wave in V_1	Dominant S wave in V_1
Tall R waves and inverted T waves in leads V_1–V_3	Tall S waves and inverted T waves in leads V_4–V_6

Based on information from reference 1.

filling and helping maintain cardiac output. It also can take over as the dominant pacemaker if the sinoatrial node fails.

Some people, however, are born with an accessory pathway, ie, an alternate atrioventricular conduction route that bypasses both the atrioventricular node and the His system. This results in preexcitation, where the ventricles contract prematurely (**Figure 2**). The accessory pathway makes patients vulnerable to 2 forms of arrhythmia:

- Reentrant arrhythmias such as reentrant supraventricular tachycardia, when impulses travel down the atrioventricular node and then retrograde (up) through the accessory pathway
- Accelerated conduction of atrial arrhythmias, as the accessory pathway, unlike the atrioventricular node, does not delay the electrical impulse. This condition poses a significant risk in those who have atrial fibrillation by transmitting the rapid atrial rate directly to the left ventricle, potentially leading to ventricular fibrillation and sudden cardiac death.

DIAGNOSIS: SYMPTOMS PLUS ELECTROCARDIOGRAPHIC SIGNS

An accessory pathway can go undetected until the patient develops symptoms such as palpitations, chest pain, shortness of breath, dizziness, lightheadedness, and syncope associated with arrhythmias. However, surface electrocardiography may reveal the distinctive WPW pattern: a short PR interval (< 120 ms) and the pathognomonic finding of a delta wave, ie, a slurred upstroke of the QRS complex.

Traditionally, cardiologists used to further classify the electrocardiographic findings as 1 of 2 types (**Table 1**):

- **Type A (Figure 3)**, with delta waves in the septal leads (V_1–V_3), associated with an accessory pathway on the left side of the heart, or
- **Type B (Figure 4)**, with delta waves in the lateral leads (V_4–V_6), associated with an accessory pathway on the right.[1]

But it is not so simple. Accessory pathways can exist anywhere along the atrioventricular border, resulting in patterns different from type A and type B, and even in conduction changes that are not detectable on electrocardiography. We don't typically classify WPW accessory pathways based on type A and type B features anymore, but the classic type A and type B patterns are still commonly described in educational and reference material, as they reflect some of the most common accessory pathway locations. No specific symptoms or clinical presentations associated with a specific WPW pattern or accessory pathway location have been described.

A distinction: *WPW pattern* is diagnosed in patients who have no symptoms but who do have the aforementioned electrocardiographic signs, while a diagnosis of *WPW syndrome* means the patient has a WPW pattern and symptoms related to arrhythmias caused by the accessory pathway.

Of note, a patient can have an accessory pathway without the electrocardiographic signs, as some pathways are activated only at specific heart rates, in a specific conduction direction, or by impulses generated by the ventricle, such as premature ventricular contractions. This is important, as patients with no diagnostic electrocardiographic signs but with high clinical suspicion of having an accessory pathway may benefit from a cardiology consultation after initial evaluation in a primary, urgent, or emergency care setting.

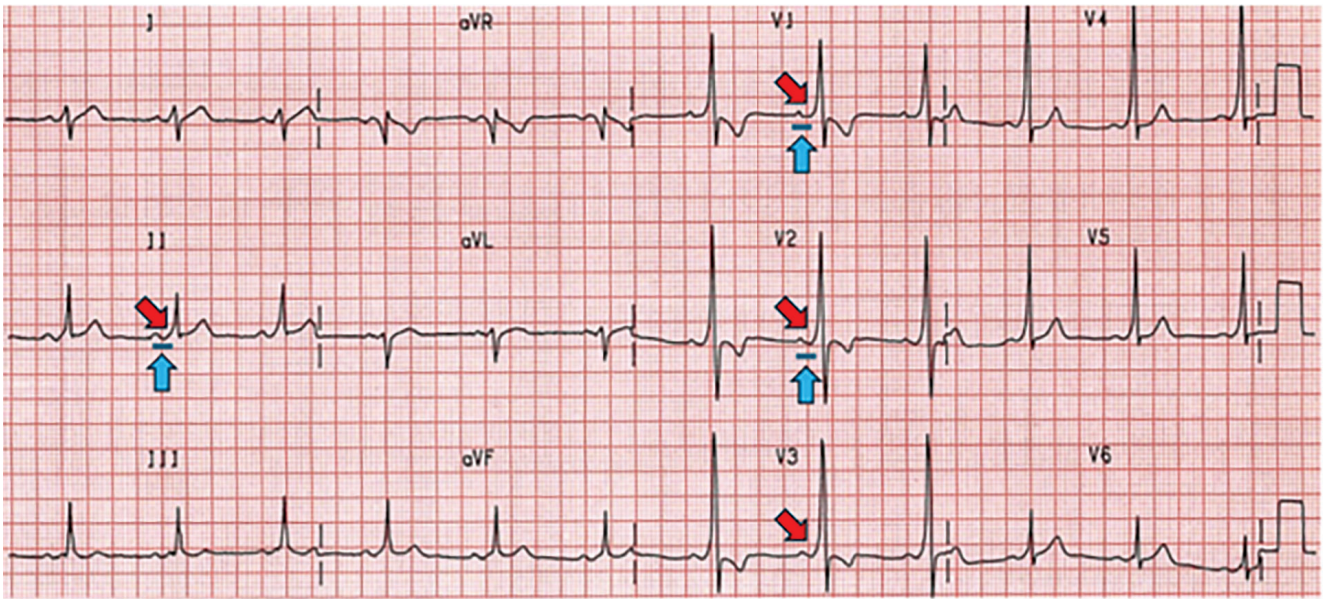

Figure 3. Characteristic Wolff-Parkinson-White type A pattern, including a short PR interval (blue arrows), wide QRS, and delta waves (red arrows). Positive delta waves in V_1–V_3 suggest a left-sided accessory pathway (**Figure 2**).

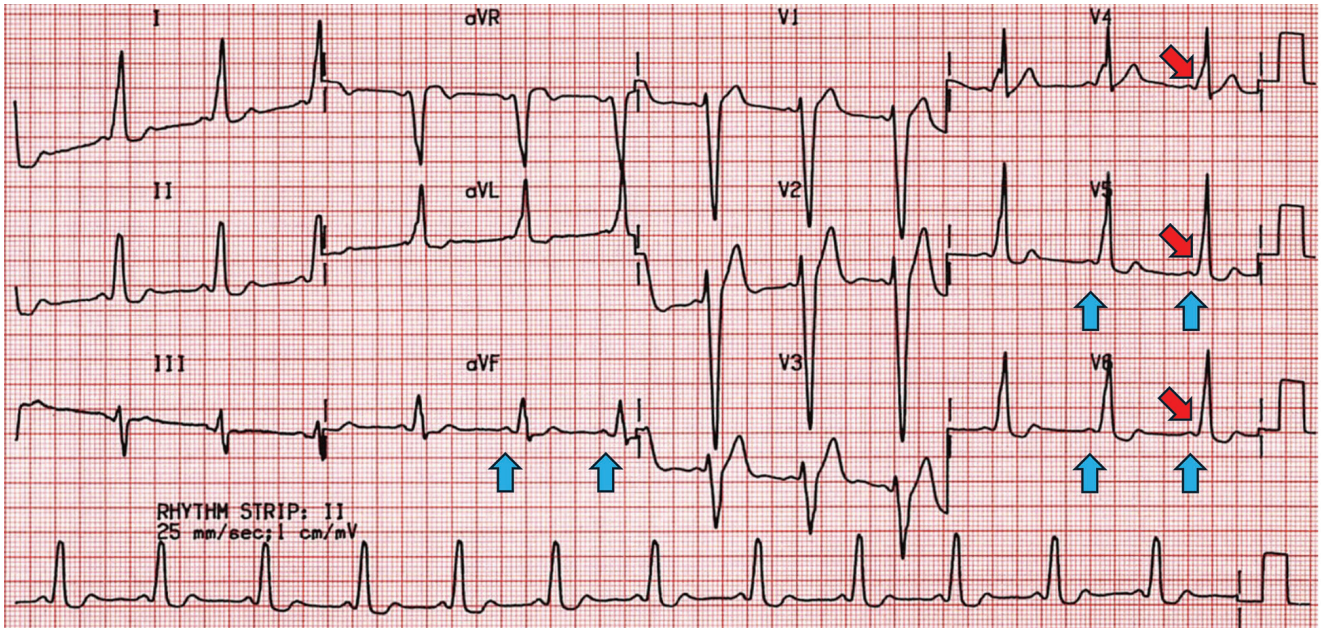

Figure 4. Characteristic Wolff-Parkinson-White type B pattern, including a short PR interval (blue arrows), wide QRS, and delta waves (red arrows). Precordial transition after V_2 suggests a right-sided accessory pathway.

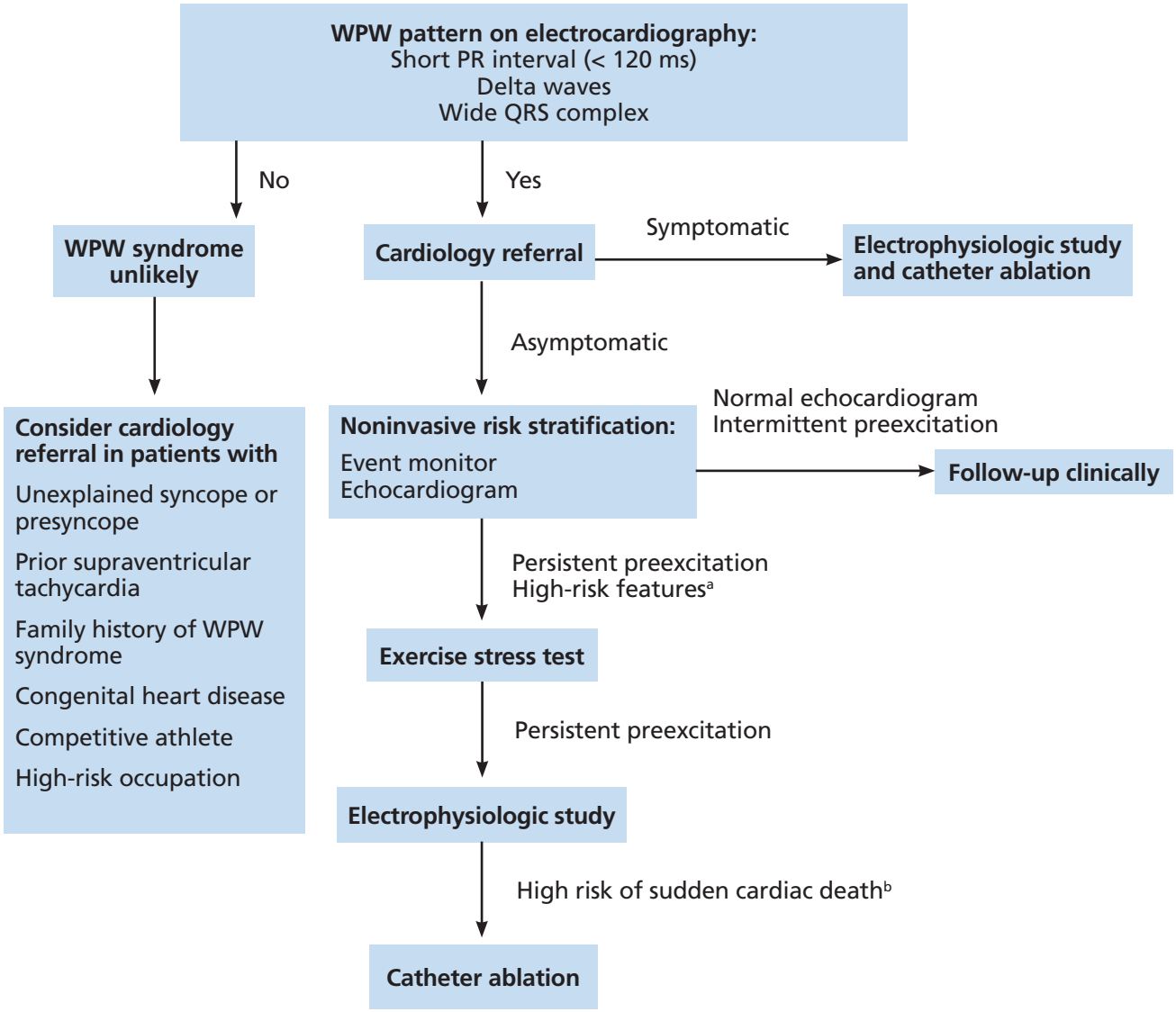

Figure 5. Our proposed diagnostic and management guideline for patients with high clinical suspicion, Wolff-Parkinson-White (WPW) pattern, and WPW syndrome.

[a]High-risk features: male sex, age less than 30, history of atrial fibrillation, family history of WPW syndrome, congenital heart disease, competitive athlete, high-risk occupation.

[b]High risk of sudden cardiac death: multiple accessory pathways; preexcitation persists during induced atrial fibrillation; shortest RR interval < 250 ms during incremental atrial pacing, premature atrial contraction, or when in atrial fibrillation.

WOLFF-PARKINSON-WHITE SYNDROME IN THE GENERAL POPULATION

WPW syndrome affects an estimated 1 to 3 individuals per 1,000 worldwide.[2,3] Most people with WPW pattern have no symptoms and go on to have no clinical events related to the accessory pathway.

While most patients have normal anatomy, WPW syndrome is associated with Ebstein anomaly and hypertrophic cardiomyopathy.[3,4] Approximately 10% to 34% of patients with Ebstein anomaly[5,6] and 0.4% of patients with hypertrophic cardiomyopathy have WPW syndrome.[7,8]

In those with WPW pattern on electrocardiography who present with tachycardia, atrioventricular

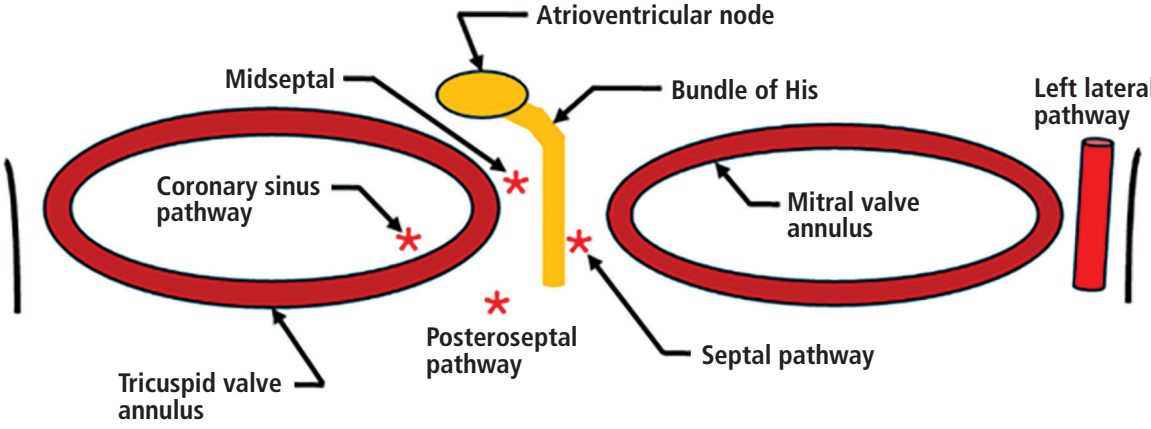

Figure 6. The most reported accessory atrioventricular pathway location is the left lateral mitral valve annulus (30% to 58% of reported cases), followed by the posteroseptal region (about 25% of reported cases.[25,26] The remainder of reported accessory pathway locations surround both the tricuspid annulus and the mitral valve annulus. Success rates of accessory pathway ablation vary by location, with highest success rates reported in those localized in the anterior, posterior, and lateral distribution (success rate of 90% and above), and lowest in those surrounding the coronary sinus (50%) and in the septal (50%) and midseptal distribution (73%).[26]

reentrant tachycardia is the most common arrhythmia. While atrial fibrillation is the predominant atrial arrhythmia in the general population, its incidence in patients with WPW is only 6%.[8] The most severe and feared complication is sudden cardiac death, owing to the rapid atrial rates in atrial fibrillation that are transmitted directly to the ventricles by the accessory pathway, causing ventricular fibrillation. In the general population, the rate of sudden cardiac death is estimated to be 0.1% per year for patients with the WPW pattern (ie, without symptoms),[9] and 0.8% per year in those with WPW syndrome (ie, with symptoms).[10]

MANAGEMENT STRATEGIES

Catheter ablation has a class I (strong) recommendation in patients who have symptoms and the WPW pattern (WPW syndrome).[11] Catheter ablation has a high success rate (> 94%) and low complication rate (< 1%).[12] Reported recurrence rates vary, but one estimate is 6.2%, and further declines are expected as techniques improve.[12]

The management challenge lies in those with WPW pattern but no symptoms. The goals are to alleviate symptoms related to tachyarrhythmias and to prevent the most feared complication, sudden cardiac death. While it is difficult to predict the risk of sudden cardiac death in these patients, the risk is higher in those who are male, are younger than 30 years, have a history of atrial fibrillation, have a family history of WPW syndrome, have congenital heart disease, or are in a high-risk profession such as competitive athlete, airline pilot, or professional driver, all of which should be considered when deciding on treatment.[13]

Noninvasive risk stratification

Noninvasive risk stratification can help guide the decision for catheter ablation.

A cardiac event monitor can be worn for as little as 24 to 48 hours and helps detect not only an abnormal heart rate and electrical impulse patterns but also preexcitation. The risk of sudden cardiac death is higher if the patient has multiple accessory pathways (which the monitor can also detect), whereas intermittent preexcitation whereby delta waves intermittently disappear even at normal heart rates suggests a lower risk profile.[14,15]

Echocardiography can further elucidate the risk by detecting underlying structural or congenital heart disease, as WPW syndrome is associated with Ebstein anomaly and hypertrophic cardiomyopathy.[3,4]

Exercise stress testing is used to find out whether the delta waves abruptly and persistently disappear with exercise, suggesting a lower risk.[14,15] While this can be reassuring, it does not guarantee that atrial fibrillation will not be conducted through this pathway. There is a subset of patients who are not considered to be at high risk by noninvasive testing, but meet high-risk criteria

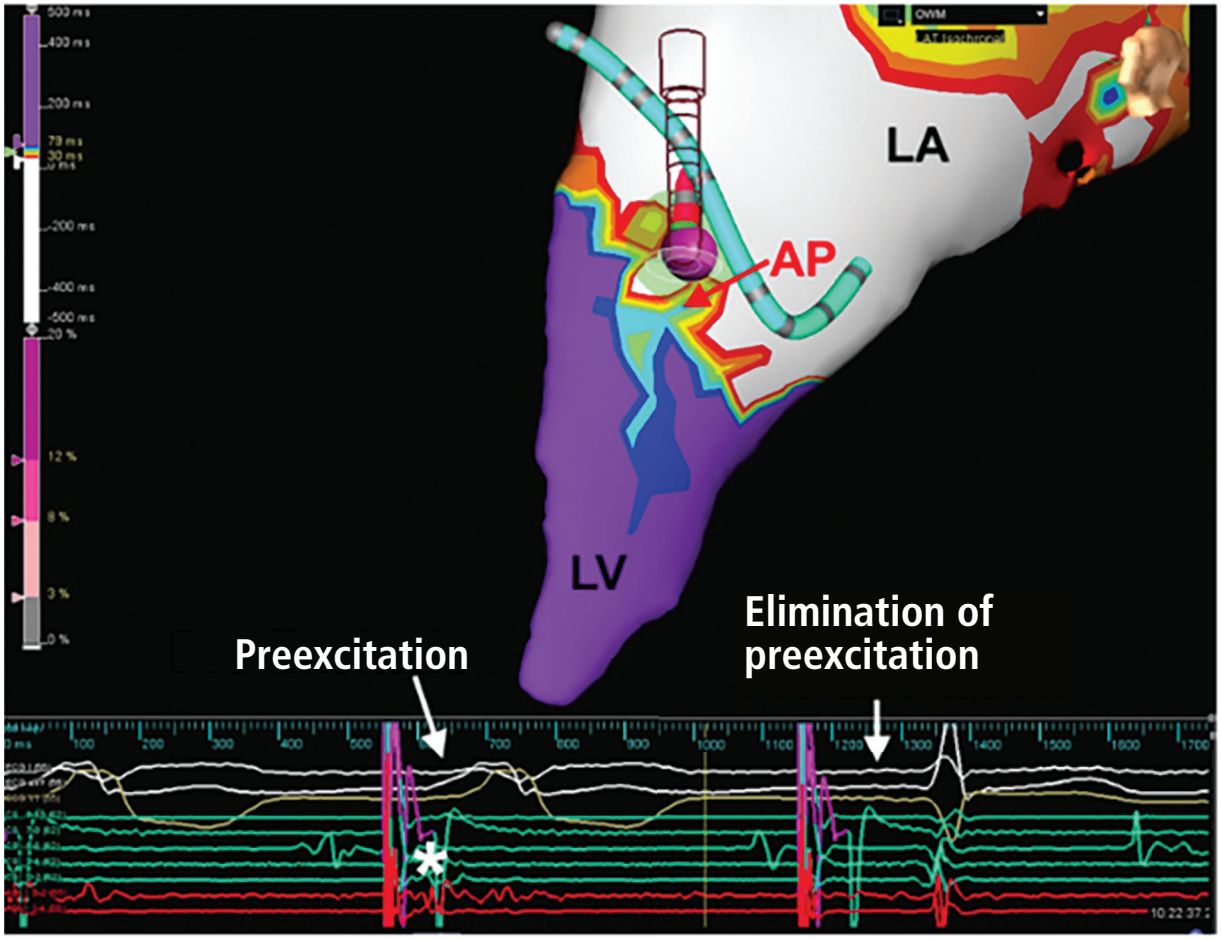

Figure 7. Catheter ablation of a left anterolateral accessory pathway in a 21-year-old patient. Open window mapping localized the accessory pathway (AP) to the anterolateral mitral annulus, where ablation (purple ball) eliminated the accessory pathway, with surface (white) and intracardiac electrocardiograms (red) showing loss of preexcitation and Kent potential (*) from the first to the second beat.

LA = left atrium; LV = left ventricle

by electrophysiologic study. Therefore, loss of preexcitation by exercise stress testing may not completely exclude an accessory pathway.[15]

Invasive testing (electrophysiologic study)

Electrophysiologic studies are invasive, involving intracardiac electrodes and catheters to look for and evaluate the characteristics of accessory pathways. WPW pattern or syndrome is deemed to pose a high risk for sudden cardiac death if preexcitation persists during induced atrial fibrillation or if the shortest RR interval is less than 250 ms during incremental atrial pacing, premature atrial contraction, or when in atrial fibrillation.[16] While the European Society of Cardiology[11] and the American Heart Association[17] guidelines differ regarding methods of risk stratification, they both recommend invasive risk stratification in patients at higher risk of sudden death, including athletes and those whose sudden death could endanger other people, such as pilots and commercial drivers. **Figure 5** provides our proposed management approach when a patient is found to have a WPW pattern.

More electrophysiologists now than in the past may be performing electrophysiologic studies in patients with an asymptomatic WPW pattern regardless of noninvasive findings.[18] The shift in strategy is believed to be due to the procedures becoming safer, with lower complication rates. Given the low risk and potential

for a permanent cure via catheter ablation, there is an incentive to identify and manage WPW syndrome proactively. Additionally, recent studies have suggested that patients may experience potentially life-threatening complications of WPW syndrome even if they had no prior symptoms or "high-risk" features on noninvasive studies, providing a rationale for the current approach of evaluating patients with electrophysiologic study for risk stratification and considering ablation.[19–21] This is compelling, considering the rates of electrophysiology study–related complications are reported to be as low as 1% (largely related to pneumothorax and access-site complications),[22] and serious ablation-related complications are as low as 0.1% (third-degree atrioventricular block).[23]

Bunch et al[24] in 2015 reported that long-term mortality rates for patients with WPW pattern were low and comparable to those of a control group matched by age and sex; however, patients with asymptomatic WPW pattern who underwent ablation had a lower risk of death than those who did not. This highlights the importance of careful monitoring and management of patients with WPW pattern and syndrome, given the potential for serious complications even without prior symptoms and high-risk features.

As noted above, accessory pathways can exist anywhere on the atrioventricular plane but most commonly in the left lateral mitral valve annulus (30% to 58% of reported cases), followed by the posteroseptal region (about 25% of cases), where the reported success rates of catheter ablation are excellent (> 90%). Other accessory pathway locations are associated with much lower ablation success rates, such as those surrounding the coronary sinus (50%) and in the septal (50%) and midseptal regions (73%) (**Figure 6**).[25,26]

Figure 7 shows a characteristic WPW catheter ablation of a left anterolateral accessory pathway in a 21-year-old patient.

In patients who remain asymptomatic and do not require ablation, observation with conservative management is an acceptable approach.[11] However, given the persistence of the accessory pathway, medications that block conduction through the atrioventricular node (verapamil, diltiazem, amiodarone, digoxin, adenosine, or beta blockers) should be avoided because they can predispose to preferential conduction through the accessory pathway in the event of an atrial tachyarrhythmia, which can result in hemodynamic collapse.[27]

DISCLOSURES

Dr. Ho has disclosed ownership interest (stock, stock options in a publicly owned company) in Vektor Medical Inc. 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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Address: *David Torres Barba, MD, PhD, Department of Cardiovascular Medicine, University of California San Diego, 4167 Balboa Way, San Diego, CA 92117; Dtorresbarba@health.ucsd.edu*

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