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Unexplained pathology is not always autoimmune

Asymptomatic oral plaques and erosion

Acute left-sided colonic diverticulitis: A surgeon's perspective on the ACP guidelines

Amiodarone-induced thyrotoxicosis

A new paradigm for adult ADHD: A strategy to monitor treatment

Atypical hyperplasia of the breast: Management strategies

Surgical de-escalation: Are we ready for 'observation' of benign high-risk breast lesions found on core needle biopsy?

Autoimmunity and postural orthostatic tachycardia syndrome: Implications in diagnosis and management

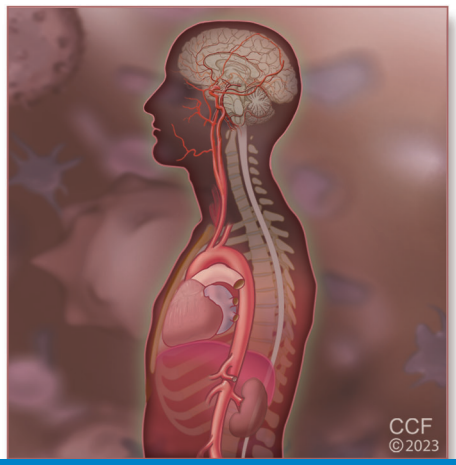

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Table of Contents

CONTINUED ON PAGE 393

Upcoming Features

- Metformin for weight loss in adults with obesity
- Evaluating troponin elevation in chronic kidney disease

CONTINUED FROM PAGE 389

CME MOC

2023

JULY

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: COACHING AND MENTORING ESSENTIALS FOR HEALTHCARE PROFESSIONALS
July 12
Live stream

CLEVELAND SPINE REVIEW: HANDS-ON 2023
July 19–24
Cleveland, OH

MIDWEST MELANOMA SYMPOSIUM
July 20
Cleveland, OH

AUGUST

STATE-OF-THE-ART TOPICS IN CARDIOLOGY
August 4–6
Cleveland, OH

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
August 11–13
Washington, DC

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) SPECIALIST COURSE
August 23–25
Cleveland, OH

CLEVELAND BREAST CANCER SUMMIT: COLLABORATING FOR A CURE
August 25
Cleveland, OH

PEDIATRIC BOARD REVIEW
August 27–September 1
Cleveland, OH

SEPTEMBER

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: HEALTHCARE PROFESSIONALS COACH TRAINING
September 6–7
Live stream

HOSPITAL MEDICINE 2023
September 7–8
Cleveland, OH

INNOVATIONS IN NEUROSCIENCE
September 8
Cleveland, OH

SPASTICITY AND NEUROREHABILITATION: PEDIATRIC AND ADULT WORKSHOPS 2023
September 9
Warrensville Heights, OH

CLEVELAND CLINIC SYMPOSIUM ON TRIGEMINAL NEURALGIA
September 15
Live stream

OBESITY SUMMIT
September 21–22
Cleveland, OH, and live stream

PRACTICAL MANAGEMENT OF STROKE
September 22
Warrensville Heights, OH

COMPREHENSIVE, LIFELONG, EXPEDITIOUS (CLE) CARE OF AORTIC DISEASE
September 22–23
Cleveland, OH

WAKE UP TO SLEEP DISORDERS 2023: A CLEVELAND CLINIC SLEEP DISORDERS CENTER UPDATE
September 22–24
Cleveland, OH

OHIO OCULAR ONCOLOGY SYMPOSIUM
September 23–24
Cleveland, OH

GLOBAL EP
September 29–30
Cleveland, OH

OCTOBER

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: COACHING AND MENTORING ESSENTIALS FOR HEALTHCARE PROFESSIONALS
October 11–12
Live stream

THE PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE: A CONTEMPORARY UPDATE
October 12–13
London, UK

INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM
October 13–15
Cleveland, OH

HEADACHE TREATMENT: HITTING A HOME RUN WITH PATIENTS
October 14
Chicago, IL

CARDIOVASCULAR UPDATE FOR THE PRIMARY CARE PROVIDER: IMPROVING CV CARE ACCESS AND OUTCOMES ACROSS ALL COMMUNITIES
October 19–20
Cleveland, OH

RESTORING NEUROLOGICAL FUNCTION: THE CROSSROADS OF NEUROLOGY, PSYCHIATRY, AND NEUROSURGERY
October 27
Cleveland, OH

UTILIZING ARTIFICIAL INTELLIGENCE IN THE PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE: APPLICATIONS, BENEFITS, AND CHALLENGES
October 27–28
Chicago, IL

NOVEMBER

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: HEALTHCARE PROFESSIONALS COACH TRAINING
November 1–2
Live stream

ADVANCING CARDIOVASCULAR CARE: CURRENT AND EVOLVING MANAGEMENT STRATEGIES
November 3
Columbus, OH

GASTROENTEROLOGY UPDATE: CONTROVERSIES, INNOVATIONS, RESEARCH
November 4
Warrensville Heights, OH

PRIMARY CARE +: UPDATES IN PRIMARY CARE, WOMEN'S HEALTH, AND BEHAVIORAL MEDICINE
November 9–12
Beachwood, OH

LIFESTYLE INTERVENTIONS FOR EPILEPSY (LIFE)
November 10–12
Beachwood, OH

DECEMBER

ADVANCES IN THE TREATMENT PARADIGM OF MYELOID MALIGNANCIES: FROM BIOLOGY TO CLINICAL PRACTICE
December 8
San Diego, CA

A CASE-BASED APPROACH TO MASTERING THE AORTIC VALVE: IMAGING, INNOVATION, AND INTERVENTION
December 15–16
New York, NY

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Unexplained pathology is not always autoimmune

The evolution of our understanding of human disease has been a remarkable journey, spanning centuries of scientific progress and shifting paradigms. Illness was originally attributed to the imbalance of bodily fluids or the involvement of evil humors and miasmas, concepts rooted in superstition and religious beliefs.

Over centuries, a usually more scientific and technologically focused understanding of disease has emerged. The germ theory revolutionized our understanding of infections. Advances in molecular biology and genetics have provided insights into pathophysiology, and in some areas of medicine we are able to practice personalized care utilizing our knowledge of immunology and molecular pharmacology to deliver targeted therapies.

So it seems somewhat ironic that when faced with common, complex, and confounding syndromes that we can't fully explain, we revert to attributing them to a current iteration of an evil humor: autoimmunity. Our strides in understanding well-defined autoimmune diseases have been huge, with the development of dozens of extremely effective therapies directed at immune mechanisms. Every subspecialty in medicine has benefited from these advances. But perhaps these successes have made us too willing to attribute yet-unexplained conditions to autoimmunity simply because they share symptomatology (often nonspecific) with defined systemic disorders such as systemic lupus erythematosus (SLE).

Postural orthostatic tachycardia syndrome (POTS), as discussed by Aboseif et al[1] in this issue of the *Journal*, is a clinically defined positional intolerance syndrome. Our understanding of its pathophysiology is incomplete. Patients often can temporally link the onset or worsening of their cardiovascular (positional) symptoms to a medical or stressful life event, but additional discussion often reveals that many other symptoms that seem to be associated with POTS had been present prior to recognition of the tachycardia. It is the presence of these other symptoms—symptoms also common in patients with chronic inflammatory syndromes—that prompts patients and their physicians to search for another underlying systemic condition,[2] or to attribute the cause of POTS (and related disorders) to autoimmunity.

I am seeing more and more patients in the clinic referred with a diagnosis of POTS or dysautonomia and "autoimmune disease." The autoimmune concern is frequently fueled by the finding of a positive antinuclear antibody (ANA) or SSA antibody, often at a low level. The symptoms that prompted the initial search for autoantibodies as a reflection of a possible autoimmune process often included some combination of fatigue, brain fog, generalized pain without objective findings, irritable bowel syndrome, bladder dysfunction, exertional intolerance, dysesthesias, dry eyes, and dry mouth. These symptoms are also shared by many patients diagnosed with fibromyalgia and are often exacerbated after acute medical illnesses such as Lyme disease, mononucleosis, and COVID-19 infection (aka long COVID). And while many of these symptoms are present in patients with SLE, multiple sclerosis, Sjögren syndrome, and inflammatory bowel disease, they are not disease-defining symptoms. Plus, as background, it must be remembered that a positive and usually low-titer ANA test can be detected in roughly 20% of young women.

There is much about fibromyalgia, POTS, and myalgic encephalomyelitis that we do not understand, including the frequent link with major stressors earlier in life in many but certainly not all

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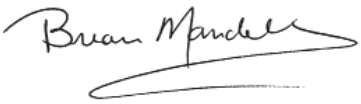
patients. The potential role of a viral vector persisting within select nerve cells or microglia[3] after an infection in some patients with chronic fatigue and other symptoms cannot be totally dismissed as a pathogenic contributor, but at present we cannot test or treat for this. Many patients with chronic systemic inflammatory disorders report similar symptoms, but this does not imply that all patients with SLE and related syndromes have chronic viral infections any more than implying that patients with POTS who share these symptoms have SLE. The fact that rare patients with Sjögren syndrome have been reported to have a sensory ganglionopathy or marked dysautonomia should not imply that patients with any symptoms suggesting autonomic dysregulation should be tested for the presence of nonspecific autoantibodies such as SSA (associated with, but not specific to the diagnosis of Sjögren). That many of these patients display features of autonomic dysfunction is of interest given our burgeoning understanding of the interplay between vagal nerve activity and inflammation,[4] but our understanding of this at present is far too limited to do any more than recognize intriguing relationships and possible therapeutic pathways.

At present, in patients with POTS and related syndromes, there is no reproducibly documented pathogenic antibody, laboratory abnormality, or histopathologic finding of inflammation akin to what we document in patients with defined systemic autoimmune diseases. I strongly agree with Aboseif et al[1] that there are yet no convincing data that warrant institution of immunosuppressive or immunomodulatory therapy in our patients with POTS. I would go further and say that a random search for autoantibodies in the absence of specific physical findings or suggestive laboratory studies (leukopenia, thrombocytopenia, adenopathy, neuropathy), outside of an organized clinical study, is not likely to be in the patient's best interest, and is more likely to trigger a flurry of additional tests and anxiety. There are indeed shared symptoms between patients with POTS and those with defined systemic autoimmune diseases (eg, SLE, Sjögren), but those symptoms are not the symptoms that define these autoimmune disorders and thus should not be invoked as evidence for the presence of autoimmunity. And if an autoantibody is detected, it is not proof of causation warranting therapeutic intervention.

We have a lot more to learn about the pathogenesis of POTS—and about autoimmune diseases. Clinical studies and interventional trials are being done. This may change, but for the moment, I am not convinced that the two are linked.



Brian F. Mandell, MD, PhD
Editor in Chief

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Asymptomatic oral plaques and erosion

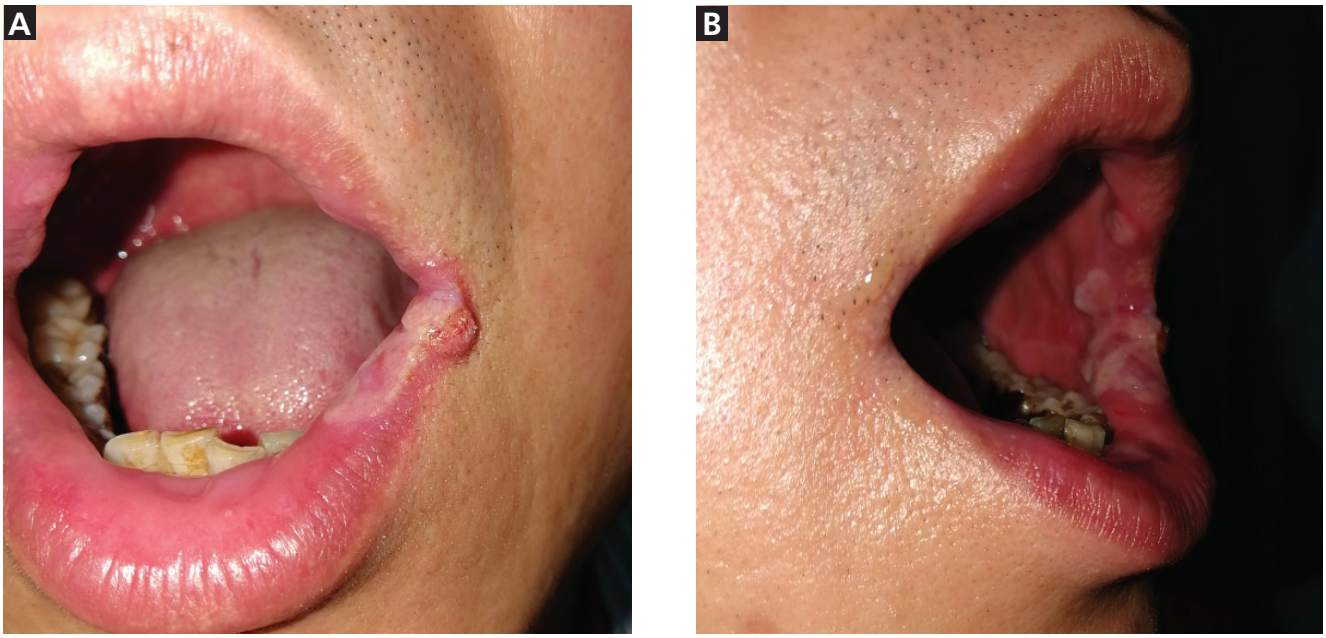

Figure 1. (A) An indurated and painless nodule and plaque on the lower lip. (B) Multiple off-white plaques and erosion on the left buccal mucosa.

A 47-year-old male presented with a 4-week history of asymptomatic plaques and erosion on the left buccal mucosa and lower lip (**Figure 1**). He reported seeing a stomatologist, but the prescribed treatment was ineffective. He was then referred to the dermatology department because similar lesions later appeared in genital and perineal regions (**Figure 2**). He had several high-risk sexual behaviors in the past year.

Treponema pallidum particle agglutination testing was positive, and the toluidine red unheated serum test titer was high at 1:32. These results along with the presence of oral and genital-perineal condyloma lata confirmed the diagnosis of secondary syphilis. The patient was treated with benzathine penicillin G 2.4 million units intramuscularly once a week for 3 weeks. His lesions entirely resolved at 6 weeks.

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ACQUIRED SECONDARY SYPHILIS

Syphilis has resurfaced in recent years, with oral manifestations occurring at an increased rate.[1] The clinical diagnosis of acquired oral syphilis is challenging due to its diverse manifestations. It is more common in young and middle-aged men.[1,2]

Primary oral syphilis is characterized by a chancre, a single painless ulcerated oral lesion on the lip, labial

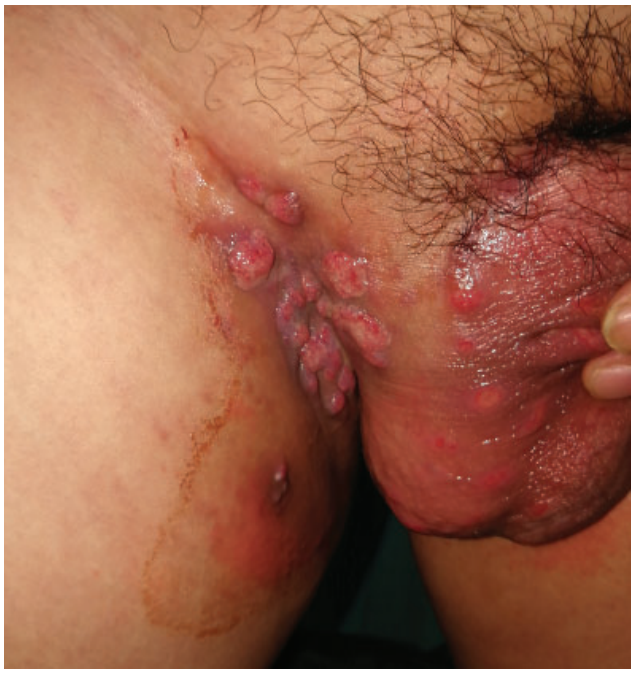

Figure 2. The lesions in the inguinal and genital regions at presentation.

commissure, or tongue.[2,3] In most patients, primary oral syphilis is accompanied by nontender regional lymphadenopathy.[2,3] The majority of cases of oral syphilis represent the secondary stage of syphilis.[1,2] Secondary oral syphilis usually presents as multiple subacute erosive or ulcerative lesions, mucous patches on the tongue, nodular lesions, and leukokeratotic lesions.[4] Tertiary syphilis is a painless localized granuloma that presents as hardened, nodular, or ulcerated lesions on the hard palate or the dorsal surface of the tongue.[3]

BROAD DIFFERENTIAL DIAGNOSIS

The range of differential diagnoses is wide and includes infectious diseases, potentially malignant oral disorders, malignant neoplasms, and immune-mediated diseases.[1,2] Painful lesions that need to be considered include aphthous ulcer, traumatic ulcer, Behçet disease, inflammatory bowel disease, pemphigus vulgaris, erythema multiforme, candidiasis, and leishmaniasis.[1] The differential for painless lesions includes frictional keratosis, necrotizing sialometaplasia, lichen planus, sarcoidosis, tuberculosis, blastomycosis, leukoplakia, erythroplakia, squamous cell carcinoma, and soft-tissue and mesenchymal tumor.[1]

VALUABLE CLUES TO DIAGNOSIS

Symptoms of oral syphilis are nonspecific, so serological studies remain the gold standard.[2,3] However, we need to be aware that syphilis serology may be nonreactive in the very early stage and falsely negative due to the prozone reaction or acquired immunodeficiency syndrome. In the absence of serological evidence, the valuable clues are based on a complete medical history (unprotected sexual and orogenital contact, multiple partners, men who have sex with men, drug use, and history of other sexually transmitted diseases), careful physical examination (extraoral syphilitic manifestations), and timely pathological examination (diffuse or perivascular infiltration of lymphocytes and plasma cells). It needs to be noted that dark-field microscopic examination, immunohistochemical techniques, and silver staining are not specific to oral syphilis diagnosis due to the presence of commensal treponemes.[5]

Promoting awareness of oral syphilis is vital for early diagnosis, treatment, and prevention of onward transmission.

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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COMMENTARY

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Acute left-sided colonic diverticulitis: A surgeon's perspective on the ACP guidelines

The updated guidelines on the management of acute left-sided colonic diverticulitis from the American College of Physicians (ACP), published in 2022,[1,2] are practice-changing, with a push for less-aggressive management of uncomplicated diverticulitis in selected patients. This change is based on a better understanding of the underlying etiology of diverticulitis and on data from recently published randomized controlled trials.

Because diverticulitis is a common disease encountered by both surgeons and internists, this commentary reviews the updated ACP guidelines from a surgical perspective. The updated ACP guidelines closely echo those published recently by the American Society of Colon and Rectal Surgeons (ASCRS),[3] reflecting a growing consensus in the management of uncomplicated diverticulitis.

In the ACP guideline recommendations discussed here, the grading of strength of recommendation is conditional and the grading of certainty of evidence is low (conditional recommendation; low-certainty evidence). Complicated disease resulting in perforated bowel, intestinal obstruction, pericolic abscess, or fistulae is typically managed surgically or by interventional radiology and is not addressed here.

ACP recommendation: Use abdominal computed tomography when there is diagnostic uncertainty with suspected acute left-sided colonic diverticulitis

The diagnostic modality of choice for acute diverticulitis is cross-sectional imaging of the abdomen and pelvis with computed tomography (CT). This recommendation is shared by the ACP, the American Gastroenterological Association, and the ASCRS in patients with suspected diverticulitis when there is diagnostic uncertainty.[1,3,4] The differential diagnosis for lower abdominal pain is wide, particularly in females. CT is highly sensitive and specific for diverticulitis and can simultaneously rule out other underlying causes of abdominal pain. It can also be used to assign a modified Hinchey classification, which categorizes diverticulitis into 4 stages of severity.[5] Pericolic and pelvic abscesses (stage Ia/Ib and stage II) represent uncomplicated disease that can typically be managed with antibiotics and a drain placed by interventional radiology. Purulent and feculent peritonitis (stages III and IV) represent complicated disease that may require emergency surgery.

CT imaging can quickly differentiate uncomplicated from complicated disease, with the potential to alter management decisions. Further, the severity of inflammation seen on CT is prognostic of treatment failure, risk of disease recurrence, and risk of future stricture formation.[6–8] The use of oral and intravenous (IV) contrast is preferred, although noncontrast CT has similar diagnostic utility and can be used in patients with poor kidney function.

CT may not always be readily available in the outpatient setting and may not be needed. For example, a 50- to 60-year-old patient with diverticulosis on a previous screening colonoscopy who presents with typical symptoms of left lower quadrant abdominal pain may not need abdominal imaging if another diagnosis is unlikely. Red-flag symptoms such as severe abdominal pain with high fever, rectal bleeding, signs of intestinal obstruction, peritonitis identified on examination, or suspected underlying malignancy warrant admission to a center with CT capabilities and a surgical team for prompt assessment.

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If available, outpatient CT should be ordered liberally, particularly for patients presenting with their first episode of suspected diverticulitis. Complicated disease most frequently presents during the index episode of diverticulitis, and confirming the diagnosis on imaging may prove useful in future treatment planning.[6] In-office ultrasonography can help rule out other differential diagnoses, such as gynecologic pathologies, although it is user-dependent and generally ineffective in evaluating the colon.

ACP recommendation: Manage most acute uncomplicated left-sided colonic diverticulitis in an outpatient setting

The ACP guidelines suggest that most patients with uncomplicated diverticulitis can be managed safely in the outpatient setting. Although that is applicable to most patients, we recommend judicious decision-making based on clinical presentation and the results of testing. US hospitals admit more than 300,000 patients for diverticulitis annually at an estimated annual cost of $2.6 billion per year.[9,10] Many of these patients do not benefit from admission, which represents a target for improving value of care in an already financially burdened healthcare system.

Inpatient vs outpatient outcomes for uncomplicated diverticulitis were assessed in the DIVER trial,[11] where 132 patients were randomized to inpatient or outpatient care. Both groups received a 10-day course of antibiotics. No statistically significant differences were seen in the rate of readmission, need for emergency surgery, or quality of life at a follow-up of 2 months.[11]

The DIVER trial is the first and only randomized controlled trial to address this question, but multiple observational studies have reported similar results.[12–14] The healthiest patients were carefully selected for inclusion in these studies, so physicians in clinical practice should avoid generalizing these results to all patients with uncomplicated diverticulitis. Of the 453 patients with diverticulitis initially evaluated in the DIVER trial, only 132 were ultimately selected for randomization.[11]

Patients should be assessed for severity of disease with a thorough history, physical examination, and basic laboratory tests before being sent home. Fitness for outpatient management requires immunocompetence, well-controlled comorbidities, tolerance of a liquid diet, and strong support at home with the ability to follow up. High fevers, poor oral intake, rectal bleeding, a palpable mass on digital rectal examination, or focal peritonitis with guarding are concerning and generally warrant admission. Inflammatory markers like C-reactive protein (CRP) and white blood cell count are useful adjuncts to the history and physical examination. In a validated prediction model, a CRP less than 100 mg/dL, a white blood cell count less than 1.5×10^9/L, and no guarding on physical examination have a negative predictive value of 96% when assessing for complicated diverticulitis.[15]

ACP recommendation: In selected patients with acute uncomplicated left-sided colonic diverticulitis, manage initially without antibiotics

The underlying pathophysiology of diverticulitis has recently been called into question. Inflammation, genetics, and gut microbiome appear to play a greater role in the development of diverticulitis than primary infection of pre-existing diverticula. Prescribing antibiotics for patients without perforation or abscess may therefore do little to shorten symptom duration or prevent progression of disease. Evidence from multiple randomized controlled trials now supports selective use of antibiotics. Although this is a conditional recommendation by ACP, it is a strong recommendation (grade 1A) from ASCRS.

In the Swedish multicenter AVOD trial,[16] 623 patients with CT-confirmed uncomplicated diverticulitis were randomized to receive either 7 days of antibiotics or IV fluids alone. There was no difference in time to recovery, complications, serious events, or need for emergent colectomy between groups.[16] We now know that the most severe episode of diverticulitis is typically the first one and that cases of recurrent disease tend to be the same or milder.[17] Nearly 40% of the patients in the AVOD trial presented with recurrent diverticulitis.[16] The investigators may have therefore inadvertently selected for patients who were unlikely to have adverse events, irrespective of the assigned treatment arm. This limitation was addressed in the Dutch DIABOLO trial,[18] where 528 patients presenting with their first episode of uncomplicated diverticulitis were randomized to receive antibiotics or IV fluids. Again, no differences in progression to complicated disease, readmission, need for colectomy, or adverse events were observed between groups.[18]

Subsequent trials published after the 2022 ACP recommendations further support selective use of antibiotics in patients with uncomplicated diverticulitis in the outpatient setting.[19] Evidence is also accumulating that patients with pericolic abscesses (Hinchey stage Ib) fare no better with antibiotics. However, antibiotics should be prescribed for these patients until this question is addressed in larger randomized studies.

A pragmatic approach to incorporating this new recommendation into clinical practice is to first determine if the patient's condition warrants hospital admission. Patients deemed fit for outpatient management meet the same criteria as those for management without antibiotics. Ideally, patients should have imaging to support the diagnosis of uncomplicated diverticulitis and should have ample support at home with the ability to quickly return to the hospital if symptoms become worse. Antibiotics are still appropriate for higher-risk patients who have comorbidities, are immunosuppressed, or have signs of systemic infection.

ACP recommendation: Refer for colonoscopy after an initial episode of complicated left-sided colonic diverticulitis in the absence of recent colonoscopy

Six weeks after a first episode of diverticulitis, the patient should be referred for colonoscopy to rule out underlying malignancy or inflammatory bowel disease.[1,2] Generally, a patient who has had a normal screening colonoscopy within 2 years of an episode of uncomplicated diverticulitis can stick to their current screening schedule. The risk of finding an underlying malignancy in these patients is comparable to that of the general population.[20,21] Unexplained weight loss, rectal bleeding, or narrowing of the stool in relation to an episode of diverticulitis should raise concern for malignancy and warrants colonoscopy regardless of a recent normal colonoscopy. All patients who present with complicated diverticulitis should undergo colonoscopy in 6 weeks to assess for underlying malignancy, which is present in 7.9% to 11% of patients.[22,23]

ACP recommendation: Discuss the merits of elective surgery to prevent recurrent diverticulitis after initial treatment with patients who have either uncomplicated but persistent or recurrent diverticulitis or complicated diverticulitis

Elective sigmoidectomy has been shown to decrease symptom recurrence and improve quality of life in select patients with recurrent or chronic "smoldering" diverticulitis.[24] Patients should be informed that elective surgery reduces but does not eliminate the risk of recurrent diverticulitis.[2] In a retrospective study of patients treated for 2 or more bouts of uncomplicated diverticulitis, the recurrence rate was 15% at 5 years after elective sigmoidectomy compared with 61% in those treated nonoperatively.[25]

As with any surgery, there are associated risks. The decision to pursue elective sigmoidectomy should be individualized for each patient based on a discussion of potential benefits, harms, costs, and the patient's preferences. Most patients with uncomplicated diverticulitis will not have another episode, but the risk of recurrence increases with each subsequent flare. In a large retrospective study of more than 181,000 patients, 23% of patients admitted for 2 attacks were admitted a third time. Of these, 37% were admitted for a fourth time.[26]

Patients who are frequently hospitalized, must take time off work or miss family events, or have persistent low-grade symptoms should be referred to a surgeon to discuss the pros and cons of elective sigmoidectomy. In the elective setting, this surgery can often be performed via a minimally invasive approach and does not typically require an ostomy. All patients who present with an initial episode of complicated disease should be referred to a surgeon for evaluation for elective sigmoidectomy, as the risk of readmission and future complicated episodes is higher in this group.[23]

Medical treatments for recurrent diverticulitis such as 5-aminosalicyclic acid (mesalamine), probiotics, or rifaximin have not been shown to improve outcomes and are not recommended by the American Gastroenterological Association.[2] Patients should be encouraged to eat a diet high in fiber from fruits, vegetables, and grains and to exercise regularly. Despite widespread opinion to the contrary, there are no compelling data to support avoiding nuts or seeds to prevent future attacks.[27]

PRACTICE APPLICATIONS

Diverticulitis is commonly encountered by surgeons and internists. The most recent society guidelines from both specialties conclude that we have been overtreating many patients with this disease and that admission for bowel rest and antibiotics is often unnecessary. However, admission and medical treatment do play a critical role in all but the healthiest patients presenting with uncomplicated diverticulitis. It is incumbent on physicians to identify patients at risk for failure of medical treatment and to escalate care appropriately. Along with a thorough history, examination, and laboratory tests, imaging with CT is generally helpful and should be ordered frequently, particularly at the index episode of diverticulitis. If there is any question of perforation on imaging or examination, a surgical consult is indicated.

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: How do I diagnose and treat my patient's amiodarone-induced thyrotoxicosis?

A: A diagnosis of amiodarone-induced thyrotoxicosis (AIT) should be considered in a patient started on amiodarone therapy who develops symptoms such as unexplained weight loss, diaphoresis, tremor, palpitations, or anxiety. Prompt diagnosis with serologic testing of thyroid-stimulating hormone (TSH), free thyroxine (T4), and triiodothyronine (T3) levels is crucial.

AIT can be classified as type 1 (AIT-1) or type 2 (AIT-2). AIT-1 occurs in the setting of underlying thyroid disease (often undiagnosed) while AIT-2 is due to amiodarone toxicity without underlying glandular pathology. Differentiation between these forms of AIT requires radioactive iodine uptake and Doppler ultrasonography.[1,2]

Radioactive iodine uptake studies typically show normal or increased uptake in AIT-1, whereas AIT-2 typically has decreased uptake. In fact, uptake in AIT-1 may be decreased due to high iodine load in amiodarone competing with uptake by the thyroid gland. Due to related concerns regarding inadequate accuracy of radioactive iodine uptake studies in distinguishing between AIT-1 and AIT-2, technetium Tc 99m methoxyisobutylisonitrile thyroid scintigraphy has emerged as a more sensitive and accurate diagnostic imaging modality. Increased uptake and retention of technetium Tc 99m methoxyisobutylisonitrile in thyroid tissue is seen in AIT-1, whereas low uptake is seen in AIT-2.[1,2]

Doppler ultrasonography shows increased vascularity and blood-flow velocity in AIT-1, whereas these findings are absent in AIT-2. AIT-1 is best treated with antithyroid drugs and potassium perchlorate. AIT-2 is typically self-limited and can be treated with steroids. Mixed forms with imaging and clinical findings of both AIT-1 and AIT-2 are also seen and are difficult to diagnose. Management of these forms involves a combination of thionamides and steroids. Thyroidectomy may be done in cases of hemodynamic instability or clinical worsening.

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PHYSIOLOGY OF AMIODARONE-INDUCED THYROTOXICOSIS

Amiodarone is an iodine-rich antiarrhythmic drug[3] that can cause thyrotoxicity through several mechanisms. Iodine is required for thyroid hormone synthesis. Due to its structural similarity to the hormone T3, amiodarone can mimic the actions of T3 and lead to thyrotoxicosis.[4]

Amiodarone is a benzofuran derivative with 2 iodine atoms that are released into systemic circulation. The recommended daily intake of iodine is about 0.2 mg. However, a maintenance dosage of amiodarone at 200 mg/day provides 7.5 mg of organic iodide per day. The accumulation of systemic iodine is also known to precipitate thyrotoxicosis. Amiodarone has a half-life of 100 days, with a large volume of distribution, which further enhances its toxicity and predisposes to drug withdrawal.[5]

Normally, autoregulatory mechanisms prevent large quantities of iodine from accumulating and leading to excessive production of thyroid hormones. The Wolff-Chaikoff effect is a protective phenomenon wherein elevated plasma iodine concentrations temporarily halt the synthesis of thyroid hormones.[3] The escape from this protective effect leads to the Jod-Basedow effect, wherein thyroid gland hyperactivation or autonomous production by thyroid nodules

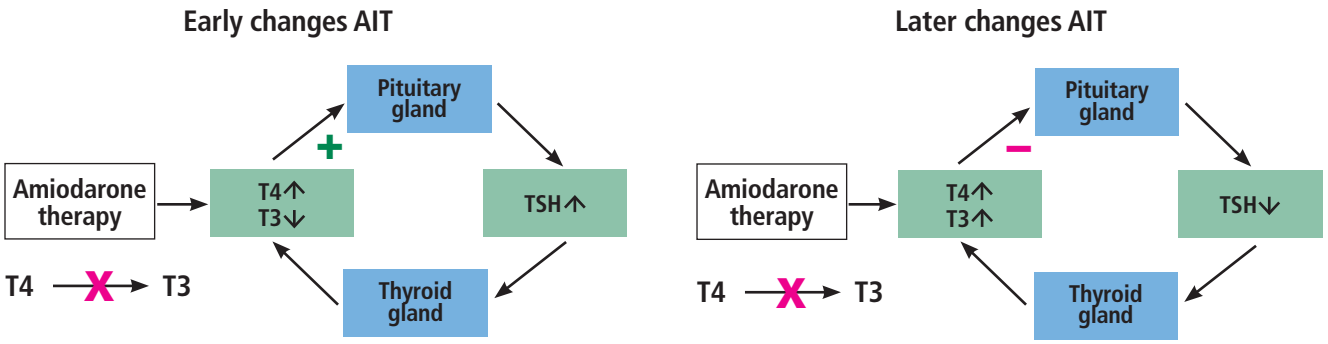

Figure 1. Early and late stages of amiodarone-induced thyrotoxicosis (AIT). (A) In early AIT, amiodarone blocks the conversion of thyroxine (T4) to triiodothyronine (T3), leading to increased levels of T4 and decreased levels of T3. Through feedback, the pituitary gland is stimulated to produce more thyroid-stimulating hormone (TSH), which promotes thyroid hormone production by the thyroid gland. (B) In late AIT, after the increased TSH production and stimulation of the thyroid gland, T3 and T4 levels both become elevated. Through negative feedback on the pituitary gland, less TSH is secreted.

occurs in the absence of negative feedback to the pituitary gland.[3]

Amiodarone-induced thyrotoxicosis can be confirmed by low TSH, high T4, and high-normal or high T3. Additionally, patients may be asymptomatic or may exhibit signs of overt thyrotoxicosis, including palpitations, tremors, diaphoresis, and weight loss.[4] AIT-1 is caused by the excessive iodide content of amiodarone leading to increased thyroid hormone synthesis in the absence of TSH stimulation. The new steady state in AIT-2 consists of elevated T4, low T3, and normal TSH levels (**Figure 1**). AIT-2, also known as destructive thyroiditis, is due to the toxic effects of amiodarone on thyroid follicles, leading to the release of stored thyroid hormones.

TYPE 1 AMIODARONE-INDUCED THYROTOXICOSIS

AIT-1 is a form of true hyperthyroidism driven by autonomous thyroid hormone production in the presence of iodine overload.[4] It occurs in patients with concomitant thyroid disorders, such as nodular goiters or Graves disease.[6]

Diagnosis of AIT-1 typically includes radioactive iodine uptake studies that show normal or increased uptake. Additionally, color-flow Doppler ultrasonography helps distinguish AIT-1 from AIT-2. Increased vascularity and blood-flow velocity on color flow Doppler suggest AIT-16 (**Table 1**). Treatment of AIT-1 involves antithyroid agents like methimazole and propylthiouracil, which inhibit iodide uptake by the gland and by new hormone synthesis. In addition, propylthiouracil inhibits conversion of T4 to T3. The addition of potassium perchlorate can increase the response to the aforementioned thionamides and further inhibit iodine uptake.[4] Medical therapy is usually required for several weeks to achieve a euthyroid state. For medically refractory cases of AIT-1, thyroidectomy can be considered.[4]

TYPE 2 AMIODARONE-INDUCED THYROTOXICOSIS

AIT-2, a form of drug-induced destructive thyroiditis, occurs due to true toxicity from amiodarone rather than underlying thyroid disease as in AIT-1. Due to the overlap in presentation between both types of AIT, radioactive iodine uptake studies and color-flow Doppler can aid in the diagnosis. Radioactive iodine uptake is typically less than 3% in AIT-2, and Doppler ultrasonography usually has no hypervascularity pattern or blood-flow velocity.[6]

AIT-2, unlike AIT-1, is commonly self-limited and is best managed with corticosteroid therapy. Treatment with weight-based dosing of prednisone (0.5–0.7 mg/kg/day) for 1 to 3 months has been shown to be effective very early on, and around 50% of patients with AIT-2 have complete resolution of disease in 4 weeks[6] (**Table 1**).

MIXED AMIODARONE-INDUCED THYROTOXICOSIS

In some cases, patients may have a mixed form of AIT, ie, AIT-1 and AIT-2, physiologically driven by pathological mechanisms that also drive AIT-1 and AIT-2. As such, the mixed form can present phenotypically as either AIT-1 or AIT-2, making diagnosis a challenge.

TABLE 1
Features of type 1, type 2, and mixed amiodarone-induced thyrotoxicosis

	Type 1 AIT	Type 2 AIT	Mixed AIT
Mechanism of disease	Excess iodine	Destructive inflammatory thyroiditis	Features of both
Underlying thyroid disease	Present	Absent	Features of both
Goiter	Multinodular or diffuse goiter normally present	Infrequent; may have small, diffuse, firm, or tender goiter	Features of both
TSH, early disease course	Elevated	Normal	Variable
TSH, late disease course	Elevated	Normal	Variable
Thyroid autoantibodies	Present	Absent	Features of both
Radioactive iodine studies	Normal or increased uptake	Little or no update	Features of both
^{99m}Tc-MIBI	Increased uptake	Decreased uptake	Features of both
Color-flow Doppler ultrasonography	High vascularity	Absent vascularity	Features of both
Treatment	Thionamides	Steroids	Combination of both
Spontaneous remission	No	Possible	Features of both
Late hypothyroidism	No	Extremely rare	Features of both

^{99m}Tc-MIBI = technetium Tc 99m methoxyisobutylisonitrile; TSH = thyroid-stimulating hormone

Management typically involves thionamides and steroids. Potassium perchlorate may also be used but is not readily available in the United States. Early initiation of therapy is crucial, as studies have shown increased rates of mortality in patients with mixed AIT, especially in patients with underlying cardiac dysfunction.[7]

CONTINUATION OF AMIODARONE AFTER THYROTOXICOSIS

The decision to continue or discontinue amiodarone after resolution of AIT is controversial. Ultimately, this decision needs to be made on an individual basis. Some case reports suggest that continuation of amiodarone is acceptable in patients suffering from life-threatening arrhythmias or arrhythmias that have been resistant to other medical therapies.[4] If amiodarone therapy is maintained, it is important to note the risk for recurrent thyrotoxicosis and inform patients of this risk during shared decision-making. Pacemakers or implantable cardioverter defibrillators may also be utilized along with other medical methods of arrhythmia control.

THE BOTTOM LINE

- Differentiating between AIT-1 and AIT-2 requires a combination of serologic testing, color Doppler ultrasonography, and radioisotope studies.
- Treatment of AIT-1 requires antithyroid agents like methimazole and propylthiouracil whereas AIT-2 is typically self-limited and treated with steroids.
- Thyroidectomy may be performed in both types of AIT if the patient is hemodynamically unstable. ■

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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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COMMENTARY

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A new paradigm for adult ADHD: A focused strategy to monitor treatment

Medical professionals face a significant challenge when treating adults with attention deficit hyperactivity disorder (ADHD). Although adult ADHD bears similarities to its childhood expression, the distinct features are associated with ADHD across the life span, with particular attention focused on the ADHD symptom-generated *task incompletion* as the single, primary dysfunction in adults with ADHD.

Shifting the paradigm of treatment from reducing symptoms to one of effectively increasing task completions allows for the physician and patient to quickly determine treatment effectiveness that accrues from pharmacotherapy. Rather than review changes in their patients' symptoms checked off on an ADHD behavior scale, the physician can review the patient's report on the status of incompletions (no change, increase, or decrease) and thereby play a prominent role in management of adult ADHD. This shift in the paradigm of treatment effectiveness allows the physician to reinterpret task incompletions, encourage the patient to form collaborative partnerships to enlist assistance of others to improve work completion (an effective strategy called "social scaffolding"), and objectify and name problematic effortful attention to tasks.

Further, this transforms the ADHD problem from a perspective of mental health disorder existing inside the skin to a single, functional condition occurring outside the skin, ie, in the world of manageable action and behavior. Adopting this new paradigm in the context of medical management allows a necessary step in effective treatment plans for adults diagnosed with ADHD. We suggest herein that the medical model paradigm of reducing multiple dysfunctional symptoms be changed to the evaluation of the single behavior of task completions to address this shift in thinking.

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DIAGNOSING ADHD

The estimated prevalence of current adult ADHD in the United States is 1% to 6%,[1] lower than the 11% childhood prevalence identified by the US Centers for Disease Control and Prevention.[2] ADHD dysfunction changes over time,[3] with numerous factors impacting the age of diagnosis, including intelligence, symptom severity, environmental support, and changes in task demands. Because of increased awareness of ADHD in the adult population, physicians are likely to see more adults seeking treatment.

ADHD diagnosis requires the presence of dysfunctional symptoms of inattention, hyperactive/impulsive behavior, or both, as noted in **Table 1**,[4,5] with clinicians examining the presence of reported symptoms in context. A person's highly reactive, impulsive behavior may be effective on the college football field but dysfunctional in a classroom lecture. Thus, ADHD behavior must meet the following criteria:

- Problematic in 2 or more settings
- Interfere with daily life functioning
- Not be due to another mental health disorder
- Be present (but not necessarily impairing) in childhood prior to age 12.[5]

The clinician must confirm the presence and intrusiveness of at least 5 behaviors for inattention, hyperactivity/impulsivity, or both, as outlined in **Table 1**.[4,5] It is not enough that the patient engages in the behaviors associated with ADHD sometimes, as everyone exhibits them from time to time. It is critical to determine that the behaviors present a problem in daily functioning. As noted above, adult ADHD

TABLE 1
Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria for attention deficit hyperactivity disorder in adults[4,5]

Symptom criteria (minimum 5/9) for inattention

- Makes careless mistakes when working on boring or difficult tasks
- Difficulty sustaining attention while working on boring or repetitive tasks
- Difficulty concentrating on what people say even when spoken to directly
- Difficulty wrapping-up final details; fails to complete tasks
- Difficulty with organization and getting tasks in order
- Avoids or delays tasks requiring sustained mental effort
- Loses or misplaces personal possessions; difficulty finding things
- Easily distracted by surrounding activity or noise
- Forgetful; difficulty remembering appointments or obligations

Symptom criteria (minimum 5/9) for hyperactivity/impulsivity

- Fidgets or squirms with hands or feet
- Leaves the seat in meetings or situations where sitting is expected
- Feels restless or needs to be chronically active
- Difficulty unwinding, relaxing, or engaging in leisure activities quietly
- Feels compelled to stay active ("on the go" or "driven by a motor")
- Talks excessively in social situations
- Blurts out or finishes sentences of others who are talking
- Difficulty awaiting turn; has to have demands met immediately
- Interrupts or intrudes on others when they are busy

dysfunction is primarily associated with task incompletion or actions a person said they would complete (ie, said to themselves or to another) but did not. The behaviors are not deliberate attempts by an individual to be lazy but rather involve avoidance behaviors associated with an inability to easily use a faculty of the brain referred to as directed attention (discussed below). Directed attention is effortful and difficult for a person with ADHD to exercise, thus conferring the appearance of deliberate task avoidance.

UNIQUE CONSIDERATIONS IN DIAGNOSING AND TREATING ADHD IN ADULTS

The expression of ADHD across the life span is variable. Thus, it is important for physicians to consider the following 3 factors when treating adults with ADHD:

- **Subthreshold ADHD.** Adult patients may not meet all Diagnostic and Statistical Manual of Mental Disorders-5 symptom criteria for the disorder, nevertheless subsyndromal presentation may still result in significant functional impairment that necessitates treatment.[6]
- **Childhood ADHD diagnosis is not required.** Enduring presentation of symptoms is necessary, though childhood dysfunction may not have been observed. The absence of the diagnosis of childhood ADHD does not preclude an adult diagnosis, as intellectual strengths and social scaffolding (ie, structured daily activity like a well-ordered school day with persistent parent and teacher oversight) may have allowed for academic success in childhood but masked ADHD symptom presentation.[7]
- **Pharmacotherapy combined with focused behavioral strategies is the ADHD gold standard for treatment.** We underscore that behavioral intervention plus stimulant pharmacotherapy is the gold standard for treatment. We suggest here that when physicians monitor a single behavior—change in incompletions—during adult pharmacotherapy, outcome of therapy may be readily discerned. It is best to conduct an inquiry of previously attempted behavioral strategies and pharmacotherapy (ie, licit and illicit) to assist in treatment. The efficacy of stimulant treatment in adults has been demonstrated consistently.[8] Over 80% of adults respond favorably to stimulants (commonly methylphenidate or amphetamine, or both) with few if any intrusive side effects.[9] Behavioral interventions are also helpful to address shortcomings associated with ADHD.[7]

It should be noted that the best assessment practice involves 3 steps. First, confirm the presence of symptom criteria reported by multiple informants (ie, to address the possibility of reporter bias). Second,

TABLE 2
Stimulants to treat attention deficit hyperactivity disorder

Immediate-release[a]	Extended-release[a]
Methylphenidate	
Methylphenidate HCl chewable, 3–4 hrs Methylin liquid, 3–4 hrs Ritalin, 3–4 hrs	Adhansia XR, > 12 hrs (discontinued) Aptensio XR, 12 hrs Concerta, 12 hrs Cotempla XRODT, 12–13 hrs[b] Daytrana (patch), 9 hrs wear-time Jornay PM (night before), 12–14 hrs Metadate CD, 8–10 hrs Methylphenidate HCl, 6–8 hrs Quillichew ER, 8 hrs Quillivant XR (suspension), 12 hrs Ritalin LA, 8–12 hrs Ritalin SR, 8 hrs
Serdexmethylphenidate and dexmethylphenidate	
	Azstarys, 13 hrs
Dexmethylphenidate	
Focalin, 4–6 hrs	Focalin XR, 8–12 hrs
Amphetamine	
	Adzenys ER, 10–12 hrs Adzenys XR-ODT, 10–12 hrs Dyanavel XR (suspension), 13 hrs
Dextroamphetamine	
Dexedrine, 3–4 hrs Procentra (suspension), 3–6 hrs Zenzedi, 4–6 hrs	Dexedrine ER, 5–10 hrs Xelstrym (patch), 9 hrs
Methamphetamine	
Dexosyn, 4–6 hrs	
Mixed amphetamine salts	
Adderall, 4–6 hrs	Adderall XR, 10–12 hrs Mydayis, 14–16 hrs
Amphetamine sulfate	
Evekeo, 4–6 hrs	
Lisdexamfetamine	
	Vyvanse, 10–13 hrs Vyvanse (chewable), 10–13 hrs

[a]Numbers following drug name represent approximate upper limit of duration of action in hours.
[b]Extended-release orally disintegrating tablet.

CD = controlled delivery; ER = extended release; HCl =hydrochloride; LA = long-acting; ODT = orally disintegrating; SR = sustained release; XR = extended release

Adapted from references 10 and 12

rule out alternative causes (eg, poor sleep hygiene, depression) for why the symptoms are present. Third, identify comorbid conditions (eg, depression, anxiety) that may affect the presentation of attentional dysfunction. Both alternative causes and comorbid conditions often have a more complex expression in adults and therefore require scrutiny. Because disorder cannot occur without dysfunction, it is imperative for physicians to understand how ADHD behaviors interfere with daily activity.

Pharmacotherapy

A thorough review of US Food and Drug Administration-approved pharmacotherapy can be found in published reviews,[10,11] and we refer the physician elsewhere for alternative counsel on pharmacologic methods to treat adults (**Table 2**).[10,12–14]

CHANGE IN EXPRESSION OF ADHD FROM CHILDHOOD TO ADULTHOOD

Automatic vs directed attention

In adults as well as children, ADHD attentional impairment stems from differential facility with 2 distinct types of attention: automatic attention and directed attention.[15,16]

- **Automatic attention**, also referred to as "bottom-up" attention, functions in the brain's *default-mode* network and is largely associated with motivation and reward. It is self-activating and is called up automatically when tasks are of high interest or they avoid aversive consequences (eg, submitting taxes on time to avoid penalties).
- **Directed attention**, also referred to as "top-down" attention, functions in the brain's executive *task positive mode* network, and is associated with concentration and effort for difficult or low-interest tasks (eg, doing taxes, cleaning bathrooms, finishing dull homework). Rather than called up automatically, executive functions are generated with concerted effort through the medium of language to force completion of necessary and often distasteful tasks (eg, copying sentences, memorizing math facts, doing chores, paying bills).

Task management

Adult task management differs from task demands in childhood.[17] Children mostly face externally generated demands and use effortful, directed attention when they complete tasks that parents and teachers assign (eg, homework, chores). When children fail to complete tasks directed or assigned by adults ("other-directed tasks"), parents may assign proactive consequences to facilitate task execution (eg, parental reminders). This is in striking contrast to what happens when adults fail to complete other-directed tasks (ie, assignments at work, home chores). Rather than the supportive consequences received in childhood, adults more often experience negative consequences (eg, loss of a job, criticism from a spouse, traffic violation fines). While firm and supportive consequences for children help manage ADHD symptoms, adults often react to adverse consequences with guilt, shame, and anger.

Expectations levied on adults often necessitate that adults ignore distractions, however novel or exciting the distractions may be. Adults must often complete socially mandated though mundane requirements of daily living (eg, scrubbing bathrooms, paying bills) that compete with more appealing activities. At this juncture, adults with ADHD struggle more than children for one important reason: the childhood safeguards (ie, parental or teacher support) used to redirect attention to tedious but necessary tasks are no longer available. Effortful task completion is problematic in adulthood because of the self-agency necessitated by adult status. Others may assist but do not typically hold themselves responsible for the task's completion. Thus, unlike in childhood, task completion in adulthood is less a group project as it is an individual responsibility.

Adults with ADHD must self-select, self-prioritize, and self-activate their behavior. Children engage in self-assigned activities (eg, hobbies and play) that largely rely on automatic attention. In contrast, competent adults must decide what task to do and then do it. The successful execution of directed-attention tasks is both a testimony to and a requirement of adult status. Self-agency is the code of conduct that defines an adult as "response-able."[18] This expectation for self-agency is the very thing that challenges the adult with ADHD and physicians' efforts to medically manage it. Pharmacotherapy significantly improves executive functions associated with the directed-attention network to improve self-agency and task completion. Thus, agreement-keeping (doing what one says they will do) is an excellent measure of treatment effectiveness.

Aversive consequences are often absent from self-assigned tasks in adulthood but often are endemic to other-assigned tasks. Incompletion of a hobby (self-assigned) is generally inconsequential, whereas incompletion of a work assignment is consequential (eg, a supervisor's critique). Despite this fact, adults with ADHD often postpone essential tasks stating, "I'll do it later," with the risk of task incompletion justifiably certain.

THE CORE DYSFUNCTION IN ADULT ADHD

In 1890, William James aptly identified the issue of incomplete tasking. Although he did not directly reference the condition now known as ADHD, he wrote, "Nothing is so fatiguing as the eternal hanging on of an uncompleted task."[19]

We posit that task incompletion is the single most challenging problem for adults with ADHD. This functional impairment results in job changes, latency to task completion (ie, low productivity), chronic procrastination, treatment noncompliance, and disrupted relationships owing to unfulfilled expectations, among others. Physicians, for example, likely experience a higher incidence of missed appointments (broken agreements) with respect to patients with ADHD.

The nature of incompletions

Broken agreements are the outcome of inaction. ADHD pharmacotherapy medication often addresses this by enhancing directed attention. The adage "pills don't teach skills"[20] is applicable here. Medicine does not tell a person what to do but does enhance the person's capacity to use skills that are already in their behavioral repertoire. Latent skills of time management improve with pharmacotherapy and thereby have the power to reduce task incompletion. Skills deficits emerge because of ineffective directed attention, and they improve when directed attention itself is improved through pharmacotherapy.

The current trend of multitasking—doing multiple tasks at once—deemed essential in today's world does not occur without inefficiency. The brain can be activated to address only 1 task at a time. Though a person may start several tasks and have several tasks in progress simultaneously (eg, washing the dishes while the wet clothes are in the dryer), each task is completed individually, they are not acted on at the same time unless another agent is acting on it. Parents and teachers externally manage ADHD executive dysfunction in childhood with gentle (or forceful) reminders that monitor and reinforce desirable behaviors. Adults with ADHD, often do not have the external management of a spouse or a boss. They are expected to complete the tasks they agreed to do on their own.

Integrity and ADHD

In a study of integrity in business, Erhard and Jensen[21] noted that task incompletion is a broken agreement and that out-of-integrity behavior leads to damaging consequences. This applies even to tasks that individuals assign to themselves (eg, folding their clothes before bed). Essentially, when individuals do not keep their word, bosses, coworkers, friends, treating physicians, and partners are disappointed in, angry with, and even dismissive of the adult diagnosed with ADHD when they fail to do what they said they would.

To an adult with ADHD, the sheer act of having to use directed attention is itself aversive and effortful, so that the person often fails to task-initiate (ie, they procrastinate) or they do not discriminate which strategies to use for completion (ie, difficulty prioritizing). Even when motivation to achieve is present, attentional lapses, poor time management, and other executive dysfunctions make successful execution unlikely. Though an adult agrees to complete a task (ie, wash dishes before bed, finish a report for work) and wholeheartedly intends to do so, without intervention they may still become sidetracked and not carry out the agreement.

Anxiety and depression

When a person breaks an agreement and leaves a task incomplete, anxiety and depression tend to emerge, impacting daily self-expression.[22] As a backpack metaphor, consider that each incompletion is a large rock. When a person abandons a task before completion, they deposit the rock in their backpack. The person continues to walk around, not aware of the added weight. The more incompletions accumulated, the heavier the backpack. The weight of incompletions depletes the person's energy and joy in living.

The adult becomes disappointed in his or her own behavior, becoming self-critical. Often adults with ADHD feel disempowered because they do not exercise the flexibility[23] to keep their commitments to others or themselves. As a result, they become demoralized, feel guilty, or get angry when they do not complete tasks or meet goals. Thus, the simple behavior of breaking agreements becomes a largely debilitating factor.

Such scenarios conflate "skill" with "will." Friends and family may consider the adult with ADHD as lazy or unmotivated—a problem of "will"—that implies subjective intentionality. As such, in the presence of broken agreements, people construe the adult with ADHD as incompetent, or even worse, that they did not care about doing what they said they would. This significantly exacerbates the ADHD burden and the emotional impact it places on relationships.

RECOMMENDATIONS TO MANAGE ADHD IN ADULTHOOD

Broken agreements—the central dysfunction for adults with ADHD—result from executive dysfunction and may be ameliorated via social scaffolding, wherein people establish partnerships with others to maximize agreement-keeping. Clinicians can assist their patients in a broad way to encourage and design systems that track keeping agreements.[21]

The question for both patients and the coaching physician is how to "clean up" broken agreements. Four simple strategies can support the patient to manage broken agreements:

- Name broken agreements
- Complete the named agreements
- Make new, adjusted agreements
- Cancel the original agreement.

The physician encourages the patient to write them down, clearly name them, and bring them into the physical world. Then the person selects specific broken agreements and *completes* them. The patient may also select specific broken agreements and *change* them to make them manageable (eg, reduce the scope, enroll someone else to do them) or cancel the broken agreement *with all parties agreeing* to disregard it. This strategy may be difficult to execute because of the emotional ramifications of abandoning a necessary agreement.

All 4 scenarios are actionable plans that exist in the physical world. One major reason humans fail to resolve broken agreements is that their strategies for resolution are not actionable, devolving instead into self-talk that resides only in the mind (eg, "I'll do it later"). Successful resolution is unlikely without expressed, actionable strategies. We recommend that physicians encourage patients to take a notebook to a comfortable, familiar place (eg, favorite coffee shop, easy chair) and follow the steps noted above.

The first action for each broken agreement is to schedule a by-when contingency, that is, a day and time of completion. The person transfers the agreement from the internal world of self-talk to the expressed world of collaborative-talk to make tasks actionable and accountable (ie, an expressed agreement, telling someone when the agreement will be fulfilled). The important point here is if the event is "not mentionable, it is not manageable." We recommend the patient take the agreement out of the invisible world of the mind and place it in the physical world where two or more people can base future actions on it. Also helpful here is to share the list with a spouse or trusted friend who can add to accountability.

The following are strategies for cleaning up broken agreements:

Complete agreements. Identify the "by when" of completion, then act on it. Patients can now do what they said they would do. For example, a man promised his wife that he would put up paneling in the basement (ie, the agreement). He purchased the paneling—demonstrating intention to complete the task—and stacked it in the basement, where it remained for 18 months (ie, the stacked paneling became a constant reminder of his broken agreement). He promised his wife repeatedly that he would complete the paneling the next weekend (ie, he created an actionable expectation to complete his agreement). Not surprisingly and despite his best intentions, he did things other than paneling the basement. He offered excuses as consolation while the broken agreement persisted and festered. The couple argued bitterly over his incompletion, while his excuses undermined his credibility. Finally, the man took 2 days off work, called a friend to assist, and put up the paneling to fulfill the agreement. The satisfied agreement brought relief to the couple's relationship, although completing long-overdue agreements, while a necessary step to resolve broken ones, may be insufficient to rebuild trust. Thus, encouraging patients to list their agreements and specify a completion time for them may resolve the emotional sequelae associated with a history of broken promises.

Make a new agreement. Sometimes, the originally designed plan to complete an agreement is no longer feasible for a variety of reasons, and the original agreement can be changed to a more actionable course. In our scenario above, instead of the husband relying on his own effort to panel the basement, he could request that a contractor complete the task. The agreement would be completed though changed—he is not doing it, and another person is. This new agreement still completes the husband's original agreement. Keeping agreements by changing them can ultimately resolve a chronic pattern of behavior destructive to a relationship.

Cancel the agreement. Another strategy to manage broken agreements is simply to take back the promise of action, that is, cancel the agreement. Cancelling agreements may be a reasonable option but not without detriment. In the example above, by cancelling the agreement, the spouse would report to his wife that he is not going to put up the paneling in the basement, that he will return the paneling to recoup the purchase price, and that the couple will terminate the task expectation. In such cases, it is imperative that there is clear and transparent communication about the agreement, and that the spouse accepts the cancelled agreement. If acceptance is not forthcoming, the couple's relationship is likely strained, and trust further eroded. Physicians may inquire about broken agreements in a few targeted questions (**Table 3**).

We note here that a brain with ADHD tends to be highly attuned to the physical world.[24] This accentuates the practice for people with ADHD to take action in the physical world. Placing cues (eg, notes, lists, reminders)

TABLE 3
Questions to support patients with attention deficit hyperactivity disorder regarding agreements and task completions

Physician/patient query	Agreement with home/office/family/friends/self
What did you say you would do in the past week that you *did* do? (label frequency of occurrence)	Agreements made and kept; monitor frequency
Whom did you say that to? (eg, spouse, family member, colleague)	Agreements made and kept
What is your experience of actually doing what you said you would do? (especially the effect on relationships, eg, spouse, family member, colleague)	Agreements made and kept
What did you say you would do in the past week that you *did not* do? (label frequency of occurrence)	Broken agreement; monitor frequency
Whom did you say that to?	Broken agreements with whom—spouse, family member, colleague
What is your experience of actually not doing what you said you would do? (especially the effect on relationships, eg, spouse, family member, colleague)	Empowering/disempowering
How might you clean up the things you said you would do that you didn't do?	• Complete the thing you said you would do • Change the thing you said you would do (eg, make a new agreement) • Cancel the thing you said you would do

in the physical world is quite helpful for everyone, but especially for individuals with ADHD. Nevertheless, for individuals with ADHD, just *knowing what to do* does not ensure task execution (ie, doing it).

AGREEMENT-KEEPING MAY RELY ON ENVIRONMENTAL SUPPORT TO ENSURE COMPLETION

To facilitate agreement-keeping, physicians can encourage patients to establish a realistic plan (ie, time of completion noted). Becoming proficient in assigning a time of completion—a by-when statement—is often a difficult task for patients with ADHD and may require managed practice. An agreement without a by-when cannot be broken because it does not exist in time and may remain unfulfilled indefinitely. For example, if a woman tells her spouse that she will paint the molding in the living room "soon," this agreement is insufficient (ie, without a set timeframe for completion). It cannot be broken because "soon" is always ahead. Many people are intentionally ambiguous about the by-when clause because without it, a person can avoid responsibility for the agreement—and the soon never comes.

The most important function of being specific about the timing of a task is that this determines clarity of results (ie, whether the agreement is kept or broken). The statement "the task will be completed *by* noon next Saturday" places the task in the world of recognizable behavior. When noon on Saturday comes and goes, the agreement is either kept or broken.

UNDERSTANDING TASK COMPLETION AND THE NECESSITY OF CLEANUP STRATEGIES

Incompletions with ADHD occur for a variety of reasons. First, weak activation of executive functions impairs task engagement as the person does not identify what to do, and therefore does not do it. Second, the emotional consequences associated with task incompletions (ie, angry spouse, upset boss, self-shame) cause distress and result in a negative sense-of-self that perpetuates task avoidance and more incompletions. Over time, as task demands increase in both number and complexity, incompletions mount, and a tangled web of worries and self-doubt follows. Thus, it is no surprise that people with ADHD may orient away from accepting new tasks in the complex demands of daily life. This may include tasks that are assigned by their treating physician (eg, pharmacotherapy), though they are designed to optimize health and well-being.

TABLE 4
Resources for patients with attention deficit hyperactivity disorder (ADHD)

ADHD Coaches Organization (ACO): https://www.adhdcoaches.org/
Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD): https://chadd.org/
The American Professional Society of ADHD and Related Disorder (APSARD): https://apsard.org/
ADHD World Federation: From Child to Adult Disorder: https://www.adhd-federation.org/
ADHD Success Network Coaching: https://www.adhd-coach-asn.com/
ADDITUDE ADHD Experts Podcast: https://www.additudemag.com/adhd-expert-webinars-index/

One way to improve agreement-keeping across many professional settings is to use social scaffolding, a strategy often invoked in daily activity, though it is not necessarily well-researched. In business, chief executive officers often have administrative associates whose primary job is to orient the executive toward task completion, with the assistant being tasked to orchestrate the chief's daily to-do list. Physicians themselves often work with assistants and electronic scribes to attend to the higher-order and lower-order details necessary to efficiently attend to patient needs.

These successful professionals are not chastised or berated for their failure to attend to organizational details. Rather, they rely on others who facilitate the transfer of new information to archived records. Instead of viewing social scaffolding as an unnecessary burden required by an incompetent individual, it can be recognized as an effective strategy designed to ensure task efficiency and task efficacy. Considerable research further supports behavioral coaching to decrease functional impairment of adults with ADHD.[25,26]

IMPEDIMENTS TO SOCIAL SCAFFOLDING

Adults with ADHD tend to avoid the contribution of friends and family in managing daily life (ie, social scaffolding) despite its simplicity. Resistance often stems from resentment over infantilizing, interpreting collaborative partners' assistance as criticism, poor communication skills, unclear agreements (eg, private agreements with no consequences), and ambiguity about the roles of others in the home-work relationship.

Because little is accomplished by one person acting alone in the world today, it is critically and clinically important to encourage teamwork. Collaboration to address performance inconsistencies can reduce frustrations and character-blaming associated with incompletions. For some, social scaffolding is the optimal tool to manage ADHD behavioral shortcomings and reflects a simple addition for treatment when combined with pharmacotherapy. **Table 4** outlines coaching resources for individuals with ADHD.

GUIDANCE FOR THE PHYSICIAN

Shifting the view of treatment for the adult with ADHD as a problem with the brain to a problem with behavior—breaking agreements—empowers people to view their actions differently. This shift from mental-based dysfunction to action-based dysfunction may strengthen results of treatment and make treatment simpler for the physician by making a difference in patient outcomes. Emphasizing that breaking and keeping agreements is a clinically significant side effect of ADHD and its treatment can impact the effect of pharmacotherapy.

While ADHD is a lifelong condition, it does not need to result in a demoralizing path to failure when management techniques are properly implemented.

DISCLOSURES

Dr. Manos has disclosed consulting for Supernus. The other author reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

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Atypical hyperplasia of the breast: Clinical cases and management strategies

ABSTRACT

Atypical hyperplasia of the breast is a histopathologic lesion identified incidentally on image-guided breast biopsy. It is associated with a substantial increase in lifetime risk for breast cancer. Clinicians should counsel women with atypical hyperplasia regarding risk-reducing strategies, which include preventive endocrine therapy options, enhanced surveillance imaging, and lifestyle modifications. In this review, we describe 5 different but common clinical case scenarios for atypical hyperplasia of the breast and review management strategies for each scenario.

KEY POINTS

For patients with atypical ductal hyperplasia identified on core needle biopsy, surgical consultation is recommended to discuss if surgical excision is warranted based on radiology and pathology concordance, owing to significant risk of finding an associated in situ or invasive malignant lesion.

Observation instead of surgical excision may be considered for atypical lobular hyperplasia without other high-grade lesions if the radiologic and pathologic findings are concordant.

Flat epithelial atypia without an associated high-risk lesion does not require discussion of risk-reducing endocrine therapy unless formal risk assessment using a model largely dependent on family history suggests otherwise.

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Atypical hyperplasia of the breast is a high-risk benign breast lesion that carries an increased lifetime risk for invasive breast cancer.[1] Breast biopsies are commonly performed in the United States. Follow-up of mammographic abnormalities with image-directed breast biopsy has shown atypical hyperplasia as an incidental finding in 10% of cases.[2] Histopathologically, atypical hyperplasia is classified as atypical ductal hyperplasia (ADH) or atypical lobular hyperplasia (ALH). Other findings distinct from classical atypical hyperplasia are lobular carcinoma in situ, classified as lobular neoplasia or flat epithelial atypia (FEA).[2]

See related editorial, page 433

For women with atypical hyperplasia, the cumulative breast cancer risk is approximately 1% per year.[2,3] Breast cancer risk calculators available to quantify breast cancer risk include the Breast Cancer Risk Assessment Tool (BCRAT),[4] which is also known as the Gail model,[5] and the International Breast Cancer Intervention Study (IBIS),[6] which is also known as the Tyrer-Cuzick Model Breast Cancer Risk Evaluation Tool. These models provide population-level estimated 5-year (BCRAT), 10-year (IBIS), and lifetime breast cancer risk. However, the BCRAT calculator can underestimate risk for atypical hyperplasia,[3,7] whereas the IBIS model has been shown to significantly overestimate risk, particularly for patients with a family history of breast

TABLE 1
Management of high-risk breast lesions

High-risk breast lesion	Rate of upgrade to invasive breast cancer	Management after core needle biopsy	Use of risk-reducing endocrine therapy
Atypical ductal hyperplasia	10% to > 30%[14,15]	Observation if radiologic and pathologic findings are concordant or after excisional biopsy	Yes
Atypical lobular hyperplasia	0% to 67%[17]	Observation if radiologic and pathologic findings are concordant or consider an excisional biopsy	Yes
Flat epithelial atypia	0% to 21%[16]	Observation if radiologic and pathologic findings are concordant or consider an excisional biopsy	Assess breast cancer risk factors and use available risk-assessment calculators (BCRAT or IBIS) Yes, if there is elevated risk

BCRAT = Breast Cancer Risk Assessment Tool; IBIS = International Breast Cancer Intervention Study

cancer and ADH, as the risk of family history is compounded by the risk due to atypia.[2,3] Currently, the US Preventive Services Task Force recommends discussing risk-reducing recommendations with patients who have estimated BCRAT 5-year risk greater than 3%,[8] and the National Comprehensive Cancer Network recommends discussing therapies such as annual mammograms and clinical breast examinations every 6 to 12 months for women age 35 or older and with 5-year risk 1.7% or greater.[7,8] The American Cancer Society recommends magnetic resonance imaging (MRI) breast screening for patients with a calculated lifetime breast cancer risk of at least 20% based on IBIS.[9] The American College of Radiology and National Comprehensive Cancer Network currently recommend that MRI screening be considered in addition to annual mammography for women with atypical hyperplasia.[10,11] Because studies show that the lifetime risk of breast cancer is greater than 20% for women with atypical hyperplasia, the role of annual MRI plus mammography surveillance is appropriate.[7,12]

Primary care practitioners may receive pathology reports that describe these lesions after breast biopsies. Therefore, we review 5 different case scenarios that primary care practitioners may encounter and include information on lesion presentation, management options, and clinical pearls for each case.

CASE 1

A 50-year-old woman presented to the office after abnormal mammographic screening of her right breast, which revealed a 6-mm cluster of calcifications in the upper outer quadrant. An image-guided core needle biopsy showed ADH involving 3 foci. She had a family history of breast cancer: her mother was diagnosed at age 58 and 1 of 2 maternal aunts was diagnosed at age 62.

Discussion

ADH is a marker for increased risk of breast cancer. When identified on core needle biopsy, ADH carries a risk of unsampled malignancy.[13,14] At the time of excisional biopsy, rates of upgrade to in situ or invasive malignancy range from 10% to more than 30% (**Table 1**)[14–17] for high-risk breast lesions.[13,15–19] Because of these upgrade rates, the current recommendation is for an excisional biopsy for ADH identified on core needle biopsy, although there may be some cases wherein more than 90% of the lesion is removed by biopsy and no other high-risk features exist. In these cases, excision is not required.[20]

If an excisional biopsy does not identify higher-grade lesions (in situ carcinoma, invasive carcinoma), patients should be counseled regarding risk-reducing endocrine therapy for 5 years. In a Mayo Clinic cohort study of 698 women with atypical hyperplasia of the breast, cumulative incidence of breast cancer at 25 years was 29%.[2] This risk can be further stratified based on the number of foci seen on pathology.[2,7] A 1985 study by DuPont and Page[21] followed more than 3,300 women with benign breast biopsies for a median of 17 years and showed that patients with atypical hyperplasia and family history were at significantly increased risk compared with those without a family history of breast cancer. However,

the Nurses' Health Study and the Mayo Clinic cohort study, both large studies, showed no significant risk difference for women with a family history of breast cancer.[2,3,7,22] Subgroup analyses of several large clinical trials (National Surgical Adjuvant Breast and Bowel Project, Prevention Trial [NSABP P-1], Mammary Prevention 3 [MAP.3], and IBIS-I and II) showed significant risk reduction for women with ADH taking selective estrogen receptor modulators (up to 86%)[23] or aromatase inhibitors (41% to 79%)—an even greater benefit than for women with a calculated high risk (38% relative risk reduction).[7,24,25]

Clinical pearls

- For patients with ADH identified on core needle biopsy, surgical consultation is recommended to discuss if surgical excision is warranted based on radiology and pathology concordance, owing to significant risk of finding an associated in situ or invasive malignant lesion.
- Risk-reducing endocrine therapy should be discussed with patients because of increased lifetime risk of breast cancer, estimated at 1% per year.

CASE 2

A 60-year-old woman underwent routine screening mammography that revealed heterogeneously dense breasts and a 5-mm cluster of calcifications identified in the upper inner quadrant of the right breast. Image-guided core needle biopsy showed ALH, and the radiologic findings correlate with the histopathologic findings on the core needle biopsy, confirming concordance. Patient history noted osteoporosis in the lumbar spine, with the lowest T-score of –2.8 and history of uterine hyperplasia without atypia.

Discussion

ALH is usually found in less than 1% of breast core needle biopsies.[14] The absolute risk of developing breast cancer after a diagnosis of ALH is approximately 1% per year or approximately 30% at 25-year follow-up.[3,7,14]

Rates of upgrade to in situ or invasive disease at ALH excision varied substantially among studies. A systematic review of 65 studies revealed that upgrade to any malignancy ranged from 0% to 67% for excised lesions.[17] Because of this wide variation, routine surgical management of ALH has been controversial. More recent studies suggested that surgical excision is not always indicated for ALH if radiologic and pathologic findings are concordant, and no other coexisting high-risk lesions requiring excision are found.[14] As with ADH, risk-reducing endocrine therapy for the prevention of breast cancer is associated with a 41% to 79% relative risk reduction for women with ALH.[3,7,23] The approach to discussing risk-reducing endocrine therapy for women with atypical hyperplasia should be individualized according to menopausal status, medical comorbidities, and risk of adverse effects.

In this case scenario, the patient has several relevant comorbidities, osteoporosis, and a history of uterine hyperplasia without atypia. Thus, there is a need to balance the benefits of risk-reducing endocrine therapy vs the risk of adverse effects of medications. Tamoxifen can be used for premenopausal and postmenopausal women; however, tamoxifen carries the risk of endometrial cancer, venous thromboembolism, and cataracts. For endometrial cancer, tamoxifen was shown to have a 9 per 1,000 risk of uterine cancer compared with a risk of 4.0 per 1,000 for the general population of US women ages 50 to 59.[26] Therefore, for this patient with an intact uterus and a history of uterine hyperplasia, tamoxifen should be considered cautiously. This patient also has osteoporosis, so an aromatase inhibitor would not be the best choice because of the association of aromatase inhibitors with reduced bone density. The Study of Tamoxifen and Raloxifene P-2 trial compared the effectiveness of tamoxifen and raloxifene vs placebo. Initial results from this trial revealed similar effectiveness of raloxifene and tamoxifen in reducing the risk of invasive breast cancer. An updated analysis with an 81-month median follow-up showed a 38% reduced risk of invasive breast cancer with raloxifene and 50% with tamoxifen compared with placebo.[27]

Raloxifene was not associated with an increased risk of invasive uterine cancer or uterine hyperplasia compared with tamoxifen. The rates of venous thromboembolism were lower with raloxifene than tamoxifen (2.4 vs 3.3 per 1,000, respectively) as was the development of cataracts (20% less). With the 60 months of treatment plus additional 21 months of follow up, raloxifene appeared to retain 76% of the effectiveness of tamoxifen in preventing invasive disease and grew closer over time to the effectiveness of tamoxifen in preventing noninvasive disease with fewer adverse effects.[27]

Raloxifene has been approved to prevent and treat postmenopausal osteoporosis and can provide secondary benefit for breast cancer risk reduction beyond 5 years if it is being prescribed for osteoporosis management. Vasomotor symptoms can be exacerbated with both selective estrogen receptor modulators and aromatase inhibitors. The National Comprehensive Can-

cer Network guidelines for high-risk women include breast awareness, clinical breast examination every 6 to 12 months (minimum 12-month follow-up), annual screening mammography with possible tomosynthesis (not before age 30), and possible annual breast MRI beginning at diagnosis of ALH (not before age 25).[11,15] Contrast-enhanced mammography or whole-breast ultrasonographys could be considered for those who qualify but cannot undergo MRI.

Clinical pearls

- Observation instead of surgical excision may be considered for ALH without other high-grade lesions if the radiologic and pathologic findings are concordant.
- Risk-reducing endocrine therapy should be discussed with patients who have ALH.
- Raloxifene is a good choice for patients with ALH and a history of uterine hyperplasia with atypia or osteopenia or osteoporosis.
- Supplemental screening with annual breast MRI or other imaging options, such as contrast-enhanced mammography or whole-breast ultrasonography for those who qualify but cannot undergo MRI should be considered for patients with ALH.

CASE 3

A 40-year-old premenopausal woman with a strong family history of breast cancer presented to your office after her first screening mammogram that showed 4-mm grouped amorphous calcifications in the left-to-central breast. Focused left breast ultrasonography showed no sonographic correlation. A left breast stereotactic biopsy was performed, and pathologic findings revealed flat FEA. Postbiopsy mammography confirmed removal of all calcifications. Radiologic and pathologic findings were concordant. The patient was seeking advice on management and surveillance of FEA.

Discussion

FEA, considered to be a precursor to breast cancer development, is a rare columnar cell breast lesion typically diagnosed on breast biopsies of calcifications identified on screening mammography. These lesions, which occur in 0.7% to 12.2% of percutaneous breast biopsies,[28] have enlarged terminal ductal lobular units lined by up to several layers of columnar epithelial cells with low-grade cytologic atypia and no architectural distortion. Although FEA may be associated with luminal calcifications,[29] no clinical features are present in patients with FEA.

The reported upgrade rate of FEA to ductal carcinoma in situ or invasive carcinoma following core needle biopsy to time of excision is wide-ranging, from 0% to 42%,[16,28] which has resulted in controversy regarding the need for surgical excision or observation of these lesions.[16] The amount of tissue sampled differed (core needle diameter, use of vacuum-assisted technique, and excisional biopsy quality) when comparing studies and was the suggested variable responsible for the broad difference in upgrade rate. Radiologic and pathologic concordance and improved tissue sampling showed an upgrade rate of less than 3% with pure FEA.[30] Residual calcifications after biopsy have been associated with an increased upgrade rate.[16] A recent meta-analysis of 42 studies showed a pooled upgrade rate of 1% for invasive carcinoma and 2% for ductal carcinoma in situ.[31] The upgrade rate was 0% when more than 90% of calcifications were removed with core needle biopsy.[31] The National Comprehensive Cancer Network suggests observation is acceptable in select patients with FEA,[32] for patients with radiologic-pathologic concordance when all microcalcifications are removed at biopsy and no associated mass or high-risk lesions exist.[32] Otherwise, patients should be referred to a breast specialist for consideration of surgical excision of FEA.

FEA frequently occurs in association with high-risk lesions such as ADH, ALH, or lobular carcinoma in situ and is most often identified with concurrent ADH.[14] A recent meta-analysis, however, showed a 17% rate of concurrent ADH and FEA.[31] The risk of upgrade at surgical excision to ALH or lobular carcinoma in situ was lower: 4.8% and 2.9%, respectively.[33] FEA associated with ADH, ALH, or lobular carcinoma in situ is clinically significant, and identifying one of these high-risk lesions should prompt high-risk surveillance and preventive strategies.[31]

The long-term risk of breast cancer for pure FEA is only mildly increased (relative risk, 2.0),[34] a risk similar to that of proliferative breast disease without atypia. If the excisional biopsy does not show findings of ALH or ADH, risk-reducing endocrine therapy or surveillance with high-risk breast imaging is not required for pure FEA. However, if a validated risk assessment model suggests an increased risk of breast cancer based on family history, patients can be counseled about risk-reducing endocrine therapy.

In this case, surgical excision is not indicated based on isolated FEA and a low risk of upgrade due to radiologic and pathologic concordance and removal of all calcifications on biopsy. Because of the strong family history of breast cancer, a formal risk assessment is

needed using a model largely dependent on family history, such as the Tyrer-Cuzick model (IBIS)[6] or CanRisk (https://www.canrisk.org/). If the patient's lifetime risk of breast cancer is 20% or greater, annual high-risk screening MRI and mammography are recommended, and risk-reducing medications should be offered.

Clinical pearls

- Imaging surveillance without surgical excision is reasonable after FEA on core needle biopsy without concurrent high-risk lesions and with radiologic-pathologic concordance.
- FEA without an associated high-risk lesion does not require discussion of risk-reducing endocrine therapy unless formal risk assessment using a model largely dependent on family history suggests otherwise.

CASE 4

A 42-year-old premenopausal woman underwent a left breast excisional biopsy that revealed ADH. After she was counseled regarding risks and benefits of tamoxifen, she started therapy at 20 mg per day. After 3 years of tamoxifen therapy, she returned with concerns about 3 months of irregular and heavy menstrual bleeding. Her body mass index was 32.1, was nulliparous, and had a history of polycystic ovary syndrome. She reported being sexually active with her male partner. Pelvic ultrasonography showed 2 small endometrial polyps, and the endometrial lining was 12-mm thick. An endometrial biopsy revealed atypical endometrial hyperplasia. Tamoxifen was discontinued, and she subsequently underwent dilation and curettage and hysteroscopy with polypectomy. To preserve fertility, she deferred hysterectomy.

Discussion

In estrogen-depleted postmenopausal women, tamoxifen has proestrogen effects on the endometrium, but in premenopausal women with adequate estrogen levels, tamoxifen exhibits an estrogen antagonist effect on the endometrium.[35] For women on tamoxifen therapy, endometrial cancer or hyperplasia is less common in premenopausal than postmenopausal women.[36] However, in some premenopausal patients, tamoxifen can cause endometrial subepithelial stromal hypertrophy, leading to irregular menstrual bleeding, which is common, and other uterine pathologic findings such as endometrial polyps and hyperplasia. Endometrial cancer is less common.[37]

Results of a recent review of Cochrane controlled trials showed the risk of endometrial cancer for women under age 50 taking tamoxifen to be only slightly greater than placebo, with a relative risk 1.19 and 95% confidence interval (CI) 0.53–2.65 ($P = .60$).[38] However, in a recent large retrospective Korean study of over 78,320 premenopausal breast cancer patients, those treated with tamoxifen vs placebo had higher rates of uterine pathologic findings.[39] These patients were followed for a mean 6.13 years and were shown to have increased rates of endometrial polyps (20.13 cases per 1,000 person-years), endometrial hyperplasia (13.49 cases per 1,000 person-years), and endometrial cancer (2.01 cases per 1,000 person-years).[39] The American College of Obstetricians and Gynecologists recommends against routine surveillance testing of asymptomatic patients, but all premenopausal and postmenopausal patients presenting with abnormal uterine bleeding while taking tamoxifen should receive additional diagnostic evaluation.[40] A meta-analysis evaluating tamoxifen use by the Early Breast Cancer Trialists' Collaborative Group showed an increased incidence of endometrial cancer in women over age 55.[41] The Adjuvant Tamoxifen, Longer Against Shorter trial was designed to study tamoxifen use at 5 vs 10 years and found significantly higher risk of endometrial cancer in postmenopausal women (relative risk, 1.74 [95% CI, 1.30–2.34]), suggesting a cumulative dose effect.[42] In addition to age and duration of therapy, irregular and abnormal uterine bleeding are considered risk factors for endometrial hyperplasia.

Information is conflicting regarding the association of systemic and local progestin therapies and increased risk for breast cancer, and these therapies have not been studied in women at high risk for breast cancer. Current recommendations are for shared decision-making with patients regarding local and systemic progestin therapies, especially if the breast cancer is progesterone-receptor positive. Continuous progestin-based systemic therapies such as megestrol and medroxyprogesterone acetate and localized therapies such as the 52-mg levonorgestrel intrauterine device (LNG-IUD) are used to treat endometrial hyperplasia and can be considered for patients who have contraindications to surgery or are interested in future childbearing. Megestrol (40 mg) improves endometrial hyperplasia, but it can have adverse effects.[43] Endometrial hyperplasia regressed in 91.8% of women after 6 months of treatment with depot medroxyprogesterone acetate.[44] Depot medroxyprogesterone acetate, however, can cause weight gain and lower bone mineral density.[45]

The 52-mg LNG-IUD, which delivers 20 mcg of LNG per day, has been studied for both the pre-

vention and treatment of endometrial pathology in women being treated with tamoxifen. Compared with oral progestin therapy, LNG-IUD use leads to higher resolution rates of endometrial hyperplasia without atypia.[46] High-dose local progestins induce profound endometrial suppression through epithelial atrophy, decidualization, and vascular change such that the endometrium becomes unresponsive to ovarian steroidal activity. Multiple studies have confirmed that endometrial hyperplasia and endometrial polyp formation are reduced at long-term follow-up (24–60 months) for LNG-IUD users (Peto odds ratio, 0.13 [95% CI, 0.03–0.66]).[47] The Finnish Cancer Registry study concluded that the LNG-IUD is associated with excess risk for lobular cancer (standardized incidence ratio, 1.33 [95% CI, 1.20–1.46]) and ductal breast cancer (standardized incidence ratio, 1.20 [95% CI, 1.14–1.25]) compared with nonuse.[48] However, LNG-IUD use has much less systemic exposure and could be a relatively safer option than systemic progestin therapies. In a study reviewing the recurrence of breast cancer in LNG-IUD users, risk did not increase for users vs nonusers (adjusted hazard ratio, 1.86 [95% CI, 0.86–4.00]).[49] Currently, many practitioners recommend LNG-IUD as a treatment option for endometrial hyperplasia for premenopausal women who desire to preserve fertility and who are at an increased risk for breast cancer. Additional research is needed in this area with this specific patient population.

Untreated atypical endometrial hyperplasia can progress to endometrial cancer; therefore, hysterectomy is recommended. However, in patients with endometrial hyperplasia due to tamoxifen therapy who want to preserve fertility, tamoxifen should be discontinued. After tamoxifen discontinuation, the risk of endometrial cancer decreases and is the same as for nonusers after less than 3 years of use.[50]

In this case, the patient had a dilation and curettage, hysteroscopy, and polypectomy, and after counseling for risks and benefits, she was prescribed LNG-IUD therapy to reduce the recurrence of hyperplasia. The LNG-IUD can be considered for 12 to 24 months with ongoing endometrial surveillance and monitoring of a patient's menstrual symptoms. Thereafter, tamoxifen could be restarted and continued for 2 additional years. If the patient had a hysterectomy, tamoxifen could be resumed for 2 years, for a total of 5 years of preventive therapy. In addition, when a patient is postmenopausal, she can be counseled regarding use of an aromatase inhibitor as risk-reducing endocrine therapy.

It is important to counsel premenopausal women on the use of tamoxifen, ie, that tamoxifen is a category D medication that can cause fetal anomalies, and barrier contraception is routinely recommended. In addition, barrier contraception should be continued for 2 months after tamoxifen is discontinued.

Clinical pearls

- Both premenopausal and postmenopausal women receiving tamoxifen who have irregular menstrual bleeding warrant evaluation with pelvic ultrasonography and endometrial biopsy to exclude endometrial pathology.
- Tamoxifen should be discontinued if a patient is diagnosed with endometrial hyperplasia. Short-term use of an LNG-IUD is an option to manage endometrial hyperplasia for women who want to preserve fertility or are not good surgical candidates. Thereafter, tamoxifen can be restarted as preventive therapy with barrier contraception.
- Per National Comprehensive Cancer Network guidelines, tamoxifen can be restarted in patients with tamoxifen-induced endometrial hyperplasia who had a hysterectomy or received LNG-IUD for 2 years in order to manage and treat endometrial hyperplasia.
- A shared decision-making discussion is warranted regarding the use of progestin IUDs because current data do not show an increase in breast cancer risk. A balanced discussion that accounts for the patient's age, medical needs such as contraception or controlling bleeding, and comorbidities is prudent.

CASE 5

A 56-year-old postmenopausal woman presented to your clinic for her well-woman examination. She was generally healthy, with a body mass index of 29.2. She exercised on the weekends, usually walking for 1 hour, and reported drinking 1 glass of wine with dinner. Her medical history was significant for right breast excisional biopsy for ADH diagnosed 6 years previously. She completed 5 years of risk-reducing endocrine treatment with exemestane. She requested additional information about lifestyle counseling to reduce her lifetime risk for breast cancer.

Discussion

A healthy lifestyle is associated with a reduced risk for invasive breast cancer, especially in postmenopausal women. Weight gain increases breast cancer risk. Fatty tissue is metabolically active, which can pro-

duce inflammatory markers such as adipokines, and is hormonally active, which can lead to high insulin and estrogen levels. These changes can disrupt cellular repair mechanisms, which can subsequently prompt breast cancer to develop and progress.[51] The Western diet is characterized by consumption of red meat, processed meat, animal fat, and ultraprocessed foods that can ultimately result in a higher body mass index and increased adipose tissue, and, thus, increased estrogen levels. For postmenopausal women, eating a diet low in fat (< 20%), processed meat, and red meat and high in fruits, vegetables, and whole grains can lower the incidence and mortality of breast cancer.[51,52]

Regular physical activity has the most robust effect on breast cancer among all the lifestyle factors, with regular moderate- or high-intensity exercise leading to reduced risk in postmenopausal women. The risk for premenopausal women is reduced with vigorous physical exercise done regularly and sustained over a lifetime.[53] Total physical activity (metabolic equivalent tasks per week) positively influences multiple interrelated biologic factors such as reduced adiposity and increased sex hormone binding globulin, as well as reduced estrogens, androgens, and inflammatory markers, which in turn influence menstrual function.[54] A lifestyle index that included cigarette smoking, physical inactivity, and unhealthy eating showed an inverse relationship to breast cancer.[55] Women with the highest healthy lifestyle score had 44% lower odds of breast cancer than those with the lowest score (odds ratio, 0.56 [95% CI, 0.36–0.88]; *P* for trend = .004).[55]

Even in small amounts, alcohol consumption can increase the risk of breast cancer. The mechanism by which alcohol exerts a carcinogenic effect is unclear but may be related to the effects of alcohol on sex hormones, ie, interference with estrogen pathways and estrogen receptors.[56] Women who consumed 15 g to 30 g of alcohol daily had increased levels of estrogens, androgens, and progesterone. In addition, acetaldehyde, a metabolite of alcohol, is mutagenic because it inhibits the repair of carcinogen-induced DNA damage. The National Institute on Alcohol Abuse and Alcoholism classifies a standard drink as having 14 g of alcohol (12 oz of beer, 5 oz of wine, 1.5 oz of distilled spirits). Consuming too much alcohol can negatively affect the absorption of dietary nutrients that have anticarcinogenic properties, eg, folate, beta carotene, lutein, and zeaxanthin.[57]

Tobacco use also affects lifestyle and risk of breast cancer.[58] Polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are the most well-known carcinogens; the DNA adducts they produce can circumvent cellular repair mechanisms and cause genetic variations. In pooled data from 14 cohort studies, smoking for more than 10 years before the first childbirth increased the risk of breast cancer by 18% compared with women who never smoked.[59]

Clinical pearls

- Current American Cancer Society guidelines recommend achieving and maintaining a healthy weight and limiting alcohol intake and avoiding smoking to reduce cancer risk. Individually tailored whole foods, plant-based dietary patterns, and 150 to 300 minutes of moderate intensity or 75 to 150 minutes of vigorous intensity activity each week (or a combination of these) also reduce breast cancer risk.
- Women should be made aware of the considerable decrease in breast cancer risk with healthy lifestyle choices.

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EDITORIAL

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Surgical de-escalation: Are we ready for 'observation' of benign high-risk breast lesions found on core needle biopsy?

One focus of the article by Vegunta and colleagues[1] in this issue of the *Journal* is whether benign proliferative lesions such as atypical hyperplasia diagnosed on core needle biopsy (CNB) require surgical excision. The estimated upgrade rate—that is, finding breast cancer at surgical excision—is variable, and consensus recommendations for an acceptable threshold for excision are emerging.[2] As the sensitivity of breast imaging has improved, more benign lesions are being found,[3–6] and rates of upgrade have been decreasing.

See related article, page 423

Surgical de-escalation is part of a larger movement of de-escalation of multidisciplinary breast cancer treatment. The challenge is to balance oncologic outcomes with surgical morbidity and quality of life. In this case, the de-escalation may be preceding consensus on upgrade thresholds, definitions, standardized clinical workflow, agreement on follow-up, and incorporation of patient preference.

Imaging-guided CNB to assess abnormalities detected on breast imaging has been the standard of care for decades. From 1 to 2 million benign and high-risk CNBs are performed annually in the United States.[7,8] Clear, accepted clinical guidelines are followed for the management of malignant lesions, but management of high-risk lesions differs among institutions. Further, the patient's level of risk and risk tolerance needs to be considered. The question is whether there are currently enough data so that a "recommendation against excision" can be made. One final concern is that surgical de-escalation may actually contribute to disparities.

BACKGROUND AND DEFINITIONS

The history of the surgical management of breast cancer is a continuum of de-escalation. The early Halsted radical mastectomy, developed in 1894 and used for decades, was a disfiguring surgery removing the breast, all axillary lymph nodes, and the chest wall musculature. Later in the 20th century, it was replaced by the simple mastectomy (sparing the chest wall musculature and axillary lymph nodes) after results of a national trial showed equivalent survival.[9] Toward the end of the 20th century, studies showed breast conservation (partial mastectomy with clear margins) and radiation to be noninferior to mastectomy for early-stage disease.[10–12]

The surgical management of the axilla was the next area of de-escalation, with trials showing equivalent outcomes with sentinel lymph node biopsy and axillary dissection in early-stage breast cancer.[13–16] Simultaneously, de-escalation of radiation therapy for breast conservation was investigated. Shortened courses of radiation (3 weeks compared with 5 weeks), partial breast irradiation, intraoperative radiation therapy, and the option of excluding radiation therapy in select patients (over age 70) have been explored and are finding their places.[12,17–20]

Future areas of de-escalation of surgery include active surveillance for ductal carcinoma in situ.[21–23] Cryoablation is also being investigated.[24] Large ran-

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TABLE 1
Curtailing therapy at age 70: Ageism?

Current age	Additional life expectancy, years	Estimated total years
70	17.6	87.6
75	13.7	88.7
80	10.2	90.2
85	7.3	92.3
90	5.1	95.1

Data from reference 25 and 26.

domized controlled trials documenting the safety and efficacy of these approaches have preceded and should precede clinical adoption.[21–23]

Women age 60 and older represent 59% of invasive breast cancer cases, and more than 30% occur in women age 70 and older.[25] Many trials involving de-escalation have resulted in age 70 as a threshold for alternative treatment approaches that are appropriate for most but not all older women. The US Social Security Administration provides an online life-expectancy calculator for citizens to estimate their remaining life span and plan for retirement (**Table 1**).[25,26] An average 70-year-old female has an estimated life expectancy of 17.6 years to an estimated life span of 87.6 years. An average octogenarian has an estimated life expectancy of 10.2 years to 90.2 years, and an average 90-year-old has an estimated life expectancy of 5.1 years to 95.1 years. A healthy 70-year-old may still have a significant risk of recurrence. Both disease-free survival and overall survival should be part of the shared decision-making discussion, particularly in healthy older women.

As one example of de-escalation, the Society of Surgical Oncology Choosing Wisely campaign of 2016, an initiative of the American Board of Internal Medicine Foundation, encouraged the advancement of a national dialogue on avoiding "…sentinel node biopsy in clinically node-negative women ≥ 70 years of age with early stage hormone receptor positive, HER2 negative invasive breast cancer."[27] Patients, however, are hesitant to de-escalate cancer therapy.[28] A survey of newly diagnosed patients showed that 53% accepted aggressive treatments with significant side effects for a 3-month benefit in survival.[29] It has been suggested that an upgrade of 3% or less could be a reasonable threshold for offering surveillance in place of surgery,[30] although it remains to be seen whether women with benign atypical lesions will accept this threshold for risk tolerance. Thresholds for excision based on limited evidence are concerning, and anticipated regret is a real and powerful driver of patient choice.[31]

SELECTING PATIENTS FOR NONOPERATIVE MANAGEMENT: CRITERIA NEEDED

The perception among patients and providers, however, may be that immediate surgical excision avoids underdiagnosis and undertreatment of malignancy. Well-defined, evidence-based criteria for the selection of patients for nonoperative management would help address these concerns.

Active surveillance could first be offered to patients who would have been offered nonoperative management in prospective multi-institutional trials. Two small such trials suggest that an upgrade rate of 3% or lower could be a reasonable threshold for offering surveillance vs surgery.[32,33] The first is a prospective registry of 77 patients with pure lobular neoplasia (atypical lobular hyperplasia or lobular carcinoma in situ) who had an upgrade rate of 1% to 3%. The study also includes a literature summary of upgrade rates ranging from 0% to 27% in small retrospective single-institution studies, thereby demonstrating the need for trials with prospective data.[32]

The second registry involved 116 patients with papillomas without atypia, 66% of whom presented with mammographic mass or distortion, showing a 1.7% upgrade rate (2/116).[33] The 3% threshold is similar to the upgrade rate of less than 2% for Breast Imaging Reporting and Data System Category 3 lesions recommending short-term follow-up with repeat imaging at 6 months as an alternative to biopsy, as the lesion is felt to have a less than 2% chance of being malignant.[34] Individual institutions embarking on processes for determining radiologic-pathologic concordance must agree on patient selection, imaging findings, sampling issues, and expected follow-up. It is also important to remember that the recommendation for observation does not preclude a later recommendation for surgical excision, should findings change.[35]

The stated concerns of proponents of surgical de-escalation involving benign high-risk lesions are those of overdiagnosis and overtreatment (**Table 2**). Overdiagnosis refers to biologically indolent cancers that may not go on to cause the individual harm,[36] as evidenced by the increased rates of ductal carcinoma in situ detection resulting from improved mammographic screening without resultant increases in invasive breast cancer or breast cancer mortality.[37] It is important to note that this could also be viewed

TABLE 2
Definitions surrounding surgical de-escalation

Radiologic-pathologic concordance	The imaging and pathologic findings are considered to be concordant when the pathologic result provides an acceptable explanation for the imaging feature and discordant when they do not
Overdiagnosis	Finding cases of cancer with a screening test (such as a mammography) that will never cause any symptoms
Overtreatment	Interventions that do not benefit the patient or where the risk of harm from the intervention is likely to outweigh any benefit the patient will receive

as early diagnosis, but may lead to falsely improved survival statistics given potential lead-time bias. The US Preventive Services Task Force in 2016 set forth de-escalating screening guidelines that women begin mammograms at the age of 50 and continue every other year until age 74[38] because of concerns regarding overdiagnosis, despite evidence supporting similar mortality reduction with screening mammography in women ages 40 to 49.[39] In May 2023, after recognizing that mammograms starting at age 40 and modeled every other year to save (conservatively) 19% more lives, the US Preventive Services Task Force changed its recommendations to starting at age 40, yet they still recommend screening every other year.[40] The National Comprehensive Cancer Network[41] and the American College of Radiology[42] continue to recommend annual mammograms beginning at age 40.

Overtreatment refers to the use of therapies with minimal benefit to patients.

GUIDELINE DISAGREEMENT

Accepted guidelines exist for margin width, adjuvant radiation, and sentinel lymph node biopsy in the cancer setting. However, guidelines differ for surgery vs observation for benign high-risk lesions.[43–46] Benign lesions on CNB for which surgical excision was historically recommended include atypical hyperplasia (both ductal and lobular), lobular carcinoma in situ, radial scars, and papillary lesions.[41] Though the 2016 American Society of Breast Surgeons proposed guidelines[47] suggested observation as an option for all but atypical ductal hyperplasia, pleomorphic lobular carcinoma in situ, and papillomas with atypia, the guidelines were not widely adopted. The more conservative National Comprehensive Cancer Network guidelines now recommend that atypical lobular hyperplasia/lobular carcinoma in situ, if radiologically and pathologically concordant and adequately sampled, can be observed for a period of 1 year in select patients (undefined) or excised, at the surgeon's discretion.[41] Screening magnetic resonance imaging (MRI) is not mentioned despite recommendations of the American College of Radiology to offer MRI screening to such patients.[42]

The concept of radiologic-pathologic concordance is difficult to define. Atypical lobular hyperplasia and lobular carcinoma in situ are felt to be incidental findings on performed CNBs as a result of imaging abnormalities. It is unclear how incidental findings can explain imaging abnormalities. There is also no consensus on adequate sampling (core needle size, number of passes, and degree of lesion removal), whether there is pathologic reporting regarding the extent of the abnormality, and whether the mode of detection is relevant. Some authors recommend observation for high-risk lesions in cases involving microcalcifications on a screening mammogram in an asymptomatic woman of average risk. Other authors suggest biopsy of mass lesions and architectural distortion on mammograms. Studies have dissimilar inclusion criteria, and rates of upgrade vary widely.[30] Some studies include masses or non-mass-like enhancement on breast MRI (in high-risk patients by definition). More recent studies have not included cases with these latter findings as true upgrades, partially explaining the trend toward lower upgrade rates in recent literature.

Further, subsequent high-risk screening recommendations are inconsistent, and the uptake of preventive medication is classically poor.[48–50] Many patients are noncompliant with follow-up recommendations (even for Breast Imaging Reporting and Data System-3 imaging studies with short-interval follow-up recommended).[51] Few small prospective studies of observation with limited follow-up have been published and do not seem to be generalizable to different practice settings.[51–55] For instance, Middleton et al[52] published a series of 104 patients with pure lobular

neoplasia followed for a median of 3.4 years: 5 patients were subsequently diagnosed with breast cancer (3 of 5 at an unrelated site). Laws et al[53] noted that in their high-risk clinic where MRI screening is not routinely recommended and following multidisciplinary discussion of all benign high-risk lesions, atypical lobular hyperplasia and classic lobular carcinoma in situ have been safely managed thus far without surgical excision based on 80 patients with pure lobular neoplasia and median follow-up of 27 months.[53]

Another study examined 478 patients with 483 atypical ductal hyperplasia lesions; 309 were observed and 174 underwent excision.[54] With a median follow-up of 5.2 years, 2 cancers were identified at the index site in the surgery group (1.5%) and 3 in those observed (1.2%).[54] A prospective study successfully triaged patients to surgery vs observation following the establishment of predefined firm guidelines and performance of rigorous radiologic-pathologic correlation.[55]

WORSENING DISPARITIES

Finally, it must be considered that women of color and low socioeconomic means do not receive optimal care. It has been demonstrated that Black women are more likely to be screened at nonaccredited facilities, without current equipment (including digital breast tomosynthesis, much less dedicated breast MRI), and with fewer resources for follow-up.[56,57] Disparities in uptake to MRI have been demonstrated according to educational level.[58] Disparities in cancer treatment that have been demonstrated include lower rates of genetic testing in high-risk individuals,[59] delays in diagnosis,[60] and less appropriate surgery, radiation, and chemotherapy.[61,62] Adherence to endocrine therapy in the cancer setting is suboptimal,[63–66] perhaps in part owing to insurance coverage that also impacts MRI screening and uptake of and adherence to risk-reducing medication in following patients with benign high-risk lesions. Owing to these stated concerns, careful observation of benign high-risk lesions in women of low socioeconomic status may be destined for failure due to insurmountable social barriers.

OBSERVATION MAY NOT BE READY FOR WIDESPREAD IMPLEMENTATION

In summary, the potential for upgrade to malignancy at surgical biopsy remains the principal reason for excision of benign high-risk lesions detected on CNB. In the authors' opinion, the recommendation for observation of such lesions may not be ready for widespread implementation. Appropriate surgical de-escalation requires data demonstrating lack of utility of a given intervention combined with an informed shared decision-making discussion with the patient and standardized processes in place to assure quality.

Presently, upgrade rates in the literature are variable and have an unacceptably broad range, criteria for patient selection vary, consensus statements are vague, institutions with multidisciplinary discussions of radiologic-pathologic concordance are the exception, and patients not referred for surgical consultation (particular in lower socioeconomic groups) may have reduced access to and lowered rates of adherence to appropriate imaging and preventive strategies. While many institutions have adopted observation for benign atypical lesions, long-term data on oncologic safety are lacking.

Overdiagnosis and overtreatment are of concern and add to healthcare costs and patient morbidity, but de-escalation in this setting will take time for agreement and standardization, and concern remains regarding appropriate follow-up, particularly in vulnerable populations. Offering surveillance for high-risk lesions identified by CNB is a practice change that may be premature for many institutions.

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Dr. Pederson has disclosed consulting for Myriad Genetics and Vira Health. Dr. Calhoun reports serving as advisor or review panel participant for Luminex. The other author reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

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REVIEW

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Autoimmunity and postural orthostatic tachycardia syndrome: Implications in diagnosis and management

ABSTRACT

Postural orthostatic tachycardia syndrome (POTS)—sustained tachycardia upon standing without orthostatic hypotension—can be diagnosed clinically without an extensive diagnostic evaluation unless certain atypical features suggest an alternative diagnosis. A unifying pathophysiologic mechanism has not been identified, although several have been proposed. Similarities between POTS and various autoimmune disorders suggest an immune mechanism in a subset of patients. However, no causative antibody has been identified, and associated antibodies are rarely clinically relevant. Moreover, immunotherapies are not currently recommended for POTS, although clinical trials are underway to clarify their utility.

KEY POINTS

- POTS is a heterogeneous syndrome defined by orthostatic intolerance and can be diagnosed clinically without extensive testing.
- Various mechanisms may be involved in POTS, but the initial treatment approach remains the same.
- Atypical features are important to recognize and may suggest an alternative diagnosis.
- Antibody testing is recommended only when considering an alternative diagnosis.

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Postural orthostatic tachycardia syndrome (POTS) is a common form of orthostatic intolerance, with a prevalence of 0.2% to 1% in developed countries.[1] While no single unifying etiologic mechanism has been determined, several have been proposed, including activation of the immune system.[1–3]

In this review, we describe the presentation and diagnostic evaluation of POTS for the general practitioner, including atypical features that may suggest an alternative diagnosis requiring a more extensive evaluation. We also touch briefly on its basic treatment, possible autoimmune mechanisms (including recently associated antibody targets and their clinical utility), immunosuppressive therapy, and future directions in the field.

DEFINITION AND MANIFESTATIONS OF POTS

POTS is a chronic syndrome defined by a sustained increase in heart rate of at least 30 beats per minute (bpm) within 10 minutes of standing in adults (or ≥ 40 bpm in patients ages 12 to 19) without accompanying orthostatic hypotension, which is defined as a fall in systolic blood pressure of 20 mm Hg or greater or a fall in diastolic blood pressure of 10 mm Hg or greater (**Table 1**).[1,2,4,5] In many patients, the absolute heart rate while upright remains above 120 bpm.

TABLE 1
Diagnostic criteria for postural orthostatic tachycardia syndrome

All of the following criteria are necessary:
A sustained increase in heart rate by ≥ 30 beats per minute within 10 minutes of standing or head-up tilt in adults (or ≥ 40 beats per minute for patients ages 12–19) without orthostatic hypotension (a fall in systolic blood pressure ≥ 20 mm Hg or diastolic blood pressure ≥ 10 mm Hg)
Associated symptoms of orthostatic intolerance that are worse with standing (light-headedness, fatigue, palpitations, tremulousness, blurred vision, syncope) and improve with recumbency
Symptom duration of at least 3 months
Absence of other conditions to explain sinus tachycardia (prolonged bed rest, medications, hyperthyroidism, anorexia nervosa, anemia, pain, fever, infection, dehydration)

Based on information in reference 1, 2, 4, and 5

POTS symptoms can be grouped broadly as either cardiovascular or noncardiovascular (**Table 2**).[1] Orthostatic intolerance is a defining feature of the condition, with symptoms that get worse upon standing and improve with supine posture.[5] Additional cardiovascular symptoms include palpitations, dizziness, lightheadedness, and presyncope or syncope. Noncardiovascular symptoms can involve many organ systems and include fatigue, generalized weakness, neuropathic pain, cognitive difficulty, nausea, and bladder dysfunction (**Table 3**).[1,5–7]

The onset is typically subacute and often follows a trigger such as infection, surgery, trauma, or childbirth.[6] Heat, fever, dehydration, morning hours, strong emotion, and menstruation have been known to exacerbate symptoms.[1] The typical age at onset is between 15 and 45, and at least 80% of patients are women.[1,2,6]

A typical presentation of POTS is in a young active woman with a subacute onset of lightheadedness, dizziness, and presyncope provoked by standing, often following a viral illness, surgical procedure, trauma, or prolonged period of inactivity. The patient may report that symptoms are worse in warm weather or morning hours, or when feeling particularly stressed or anxious.[1]

VARIOUS MECHANISMS MAY BE INVOLVED

A unifying pathophysiology of POTS has not been determined, although various mechanisms may be involved. These include abnormally increased sympathetic nervous system activity and circulating catecholamines resulting in a hyperadrenergic state ("hyperadrenergic POTS"), peripheral sympathetic denervation leading to venous pooling and volume dysregulation ("neuropathic POTS"), low blood volume (absolute hypovolemia), and an underlying immune dysregulation (discussed in further detail below).[1–3]

These varying mechanisms may coexist within an individual patient, resulting in a heterogeneous symptom presentation, ultimately defined by orthostatic intolerance.[5]

BARRIERS TO A TIMELY DIAGNOSIS

POTS can be diagnosed clinically by the general practitioner without extensive testing.[8] However, lack of familiarity with the condition, its nonspecific symptoms indirectly related to orthostatic intolerance, and the overlap of symptoms with those of similar conditions often result in unnecessary referrals, excessive testing, and a delay in diagnosis, as concern about missing an alternative diagnosis often adds to the diagnostic challenge.[9,10]

Using the clinical history alone, POTS can be challenging to differentiate from other causes of orthostatic intolerance such as chronic fatigue syndrome and inappropriate sinus tachycardia.[10] Fortunately, objective testing can help to identify POTS, and the initial management strategies are often similar.[10] Further information on differentiating POTS from other causes of orthostatic intolerance can be found elsewhere.[5]

Comorbid psychiatric conditions such as untreated major depression can complicate the evaluation but are important to recognize and address in equal measure to improve clinical response to treatment.[11]

APPROACH TO POTS DIAGNOSIS AND MANAGEMENT

The diagnostic evaluation of POTS starts with a focused history centering on symptom onset and progression, comorbid conditions, precipitating and

TABLE 2
Clinical presentation and associated symptoms in postural orthostatic tachycardia syndrome

Cardiovascular symptoms	Orthostatic intolerance, orthostatic tachycardia, palpitations, dizziness, lightheadedness, presyncope, syncope, exercise intolerance, dyspnea, chest pain, acrocyanosis, Raynaud phenomenon, venous pooling, limb edema
Noncardiovascular symptoms	
General	Deconditioning, fatigue, heat intolerance, fever
Nervous system	Headache, migraine, cognitive impairment, "brain fog," difficulty concentrating, tremulousness, photophobia, phonophobia, blurred vision, neuropathic pain, sleep disorder, involuntary movements
Musculoskeletal	Muscle fatigue, weakness, pain
Gastrointestinal	Nausea, bloating, dysmotility, gastroparesis, diarrhea, constipation, pain, weight loss, irritable bowel syndrome
Respiratory	Shortness of breath, hyperventilation, bronchial asthma
Urogenital	Bladder dysfunction, polyuria, nocturia, urgency, frequency
Skin	Rash, erythema, petechiae, telangiectasias, diaphoresis, flushing, pallor, dry eyes, dry mouth, sudomotor dysregulation (hyperhidrosis, hypohidrosis, anhidrosis)
Psychiatric	Anxiety, depression, panic attacks, suicidal ideation, somatic hypervigilance, catastrophizing personality

Based on information in reference 1.

exacerbating factors, and positional dependence. Other topics and investigations include the following:

Diet, including meal size and frequency and the volume of salt and water intake, is important in looking for symptom triggers and developing treatment strategies.[5] Reducing the size of meals reduces the likelihood of postprandial hypotension, with less blood flow routed away from the brain to the gastrointestinal system.[12]

Exercise tolerance (length and type of exercise) can be used to assess the severity of symptoms and evaluate treatment efficacy over time.[5]

Medications with side effects that mimic POTS symptoms include diuretics, vasodilators, antipsychotics, anticholinergics, nonstimulant medications for attention deficit hyperactivity disorder (eg, atomoxetine), and oral contraceptive pills with antimineralocorticoid action (eg, those that contain drospirenone).[3,13]

A detailed autonomic review of systems (Table 4)[5] should be performed to accurately describe symptoms and screen for features that may indicate an alternative diagnosis (**Table 5**).[14]

The physical examination should include a complete cardiac and neurologic assessment. Look for clues pointing to diseases that can produce a POTS-like phenotype, such as:

- Thyroid dysfunction (exophthalmos, goiter, hair-thinning, nail discoloration)
- Anemia (pallor, jaundice, cool or discolored extremities)
- Connective tissue disorders such as Ehlers-Danlos syndrome (joint hypermobility).

An active stand test can be performed in the office by measuring heart rate and blood pressure in the supine position and again 1, 3, 5, and 10 minutes after standing, although the changes occur within the first 5 minutes in most patients with POTS.[3,15]

Basic laboratory testing should include a complete blood cell count, electrolytes, and thyroid function testing. A 12-lead electrocardiogram is recommended to assess for an underlying arrhythmia.[3,5]

Further investigation, including ancillary cardiovascular testing (echocardiography, external electrocardiographic loop monitoring), is not recommended as part of the routine evaluation

TABLE 3
Commonly reported symptoms in patients with postural orthostatic tachycardia syndrome

Lightheadedness or dizziness	78%–87%
Palpitations	75%–92%
Fatigue	48%–90%
Headache	28%–87%
Breathing difficulty	28%–64%
Tremulousness	38%–49%

Based on information in references 1, 5, 6, and 7.

unless there is strong suspicion for structural heart disease or symptomatic arrhythmia contributing to exercise intolerance.[4] Similarly, tilt-table testing is not required for diagnosis but can be useful when a patient is unable to perform an active stand test or when other conditions such as neurocardiogenic (vasovagal) syncope or peripheral autonomic neuropathy are suspected.[7,16]

Further autonomic testing such as quantitative sudomotor axonal reflex testing, skin biopsy to evaluate epidermal nerve fiber density, thermoregulatory sweat testing, or other autonomic cardiovascular evaluation (eg, Valsalva maneuver, deep-breathing test) is unnecessary for the initial diagnosis. These tests may be pursued by a specialist primarily to understand the underlying pathophysiology of a particular patient who has had no improvement with initial conventional therapy, and when symptoms raise suspicion for an autonomic neuropathy.[5]

Nonpharmacologic treatments first

Once the diagnosis of POTS is established, initial treatment is aimed at reducing symptoms, improving quality of life, and educating the patient. Nonpharmacologic strategies should be the first intervention and include the following:

- **Volume expansion** by increasing oral intake of water to 2 to 3 L/day and salt to 10 to 12 g/day (regular intravenous fluid infusions are not recommended and are potentially harmful[2])
- **Compression garments** including abdominal and thigh compression and full abdominal and leg compression[17]
- **Sleeping with the head of the bed elevated** 4 to 6 inches
- **Removing exacerbating factors** such as large meals and medications[2,5,8]
- **A graded exercise program** featuring endurance reconditioning and lower-body resistance training can be highly beneficial[18]
- **Behavioral and cognitive therapy** should also be considered for patients with significant anxiety, somatic hypervigilance, or catastrophizing behaviors.[8]

An in-depth discussion of treatment for patients with severe or refractory symptoms is beyond the scope of this article but can be found elsewhere.[19]

RED FLAGS AND MIMICS: WHEN TO BROADEN THE DYSAUTONOMIA WORKUP

In evaluating a putative POTS diagnosis, it is important to recognize certain red-flag features that may suggest an alternative diagnosis. When these features are present, a more thorough workup should be considered.

Evolving symptoms, with widespread dysautonomia that is highly debilitating and rapidly progresses over days to weeks, should raise concern for an alternative diagnosis.[14,20]

A history of autoimmune disease or malignancy may further raise suspicion for an alternative diagnosis, especially if the initial presentation occurs after age 65.[20]

Red-flag autonomic symptoms are often widespread and severe, involving the sympathetic, parasympathetic, and enteric nervous systems. Signs and symptoms that should raise suspicion include pupillary dysfunction, hyperhidrosis or anhidrosis, urinary retention, sexual dysfunction, and severe gastrointestinal dysmotility.[14] The coexistence of these symptoms should raise suspicion for an alternative diagnosis, especially when disabling and severe.

Extra-autonomic features that should also raise concern for alternative diagnoses include involvement of the central nervous system (cerebral cortex, brainstem, cerebellum, spinal cord) or endocrinopathies (amenorrhea, syndrome of inappropriate antidiuretic hormone secretion, adrenal insufficiency, panhypopituitarism).[14]

If red flags are present

When red-flag features are present, systemic testing, neurologic testing, or both may be warranted. In these cases, testing for specific antibodies that could account for the clinical presentation is advised.

For example, a combination of sicca symptoms, impaired pupillary reflex, urinary retention, and gastroparesis should raise suspicion for a severe form of immune-mediated dysautonomia termed *autoimmune autonomic ganglionopathy*.[20] This clinical picture war-

TABLE 4
Autonomic review of systems

System	Symptoms
Sudomotor	Hyperhidrosis, hypohidrosis, anhidrosis, heat intolerance
Secretomotor	Dry eyes, dry mouth (sicca symptoms)
Cardiovascular	Postural lightheadedness or palpitations, presyncope, syncope
Gastrointestinal	Nausea, bloating, early satiety, gastroparesis, dysphagia, constipation, diarrhea
Genitourinary	Urinary urgency or retention, nocturia, incontinence, impotence, dyspareunia

Based on information in reference 5.

rants testing for the alpha-3 ganglionic acetylcholine receptor (gAChR) antibody.[20]

A limited form of autoimmune autonomic ganglionopathy that predominantly affects the gastrointestinal system is termed *autoimmune gastrointestinal dysmotility syndrome*.[21] Patients with this form develop severe subacute multilevel gastrointestinal dysmotility, sometimes presenting with intestinal pseudo-obstruction, and are often found to be gAChR antibody-positive.[21]

Alternatively, predominant sicca symptoms in the setting of dysautonomia with or without sensory abnormalities may warrant testing for Sjögren syndrome A and B (SSA and SSB) antibodies.[22,23]

Patients who present with dysautonomia in the setting of symmetric proximal weakness that improves with exercise should raise suspicion for Lambert-Eaton myasthenic syndrome and should undergo testing for P/Q-type and N-type voltage-gated calcium channel antibodies.[20]

Other antibody-associated (often paraneoplastic) neurologic disorders exist that can present with pervasive dysautonomia, often in the setting of severe nervous system dysfunction. They are beyond the scope of this review, but include disorders associated with antineuronal nuclear antibody type 1 (ANNA-1, Anti-Hu), anti-dipeptidyl-peptidase-like protein-6, anti-contactin-associated protein-like 2 antibody, and anti-collapsin response mediator protein 5.[20,24] They are rare and should not be tested for regularly unless clinically indicated, to avoid exposing patients to unnecessary and potentially harmful interventions.

The overlap of signs and symptoms among several of these autoimmune conditions and POTS has raised the possibility of an underlying autoimmune mechanism in the disease itself. The following section focuses on this topic in greater detail.

THE ROLE OF AUTOIMMUNITY IN POTS

The role of the immune system in POTS has attracted much interest in recent years. While a clear autoimmune etiology has not been identified, the shared clinical features between POTS and various autoimmune conditions suggest several immune-mediated mechanisms. These shared features have also given rise to further investigation into possible diagnostic and management avenues within the field.

Clinical similarities between POTS and autoimmune conditions

Most patients with POTS are young women, with recent estimates suggesting a 94% female predominance.[25] Symptom onset is frequently preceded by an acute stimulus such as a viral infection, vaccination, physical trauma, surgery, or pregnancy, suggesting an immune-mediated process may be at play.[25] Furthermore, many patients with POTS have associated generalized symptoms including fatigue, malaise, sleep disruption, headache, and gastrointestinal symptoms, features often observed in chronic autoimmune disease.[25]

From 16% to 20% of patients with POTS have a coexisting autoimmune disease, and many have a family history of one.[9,26,27] In a large community-based survey, the most common coexisting autoimmune conditions were Hashimoto thyroiditis (present in 6%), celiac disease (3%), Sjögren syndrome (3%), rheumatoid arthritis (2%), and systemic lupus erythematosus (2%).[9]

Furthermore, many patients with POTS have various autoantibodies, suggesting an autoimmune link. However, many of these antibodies are discovered incidentally at low titers and have unclear clinical significance.[26,28,29] One study found that 25 (25%) of 100 patients with POTS had antinuclear antibodies,

TABLE 5
Red-flag features suggesting an alternative diagnosis

Onset	Acute to subacute onset over days to weeks
Widespread autonomic involvement	Involvement of the parasympathetic, sympathetic, and enteric nervous systems, affecting multiple organ systems
Functional decline	Loss of functional independence and increased disability level due to progression of symptoms
Signs and symptoms	Pupillary dysfunction, hyperhidrosis or anhidrosis, urinary retention, sexual dysfunction, and gastrointestinal dysmotility
Relevant personal or family history	Personal or family history of autoimmune conditions or malignancy
Central nervous system dysfunction	Clinical features of cortical, brainstem, cerebellum, or spinal cord dysfunction
Endocrinopathy	Amenorrhea, syndrome of inappropriate antidiuretic hormone secretion, adrenal insufficiency, panhypopituitarism

Based on information in reference 14.

significantly more than in the general population (16%, $P < .05$).[26] Similarly, the prevalence of antiphospholipid antibodies in the patients with POTS was 7%, compared with 1% in the general population ($P < .001$).[26] Thyroid-specific antibodies have also been found in up to 33% of patients with POTS, again with unclear significance.[30] Neurologic autoantibodies directed at voltage-gated potassium channels and glutamic acid decarboxylase 65 may also be incidentally discovered but are nonspecific, and can also be seen in patients with nonimmune neurologic diseases as well as in healthy controls.[28]

While the prevalence of antibody positivity in patients with POTS may suggest an autoimmune association, the presence of these antibodies shows no clear difference in the severity of POTS symptoms or response to therapy. In clinical practice, checking for these antibodies is not recommended in patients with an otherwise typical POTS presentation without additional features of an underlying secondary disease process.[26,28]

Certain autoimmune conditions may also feature POTS-like symptoms, further complicating the diagnosis and signifying an important autoimmune parallel. For example, milder cases of Sjögren syndrome can resemble POTS.[22] Neurologic involvement of Sjögren syndrome can classically cause a subacute sensory ganglionopathy with debilitating autonomic features.[31] However, a milder form of Sjögren syndrome can present with predominant sicca symptoms (dry mouth, dry eyes) and mild autonomic symptoms due to an underlying small-fiber neuropathy.[22]

Goodman et al[22] reported a series of 13 patients with Sjögren syndrome who underwent evaluation for suspected autonomic impairment, finding that 8 met the criteria for POTS based on clinical features and autonomic testing. Importantly, all 13 patients had sicca symptoms at onset, and most had a combination of elevated SSA and SSB antibodies or pathologic findings on salivary gland biopsy, suggesting that only patients with autonomic features in conjunction with clear Sjögren syndrome symptoms warrant antibody testing.

Molecular mechanisms proposed

The molecular mechanisms linking POTS and autoimmunity remain poorly understood. One theory suggests a state of sympathetic overdrive and reduction of cardiovagal tone resulting in an elevation in the cytokine interleukin 6 inducing systemic inflammation.[32] The elevation in interleukin 6 may act centrally to upregulate further sympathetic activity, resulting in a chronic hyperadrenergic state leading to cardiovascular deconditioning.[32] This proinflammatory state may explain several systemic features associated with POTS including sleep disturbance, cognitive impairment, and hyperalgesia.[32] Additionally, elevated cytokines may be important mediators of vasodilation and vascular permeability.[33]

Others have suggested the possibility of a circulating autoantibody with a direct pathological mechanism affecting the autonomic nervous system.[34]

POTENTIAL AUTOANTIBODY TARGETS IN POTS

Thus far, several possible autoantibody targets have been studied in POTS.

The gAChR antibody, initially identified as the pathogenic antibody in autoimmune autonomic ganglionopathy, has been suggested as a possible culprit,[35] as it can be detected in low titers in up to 25% of patients with POTS.[6,36] However, it can be nonspecific, as low-titer positivity (≤ 0.05 nmol/L) has been noted in healthy controls and in various other autoimmune-mediated conditions, without clear clinical relevance.[29] McKeon et al[28] found that, of 155 patients who tested positive for gACHR antibody after being referred because of neurologic symptoms, 31% did not have autoimmune disease, 37% had low titers (≤ 0.09 nmol/L), 55% had medium titers (0.10–0.99 nmol/L), and 8% had high titers (≥ 1.00 nmol/L).[28] While the antibody has been speculated to play a role in sympathetic denervation in POTS, no clear clinical difference between seropositive and seronegative patients has been shown.[6,36,37]

Thus, it is always important to interpret antibody testing results within the clinical context, regardless of the titer level. Ultimately, testing for gAChR antibody in a patient with a classic POTS presentation without additional red flags has little clinical utility and may confound the clinical picture if the result is positive.[37]

G-protein coupled receptor (GPCR) antibodies, which target adrenergic receptors, are another class of antibodies that may be detected in patients with POTS.[34] Notably, GPCR antibodies have also been detected in patients with Sjögren syndrome, orthostatic hypotension, malignant hypertension, and preeclampsia, as well as in patients with POTS-like conditions such as inappropriate sinus tachycardia, complex regional pain syndrome, and chronic fatigue syndrome, and are thus nonspecific.[25] Specific antibodies in this class include those directed against alpha-1 adrenergic receptor, beta-1 adrenergic receptor, and beta-2 adrenergic receptor and are thought to inhibit norepinephrine action peripherally, resulting in increased heart rate and orthostatic intolerance.[34]

Angiotensin II T1 receptor antibodies have similarly been detected in patients with POTS and may act by disrupting systemic vasoconstriction in response to upright posture.[38]

Muscarinic receptor antibodies. Recent evidence has also suggested activity of muscarinic receptor antibodies (M1, M2) in contributing to POTS pathophysiology.[39]

Testing for these antibodies is currently considered experimental and thus is not available commercially. Furthermore, a recent study investigating the presence of GPCR antibodies in POTS patients compared with healthy controls showed no significant difference in antibody (adrenergic, muscarinic, and angiotensin II) concentrations by enzyme-linked immunosorbent assay testing.[40] While the presence of these antibodies raises the possibility of an autoimmune link, they do not appear to be directly pathogenic, and testing for them does not currently offer clear clinical utility in POTS.[34,40]

POTENTIAL USE OF IMMUNOTHERAPY IN POTS

Given the possibility of an immune-mediated mechanism underlying POTS, researchers have begun to investigate the efficacy of immunotherapies in its treatment, but as yet, no prospective trials have been completed.

In a case series from Rodriguez et al,[41] 6 patients with a clinical diagnosis of POTS and a positive GPCR antibody test were treated with intravenous immunoglobulin intermittently over 6 months. The patients were all young women (ages 23–31), had refractory POTS symptoms despite first-line treatment, and had tested positive for the alpha-1 adrenergic receptor antibody. Response to treatment was measured with a subjective symptom-based survey and with objective testing including a tilt-table test. The subjective and objective results appeared to be positive after 6 months of therapy, although notably, treatment tolerance was poor, with 2 patients requiring hospitalization. Also, all the patients were pretreated with intravenous fluids in addition to receiving intravenous immunoglobulin, likely resulting in a significant volume repletion that may have contributed to the overall treatment effect. This is an important confounder in assessing the use of intravenous immunoglobulin in the treatment of POTS.

Currently, a double-blind randomized control trial is investigating the feasibility, tolerability, and potential benefit of intravenous immunoglobulin treatment in POTS.[42] The study plans to enroll 32 participants with POTS who have moderate to severe symptoms and clinical or laboratory features of autoimmunity including a serum autoantibody (antinuclear antibody, gAChR antibody, extractable nuclear antigen, antiphospholipid antibody, or tissue transglutaminase immunoglobulin A), a personal or family history of autoimmune disease, evidence of small-fiber neuropathy, or history of acute to subacute onset of symptoms.

With an expected completion date in late 2023, this study will help to further clarify a clinical question that at this time remains uncertain. Until then, there is not enough rigorous evidence to suggest a benefit of immunotherapy in the treatment of POTS.

TAKE-HOME POINTS

Although the etiology and pathophysiologic mechanisms underlying POTS remain uncertain, a clinical diagnosis can be made with a focused history, examination, and basic diagnostic evaluation.

Initial treatment strategies are simple and include optimizing fluid intake, compression stockings, avoiding known triggers, exercise to improve stamina, and cognitive behavioral therapy to reduce hypervigilance.

Autoimmunity may play a role in the pathogenesis of POTS in some patients. However, if the initial clinical presentation is consistent with POTS and no major red-flag features are evident, further antibody testing is not recommended because it will not change management. Although several antibodies are being investigated that may be associated with POTS, a single causative antibody has not been identified. If red flags are present, a targeted autoimmune investigation should be considered to exclude diagnostic mimics.

There are not enough data currently to warrant treating POTS with immunosuppressive therapies. Important clinical trials are underway to explore this treatment approach further.

DISCLOSURES

Dr. Li reports serving as member of clinical practice scientific advisory board and as research principal investigator for Alexion; consulting, research principal investigator, and receiving grant support from Argenx; consulting, research principal investigator for Catalyst and UCB; advisor or review panel participant research and serving as principal investigator in an upcoming trial for Immunovant. Dr. Abbatemarco reports consulting for Alexion; advisor or review panel participant for Genentech and EMD Serono and Horizon Therapeutics; and a research grant for Horizon Therapeutics. 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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