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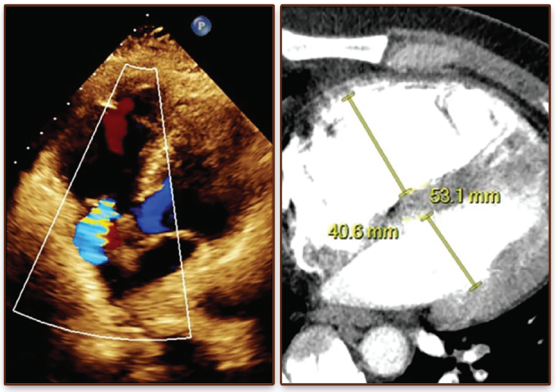

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The gift of lasting immunity

In this issue of the *Journal*, Rivard[1] reviews and discusses some of the current guidelines for vaccination of patients against measles. Reading through the practical US Centers for Disease Control and Prevention recommendations for prevention of measles[1,2] prompted me to reflect on the degree and perhaps surprising duration of immunity acquired from natural infection and the attenuated measles vaccine. Of historical interest is a detailed description by Peter Panum[3] of a measles epidemic on the Faroe Islands in 1846. A prior measles outbreak occurred on the islands in 1781. Panum estimated that 5,000 of the 6,626 inhabitants in 1846 were infected, and at least 78 died. His notable observation was that the infection rate was fairly similar across age groups, with the exception that the elderly (age > 65, those who would have been alive during the 1781 epidemic) were spared. This seminal epidemiologic observation has since been corroborated with serologic data[4] and extended to include data on the lasting serologic and clinical efficacy of the live attenuated measles vaccine.[5] This can be contrasted with the recommendation that adults should receive booster vaccinations for tetanus and diphtheria every decade.[6]

The duration of efficacy of vaccines varies significantly depending on the type of vaccine, its structure, the age at which it is given, and, likely, the pathogen it targets. Studies have shown that the measles vaccine, which is a live attenuated virus, is highly effective, with a median effectiveness of 93% after 1 dose and 97% after 2 doses.[1] The second dose in the usual regimen is not a "booster," but it provides immunity to those who do not respond to the first dose. Although not necessarily lifelong for all individuals, measles vaccine–induced immunity is quite durable. This distinguishes the measles vaccine from some others. For instance, the tetanus and pertussis vaccines (nonreplicating antigen–containing platforms) typically require booster doses every 10 years to maintain full immunity. Other nonreplicating vaccines, like the hepatitis B vaccine, provide long-term protection, often lasting decades without the need for boosters. So it is not just live vs "dead" that dictates duration of efficacy.

The measles virus, and the attenuated live virus used in the measles vaccine, are enveloped, single-stranded RNA viruses. Unlike many RNA viruses, the measles virus and attenuated live virus are extremely stable, eliminating the need for periodic vaccine modifications as required for influenza and COVID. The attenuated live virus has multiple sequence differences from the native measles virus, resulting in decreased replication in immune cells, but the full explanation for its decreased pathogenicity and lasting immunity is not known.

The durability of immunity following natural infection with measles, and of the usually self-limited but occasionally severe general immunosuppression associated with acute infection (immune amnesia), may be based in the life cycle of the infecting virus. Initial infection is mediated by uptake of the virus by several different receptors into immune cells, first in the airways, including T and B lymphocytes, dendritic cells, and activated monocytes, some of which will transport the virus to lymph nodes around the body. Humoral and cell-mediated immunity are stimulated, and the prolonged presence of virus may drive the maturation of the specific humoral response while at the same time causing suppression of both delayed hypersensitivity to recall antigens and humoral responses to preexisting nonmeasles antigens.[7] This "immune amnesia" may last several years and predispose affected patients to other infections, a contributor to the morbidity of measles infection. Interestingly, the attenuated measles vaccine does not induce this immunosuppression,[8] possibly due to decreased infection of immune cells compared with the natural measles virus.[9]

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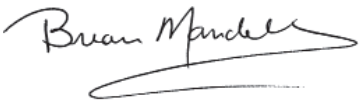
The long-lasting antimeasles immunoglobulin G antibody response is protective against reinfection, while the cell-mediated antivirus response is required to abrogate the active infection. The measles virus invades and replicates in airway columnar epithelial cells, resulting in desquamation of cells into the airway, which permits spreading of the virions and virus-infected cells through coughing and sneezing.

At present, there is no available potent antiviral treatment for measles. Given the durable efficacy of the available attenuated live measles vaccine and the lack of any nonhuman host or environmental reservoir, eradication of this disease is a potential reality.

For those interested in reading a well-referenced overview of the measles virus, I'd suggest looking at a paper by Moss and Griffin.[10]



Brian F. Mandell, MD, PhD
Editor in Chief

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In defense of the anion gap

To the Editor: In the March issue, Dr. Rodriguez Alvarez and colleagues[1] reviewed the recent update to the American Diabetes Association consensus report on hyperglycemic crises in adults with diabetes.[2] I believe the 2024 consensus report's marginalization of the anion gap, as summarized by Rodriguez Alvarez et al, is shortsighted and incorrect.

Serum electrolyte assays generally calculate and report an anion gap or delta as a "free" parameter. I certainly agree that quantitation of serum beta-hydroxybutyrate levels is much more specific and diagnostic of ketoacidosis than the anion gap. However, the anion gap still provides important clues to potentially missed, and clinically significant, disorders. Many recent reports and series describe the not uncommon scenario of diabetic ketoacidosis combined with vomiting-induced metabolic alkalosis (especially in cannabis users). These patients may present with minimal acidemia, or even alkalemia. The very large anion gap is a major clue to this mixed disorder. A large anion gap, despite a relatively unimpressive serum beta-hydroxybutyrate level, suggests that another complicating acidosis, such as lactic acidosis or a toxic alcohol ingestion–related acidosis, coexists with diabetic ketoacidosis.

The astute clinician must use all the clinical and laboratory information that is available, and the anion gap remains a very helpful parameter when confronted with a patient experiencing a hyperglycemic crisis. As a coauthor of the UpToDate chapters on hyperglycemic crises, I continue to advise clinicians to always include the anion gap in their diagnostic and therapeutic game plan.

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doi:10.3949/ccjm.92c.05001

In Reply: We thank Dr. Emmett for his interest in our article[1] and his thoughtful comments regarding the exclusion of the anion gap as a diagnostic, severity, and resolution criterion for diabetic ketoacidosis.[2]

We would like to clarify that, in our view, the anion gap remains a fundamental tool in the evaluation of any patient with metabolic acidosis, including its correction for serum albumin and the calculation of the delta anion gap/delta bicarbonate ratio. Its exclusion from the diagnostic criteria for diabetic ketoacidosis should not in any way be interpreted as discouragement of its use in acid–base assessment.

Although the rationale behind this decision is not clear to us from the text of the consensus report,[2] we believe it may be related to the observation that indirect or potential bicarbonate losses may eventually become the dominant mechanism of acidosis in diabetic ketoacidosis,[3] potentially reducing the anion gap's diagnostic accuracy. Moreover, because the anion gap is most useful when a baseline value is available, its negative predictive value may be limited in the absence of this value.

Nevertheless, Dr. Emmett rightly highlights an important subgroup of patients who present with hyperglycemia, severe ketonemia, metabolic acidosis, and a commonly coexisting metabolic alkalosis (due to volume contraction, vomiting, or both). In these cases, overt acidemia may be absent, and some patients may even exhibit alkalemia, a scenario described as "diabetic ketoalkalosis."[4] As a result, they may not meet the A (acidosis) criterion of diabetic ketoacidosis (pH < 7.3, bicarbonate < 18 mmol/L, or both),[2] and an elevated anion gap may be the only diagnostic clue. In a retrospective study, of 157 patients presenting to the emergency department with hyperglycemia, elevated anion gap, and beta-hydroxybutyrate of 3 mmol/L or greater, 30.2% did not meet the pH or bicarbonate thresholds for the A criterion, underscoring the frequency of this presentation.[5]

In summary, we concur with Dr. Emmett that excluding the anion gap from the diagnostic criteria for diabetic ketoacidosis may pose challenges, and we believe it could have been retained as an alternative component within the A criterion for diagnosis. However, we can appreciate the rationale behind its removal from the severity and resolution criteria in favor of including beta-hydroxybutyrate levels. Ketonemia is the hallmark of diabetic ketoacidosis, and beta-hydroxybutyrate is its principal and most specific biochemical marker.

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Tinea incognito

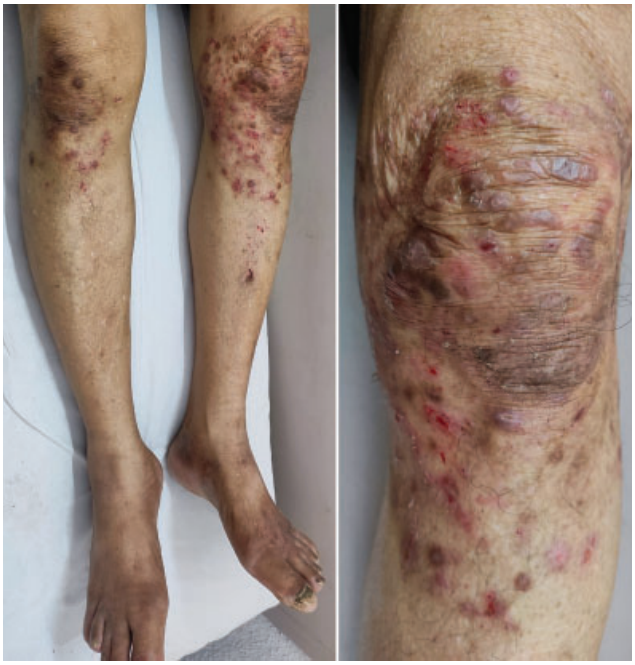

Figure 1. Erythematous plaques with discontinuous annular borders and scaling on both knees, and a close-up view of the plaque on the left knee.

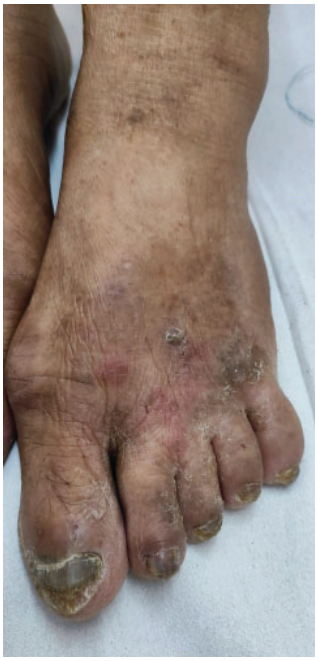

Figure 2. Ill-defined scaly plaque on the left foot with nail changes, including discoloration.

A 57-year-old man with a 20-year history of type 2 diabetes mellitus presented with a 1-year history of itchy rashes on both knees. He reported trying to treat the rashes with over-the-counter topical steroids on and off for the preceding 6 months.

Physical examination revealed well- to ill-defined erythematous plaques with overlying papules and pustules in an annular pattern on both knees (**Figure 1**). Yellow-black discoloration, distal onycholysis, and dystrophy was noted on all of his toenails (**Figure 2**). Microscopic study of a potassium hydroxide preparation of scrapings from the active borders of the lesions on his knee was positive for dermatophytes.

doi:10.3949/ccjm.92a.24099

Based on the clinical features, history of steroid use, and positive potassium hydroxide mount, a diagnosis of tinea incognito was made. The patient was treated with oral itraconazole 200 mg daily for 1 month and luliconazole cream for 2 months, resulting in clinical improvement.

ABOUT TINEA INCOGNITO

Tinea incognito is an atypical form of dermatophyte infection that results from local immune suppression from systemic or topical corticosteroids. Clinically, the lesions lack the well-defined border, central clearing, and scaling classically associated with dermatophytosis. Use of corticosteroids may further suppress

inflammatory signs, making tinea incognito lesions appear less erythematous.

Trichophyton rubrum is the most common causative organism, followed by *Trichophyton mentagrophytes* and *Epidermophyton floccosum*.[1] Extensive atypical and drug-resistant cases have been reported due to *Trichophyton indotineae*.

Majocchi granuloma is a rare form of deep fungal folliculitis that occurs in longstanding dermatophytosis and is characterized by perifollicular papules, pustules, or nodules, often appearing within an erythematous plaque on the extremities or face.[2] Although the presence of follicular papules and pustules in our patient could indicate progression to Majocchi granuloma, a conclusive diagnosis of this condition can be made only through histopathology. Areas of atrophy within the lesion may be seen due to chronic corticosteroid use.

Given the varied clinical presentations of tinea incognito, a broad differential diagnosis is essential, as it may mimic conditions such as eczema, psoriasis, lichenoid dermatitis, or blistering diseases.[1]

Diagnosis and treatment

The 2 key issues in managing tinea incognito are proper diagnosis and prevention. Diagnosis can be delayed because of the atypical appearance of the lesions, but careful examination for scaly erythematous edges aids in identification. Although newer diagnostic modalities such as dermoscopy and confocal laser scanning microscopy have become available, a potassium hydroxide mount remains an important modality for providing evidence of dermatophyte infection.[3] A fungal culture should be ordered in chronic or recurrent dermatophytosis and in cases where antifungal resistance is suspected. Emerging tools like polymerase chain reaction and matrix-assisted laser desorption ionization–time-of-flight mass spectrometry offer greater sensitivity.[3]

Treatment modalities include promptly stopping steroid use and starting topical and oral antifungals. For mild or localized tinea infections, topical antifungals like terbinafine, clotrimazole, and miconazole are the first line of treatment, applied twice daily for several weeks.[3] For severe or widespread infections, or those involving hair-bearing areas including Majocchi granuloma, oral antifungals such as terbinafine, itraconazole, or fluconazole are preferred, with treatment typically lasting several weeks to months, depending on the severity and response. Longer duration of treatment with itraconazole is required in drug-resistant cases.[4]

THE BOTTOM LINE

Diagnosing tinea incognito can be challenging due to its nonspecific clinical presentation. Poor response to prolonged steroid use, followed by a rebound increase in erythema, papules, and scaling when steroids are discontinued should prompt a reassessment of the diagnosis. It is essential for clinicians to recognize that tinea incognito can mimic other skin conditions and to have a low threshold for performing a potassium hydroxide mount in suspected cases, especially if topical steroids are the planned treatment.

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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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What diagnostic tests should be done after discovering clubbing in a patient without cardiopulmonary symptoms?

*A 50-year-old woman presents with bilateral ankle and knee swelling along with morning stiffness in both knees for the past several months. She has a remote 15-pack-year smoking history and began using electronic cigarettes 2 years ago but denies cough, shortness of breath, or orthopnea. She has no known cardiac or pulmonary diseases. Vital signs are normal. Physical examination is significant for swelling of her ankles without warmth or redness. Bilateral fingernail clubbing is noted (**Figure 1**). Given that clubbing is detected on examination, should chest imaging be obtained despite an absence of cardiopulmonary symptoms? Are any other evaluations indicated?*

A: Computed tomography of the chest is indicated based on the robust association of clubbing with intrathoracic malignancy. Chest computed tomography would also evaluate for other intrathoracic conditions associated with clubbing, including interstitial lung disease.[1] In addition, this patient's ankle swelling and knee stiffness could represent hypertrophic osteoarthropathy, and radiographs of the tibia, fibula, and ankle joints are indicated. If the radiographs do not show corroborating periosteal bone formation, bone scintigraphy should be considered, as it is more sensitive in detecting these changes.

DETECTING CLUBBING ON EXAMINATION

Most clinicians can detect advanced clubbing. However, older studies suggest that the precision and interrater reliability of the physical examination for clubbing is fair to moderate at best.[2] Clubbing, unlike other examination findings such as ascites or splenomegaly, does not have a gold standard radiographic correlate to validate against. Instead, it depends on careful observation of changes to the depth of the distal phalanx and altered nail-fold angles. In the past, plaster casts, shadowgraphs, and calipers were used to obtain the quantitative measurements that define clubbing.[2]

Different views of our patient's fingernails are presented in **Figure 1**. Early clubbing can be difficult to identify from a superior view (**Figure 1A**). The changes that define clubbing are easier to discern on profile view (**Figure 1B**). In our clinical experience, measurement of the distal phalanx depths has higher reproducibility and interrater reliability than an estimation of nail-fold angles (**Figure 1C**).

Distal phalanx depth

If the depth of the digit is larger at the nail fold than at the distal interphalangeal joint, clubbing is present. This is easier to observe from a side view, or profile view, rather than a superior view, as seen in our patient.

Nail-fold angles

The *hyponychial angle* is formed by the intersection of lines drawn from the back surface of the distal interphalangeal joint to the proximal nail fold and from the proximal nail fold to the hyponychium (skin under end of nail plate). This angle is typically a straight line (180 degrees) in a normal finger. If the hyponychium is below the line drawn from the distal interphalangeal joint to the proximal nail fold, the hyponychial angle is greater than 180 degrees, which suggests clubbing.

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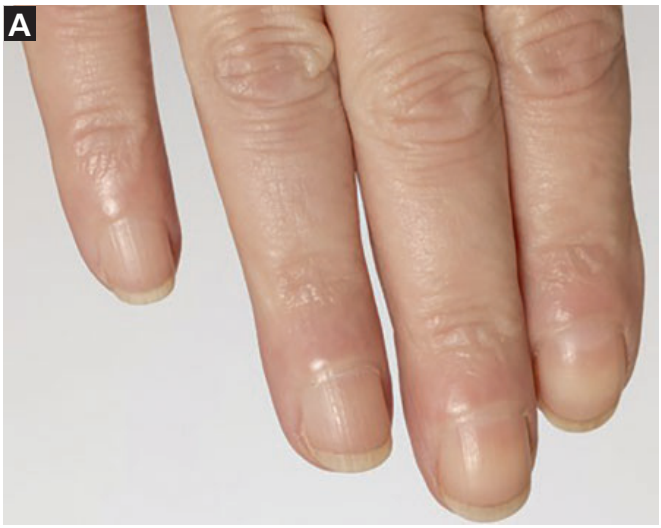

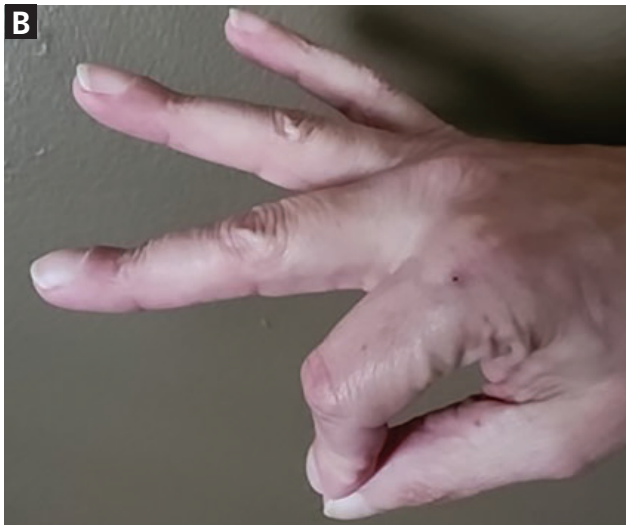

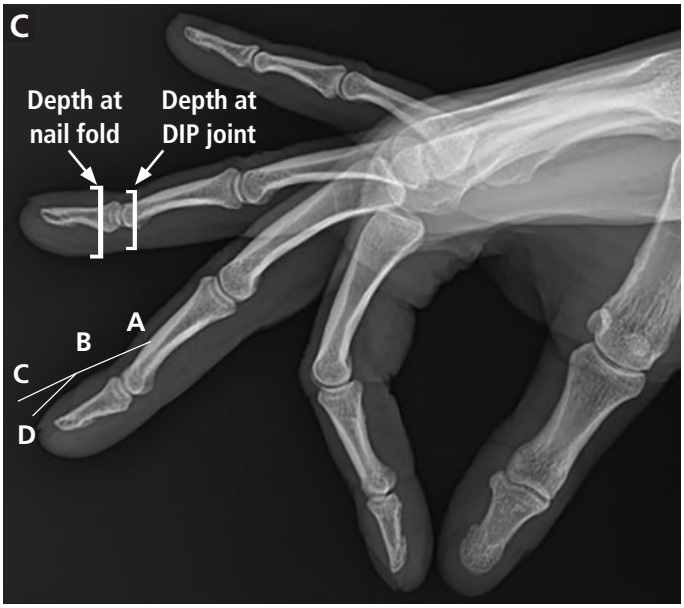

Figure 1. Views of the patient's fingers and fingernails. (A) Superior view of early clubbing. (B) Profile view of early clubbing. (C) The depth at the nail fold is greater than the depth at the distal interphalangeal joint (DIP), which confirms the presence of clubbing. Point D (the *hyponychium*) is lower than the extension of line AB created from the DIP joint to the nail fold. This angle ABD (*hyponychial angle*) is greater than 180 degrees, also confirming clubbing. The profile angle (or the *Lovibond angle*) is visually the hardest to estimate. This angle, formed by ABC, is also greater than 180 degrees, which would prevent a diamond-shaped window from appearing when this digit is opposed nail-to-nail with the corresponding digit on the opposite hand with angle ABC greater than 180 degrees (*Schamroth sign*).

The *profile angle*, also known as the *Lovibond angle*, is the angle at which the nail exits the nail fold. It is typically harder to estimate on examination. Normal fingernails placed back-to-back with the opposing nails create a diamond-shaped window. In clubbed nails, this window is not present due to the increase in the profile angle—referred to as a positive Schamroth sign.

In addition to visual inspection, distal phalanx depth can be assessed by palpating the distal interphalangeal joint with the examiner's thumb and index finger and subsequently sliding the fingers distally. If the examiner perceives an increase in the space between the thumb and index finger, then clubbing is present.

THE RELATIONSHIP OF CLUBBING TO HYPERTROPHIC OSTEOARTHROPATHY

Clubbing can sometimes occur as part of a triad of symptoms that comprise hypertrophic osteoarthropathy, a systemic syndrome. Hypertrophic osteoarthropathy has 3 manifestations: clubbing, synovial effusions, and periosteal bone formation in tubular bones including the radius, ulna, tibia, and fibula.[3] Formal diagnostic criteria require the presence of clubbing combined with radiographic evidence of periosteal bone formation in tubular bones. In other words, all patients with hypertrophic osteoarthropathy have clubbing, but only a small percentage of patients with clubbing

have hypertrophic osteoarthropathy. Some patients with hypertrophic osteoarthropathy may report deep-seated, severe bone pain most prominently in the lower extremities along with joint swelling, while others do not experience pain and may not even be aware of the clubbing changes in their fingernails.[3]

Laboratory testing and imaging studies

Current hypotheses on the pathogenesis of clubbing implicate cytokines such as transforming growth factor beta, platelet-derived growth factors from megakaryocytes, and vascular endothelial growth factor.[4] Currently, levels of these cytokines or bone turnover markers like alkaline phosphatase are not used to diagnose hypertrophic osteoarthropathy. If a patient with clubbing has bone pain or swelling, plain radiography of the bones suspected to be involved is indicated. If periosteal bone formation is not found and suspicion for hypertrophic osteoarthropathy remains high, bone scintigraphy should be considered as it is extremely sensitive in finding changes seen in hypertrophic osteoarthropathy.[5]

Plain radiographs of bones in patients with both clubbing and bone-related symptoms help establish the diagnosis of hypertrophic osteoarthropathy and exclude other causes of bone-related symptoms, such as metastasis. This can also guide symptomatic management, such as bisphosphonate therapy for hypertrophic osteoarthropathy–related bone pain. However, we do not suggest routine use of plain radiographs of long bones in patients with clubbing who do not have bone-related symptoms, because, in the absence of these symptoms, it is not known if there is a clinically actionable difference between patients who have clubbing only compared with patients who have clubbing as well as asymptomatic radiographic changes of hypertrophic osteoarthropathy.

DISEASES ASSOCIATED WITH CLUBBING

Hypertrophic osteoarthropathy can occur as a primary disease or secondary to other disease processes.[5] Primary hypertrophic osteoarthropathy is a rare inherited condition that manifests with clubbing, skin changes such as progressive thickening and furrowing wrinkling of skin on the forehead and hyperhidrosis, and periosteal bone formation. Secondary hypertrophic osteoarthropathy is much more common, comprising 95% to 97% of cases.

Clubbing observed on only 1 hand is commonly associated with hemiplegia or a local vascular disease, such as dialysis fistulas or arterial aneurysms.[1] Bilateral clubbing is associated with an extensive list of diseases, with intrathoracic disease, including lung cancer as a paraneoplastic phenomenon, being the most common.[5] It should be noted that, although paraneoplastic syndromes are more common in small cell lung carcinoma than in non–small cell lung carcinoma, non–small cell lung carcinoma is more commonly linked with clubbing. Specifically, clubbing is observed in approximately 35% of patients with non–small cell lung carcinoma vs 4% of patients with small cell lung carcinoma.[1]

Other intrathoracic causes include the following[1,2,5]:

- Metastatic lung nodules
- Interstitial lung disease
- Bronchiectasis
- Chronic mycobacterial or fungal infection
- Cyanotic congenital heart disease
- Infective endocarditis
- Esophageal carcinoma.

Extrathoracic diseases associated with bilateral clubbing include cirrhosis, inflammatory bowel disease, celiac disease, and thyroid acropachy.

Notably, chronic obstructive pulmonary disease is not associated with clubbing, but it is itself an independent risk factor for primary lung cancer, which is strongly associated with clubbing. More than 90% of cases of secondary hypertrophic osteoarthropathy are associated with malignancies or other chronic pulmonary diseases.[6]

SEARCHING FOR THE CAUSE OF CLUBBING

If the clubbing, within or outside the context of hypertrophic osteoarthropathy, is new, bilateral, and asymptomatic, we recommend chest computed tomography because of the strong association between clubbing and lung malignancy or chronic lung disease.[6] If access to chest computed tomography is delayed, chest radiography can be done, bearing in mind that chest computed tomography has higher sensitivity (93.8% vs 73.5%) in detecting nodules and malignancy at earlier stages.[7,8] Otherwise, efforts to identify the cause of clubbing should be driven by symptoms and signs. For example, a patient found to have clubbing with symptoms of intermittent bloody diarrhea will require an evaluation for inflammatory bowel disease. If a patient already has a condition known to be associated with clubbing but newly develops clubbing, we still suggest computed tomography of the chest to exclude an emerging intrathoracic malignancy. **Figure 2** presents our suggested approach to the evaluation of clubbing.

Computed tomography of our patient's chest showed a necrotic mass in the apical right lung. Pathology revealed lung adenocarcinoma. Plain radiographs of the tibia and fibula showed bilateral periosteal new bone with cortical thickening. Nuclear bone scan showed radiotracer uptake involving the tibial and fibular cortices, corresponding to periosteal bone formation. Both

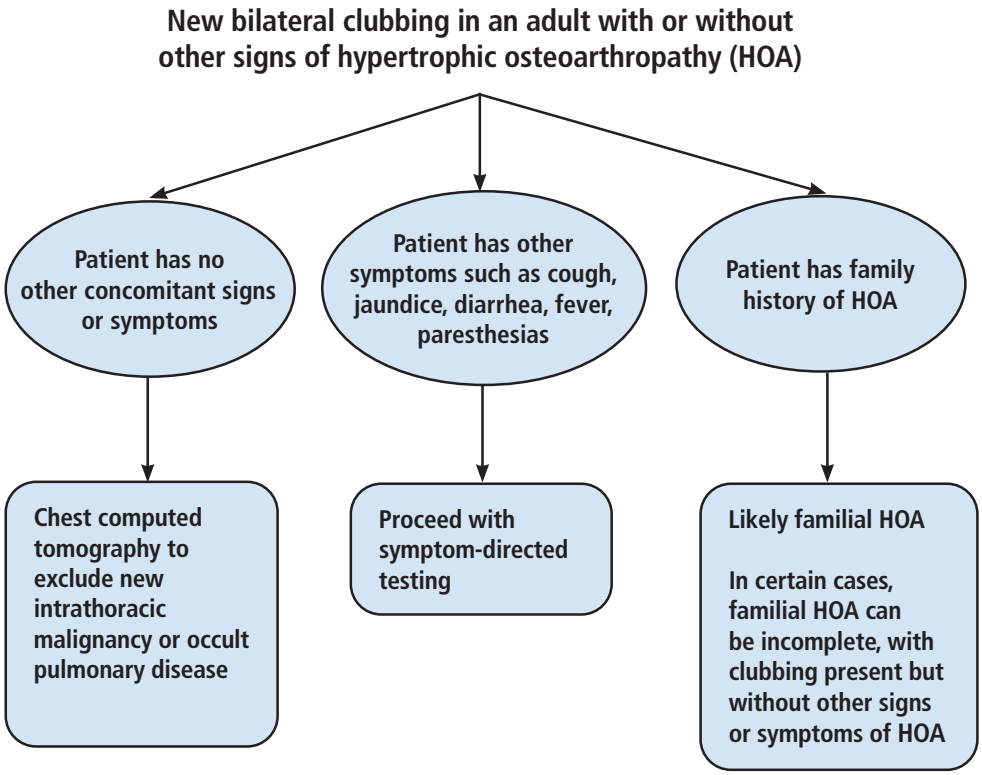

Figure 2. Suggested approach to evaluation of bilateral clubbing.

the plain radiographs and the nuclear bone scan confirmed the presence of hypertrophic osteoarthropathy.

THE BOTTOM LINE

If the presence of clubbing is uncertain, a profile view of the distal phalanx with a focus on the change in depth is more practical than estimation of nail-fold angles. If the depth increases from the distal interphalangeal joint to the nail fold, clubbing is present. If leg or wrist pain with swelling is present, plain radiographs with or without bone scintigraphy are indicated to diagnose hypertrophic osteoarthropathy. All 3 features of hypertrophic osteoarthropathy (clubbing, periosteal bone formation, synovitis) are not always present. Aggressive evaluation of new, asymptomatic bilateral clubbing with or without hypertrophic osteoarthropathy presents an opportunity to diagnose malignancy earlier. We suggest chest computed tomography as the first step in searching for the cause, even in patients without cardiopulmonary symptoms.

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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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Does my adult patient need a measles vaccine?

A: Possibly. Two doses of the measles-mumps-rubella (MMR) vaccine are recommended for children.[1] Many adults (≥ 19 years) have preexisting immunity to measles from prior infection or vaccination. Adults without acceptable presumptive evidence of immunity to measles are recommended to receive 1 dose of MMR. Two doses of MMR are recommended for adults in special situations.[1]

Measles was eliminated from the United States in 2000.[2] However, communities with reduced vaccination rates remain vulnerable to measles infection or outbreaks. As of April 18, a total of 800 confirmed measles cases have been reported in the United States this year,[3] exceeding the 285 cases reported in all of 2024. The rising number of measles cases has garnered public attention and highlights the importance of vaccination in children and adults.

MEASLES ELIMINATION IN THE UNITED STATES

Before a vaccine became available, measles was considered a routine childhood illness and nearly everyone was infected by adulthood.[2] About 500,000 measles infections were reported annually, although the US Centers for Disease Control and Prevention (CDC) estimates that the actual number of cases was much higher at 3 to 4 million per year.[2,4] Annually, there were an estimated 48,000 hospitalizations, 1,000 cases of encephalitis, and 400 to 500 deaths attributed to measles. With the development and approval of a measles vaccine in 1963, a national vaccine campaign was launched, leading to the elimination of measles in the United States several decades later.[2,4]

A steep decline in measles cases was observed after a single-dose measles vaccine for infants was introduced. By the 1980s, annual reported cases of measles dropped below 4,000, but outbreaks continued to occur in vaccinated school-age children.[2,3] To address the potential for primary vaccine failure (ie, failure to produce protective antibodies after vaccination), the CDC recommended a second dose of measles vaccine before school entry starting in 1989.[2] After high measles vaccination rates were achieved and maintained in preschool- and school-age children, measles was declared to be eliminated from the United States in 2000.[2]

MEASLES EPIDEMIOLOGY IN THE POSTELIMINATION ERA

Since measles elimination, isolated cases and small outbreaks have occurred, but these have been traced to sources originating outside the United States. These outbreaks have historically been contained because vaccination rates among school-age children met or exceeded the threshold for herd immunity (95%), halting the chain of transmission.[5] Because measles is one of the most contagious diseases in the world—1 person with measles will infect 90% of susceptible contacts—outbreaks are hard to contain in predominantly unvaccinated communities.[4]

Disruptions in routine healthcare during the COVID-19 pandemic paired with an increasing prevalence of vaccine hesitancy have negatively impacted measles vaccination rates. In 2024, the national 2-dose MMR vaccination rate in school-age children was 92.7%, and state vaccination rates varied widely, ranging from 79.6% in Idaho to 98.3% in West Virginia.[6] The United States is increasingly vulnerable to larger-scale measles outbreaks as vaccination rates decline.

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CURRENT RECOMMENDATIONS FOR MEASLES VACCINATION IN THE UNITED STATES

The live attenuated measles vaccine is highly effective in preventing measles infection by inducing both cell-mediated and humoral immunity.[7,8] Because cell-mediated immunity is challenging to measure and interpret, humoral immunity (measles-specific immunoglobulin [Ig] G) is used to assess response in the clinical setting. With 1 dose of live attenuated measles vaccine, 96% of recipients will seroconvert to measles IgG positive, and nearly 100% will seroconvert with 2 doses.[7]

The live attenuated measles vaccine is considered to provide lifelong immunity when administered to children at age 12 months or older.[7] Long-term studies demonstrate persistence of measles IgG for at least 11 years following 1 dose, and at least 15 years following 2 doses.[7,8] In people with waning or low-level measles IgG in the years following vaccination, protection is maintained due to cell-mediated immunity and an anamnestic immune response following subsequent measles exposure.[7–9] While secondary vaccine failure (ie, measles infection in a vaccine responder) is possible, it is exceedingly rare (< 0.2%) regardless of whether 1 or 2 doses are administered.[9] Given the overall low incidence of measles infection in the United States, serologic screening to identify the 4% of adults who do not seroconvert after 1 dose of a live attenutated measles vaccine is unlikely to provide an incremental benefit.

The combination live attenuated MMR vaccine is used in place of single-antigen component vaccines in the United States. MMR vaccine may be given on the same day with other injectable or intranasal live virus vaccines (eg, varicella). If administered on separate days, a minimum 28-day interval is required to prevent interference with the immune response.[10] When MMR vaccination is administered as a 2-dose series, the minimum interval between doses is also 28 days.

Children

The MMR vaccine is recommended as a routine childhood vaccination.[1,7] All children should receive 2 doses prior to school entry—the first dose at 12 months and the second dose between 4 and 6 years. The second dose may be given at an earlier age, spaced at least 28 days from the first dose.

Adults

Many adults have preexisting immunity to measles from previous infection or vaccination. Adults who meet at least 1 of the following 4 criteria are considered to have acceptable presumptive evidence of measles immunity[7]:

Born before 1957. Because of the high prevalence of measles in the prevaccine era, up to 98% of adults born before 1957 are immune to measles. However, healthcare personnel born before 1957 are excluded from this criterion and should have documentation of adequate measles vaccination or laboratory evidence of immunity to prevent disease transmission in healthcare settings.

Documentation of adequate measles vaccination after 12 months of age. For most adults, adequate vaccination is defined as written documentation of 1 dose of a live measles virus–containing vaccine. For certain adults, 2 doses are needed (see "Special situations" below). Adults who received the inactivated measles vaccine (licensed 1963 to 1968) or measles vaccine of unknown type or who do not have written documentation of vaccination do not meet this criterion.

Laboratory evidence of immunity. Adults who test positive for measles IgG on serologic testing are considered immune to measles. Adults with a negative or equivocal serologic test should be considered nonimmune, unless they meet 1 of the other criteria for presumptive evidence of immunity to measles (eg, born before 1957, documentation of adequate measles vaccination, or laboratory confirmation of disease).

Laboratory confirmation of disease. Given the extremely low incidence of measles in the United States, the validity of a clinical measles diagnosis should be questioned. Only documentation of laboratory-confirmed disease (eg, nasopharyngeal measles polymerase chain reaction) should be accepted as presumptive evidence of immunity to measles.

Adults born in or after 1957 who do not meet at least 1 of the criteria for acceptable presumptive evidence of immunity to measles should receive 1 dose of MMR vaccine.[1,7] Adults recommended to receive 2 doses are described below. Adults born before 1957 are presumed to be immune to measles, but 1 dose of MMR vaccine can be administered if the patient requests it.

Special situations

International travel. Infants 6 to 11 months should receive 1 dose of MMR vaccine before international travel and then also receive 2 doses after age 12 months (1 dose after 12 months and a second dose at 4 to 6 years).[1,7]

For children older than 12 months and for adults who do not have acceptable presumptive evidence of

immunity to measles, completion of the 2-dose MMR series is recommended before international travel.[1,7]

Adult 2-dose MMR vaccination. Adults who do not have acceptable presumptive evidence of immunity to measles should receive 2 doses of MMR vaccine in the following scenarios[1,7]:

- Household or close contacts of immunocompromised people
- People living with human immunodeficiency virus (if CD4 count ≥ 200 lymphocytes/mm^3 and CD4 percentage ≥ 15% for > 6 months)
- Healthcare personnel born before or after 1957
- People who will be traveling internationally.

Outbreaks. During a measles outbreak, state and local health departments will identify those at risk for exposure based on the epidemiology of the outbreak (ie, if a specific age group or community is affected) and confirm adequate vaccination or other acceptable presumptive evidence of immunity to measles. Healthcare providers should continue to follow the routine recommendations for MMR vaccination, unless additional guidance is provided by public health officials. In general, "booster" doses of the MMR vaccine are not recommended for adults meeting at least 1 criterion for acceptable presumptive evidence of immunity to measles. Infants 6 to 11 months should be vaccinated only in response to a measles outbreak if recommended by public health officials.[7]

Serologic screening

Serologic screening is not recommended for people with at least 1 criterion for acceptable presumptive evidence of immunity to measles. In fact, documentation of adequate measles vaccination supersedes the results of postvaccination serologic testing,[7] because serologic testing after vaccination is more likely to reflect waning humoral immunity than primary vaccine failure in an adult with a remote history of vaccination.

Prevaccination serologic screening can be considered, but is not required, in adults who do not have presumptive evidence of immunity to measles. For example, a clinician may test for measles IgG in adults vaccinated between 1963 and 1968 who may have received the inactivated measles vaccine, and then administer the MMR vaccine to those who test negative. Or clinicians may choose to administer MMR vaccine to all patients in this scenario, without measles IgG testing.

Detailed information on indications for the MMR vaccine specific to people who are not immune to rubella or mumps can be found on the CDC's Adult Immunization schedule.[1]

Contraindications to MMR vaccine

Allergy. The MMR vaccine is contraindicated in people with a history of severe or anaphylactic allergy to the vaccine or a component, including neomycin. Patients with a history of nonsevere allergy to neomycin (eg, contact dermatitis) can receive the vaccine, and it is safe to administer the vaccine to patients with egg allergy, regardless of allergy severity.[7]

Pregnancy. MMR vaccine is contraindicated in people who are pregnant or trying to become pregnant due to the theoretical risk of vaccine-induced congenital rubella syndrome. Women should be counseled to avoid becoming pregnant for 28 days after vaccination.[7]

Immunosuppression. MMR vaccine is contraindicated for individuals with immunocompromising conditions or those who are receiving immunosuppressive medications, as there have been case reports of vaccine-induced infection.[7] For a detailed list of immunocompromising conditions and therapies, refer to the altered immunocompetence section of the CDC's General Best Practices for Immunization.[10]

MMR vaccine can be administered safely to children or close personal contacts of people who are pregnant or immunocompromised.[7]

Adverse reactions to MMR vaccine

MMR vaccine is typically well tolerated; the most common reactions reported in adults are fever (< 15%), transient rash (5%), and lymphadenopathy (20%).[7] In children, the vaccine is associated with a small risk of febrile seizures (1 case per 3,000 to 4,000 doses). In postpubertal females who are not immune to rubella, MMR vaccine is associated with a 25% incidence of mild arthritis-like symptoms, which present 1 to 3 weeks after vaccination and persist for an average of 2 days.[7]

DISCLOSURES

Dr. Rivard has disclosed serving as an advisor or review panel participant for Pfizer.

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Do I need to treat supine hypertension in my hospitalized patient?

My 68-year-old patient is hospitalized for treatment of community-acquired pneumonia. There is no history of hypertension, but at a 2 AM check of vital signs, the patient's supine blood pressure (BP) was 178/96 mm Hg. Heart rate is 68 beats per minute, respiratory rate 16 breaths per minute, and oxygen saturation 96% on oxygen delivered by nasal cannula at 2 L per minute. There is no evidence of acute end-organ damage. Do I need to treat this patient's elevated BP?

A: In this hospitalized patient, antihypertensive treatment should not be considered without evaluating for changes in the orthostatic BP.

Inpatients' vital signs are most commonly checked with the patient supine at various degrees of head-of-bed elevation, despite guidelines recommending against this technique (**Table 1**).[1,2] A study showed that 50% to 70% of inpatients have at least 1 elevated BP measurement (> 140/90 mm Hg) during their hospitalization.[3] Several aspects of elevated supine BP should be considered.

In the nonacute setting, BP measurement done in the supine and seated positions gives small but statistically different readings, with diastolic BP 5 mm Hg higher in the seated position and systolic BP 8 mm Hg higher in the supine position.[1] In the hospital setting, several factors not associated with long-term consequences may cause elevated BP. These elevations have been termed *reactive* rather than significant.[4,5] Most important, the hospitalized patient should be evaluated for orthostatic changes before treatment is considered.

A sequence of steps is appropriate for our patient with supine pressure of 178/96 mm Hg:

- Confirm the pressure in the seated position
- If BP elevation is confirmed, then determine whether the patient has a preexisting diagnosis of hypertension and is receiving pharmacologic treatment; if the patient is already being treated for hypertension, then in-hospital intravenous treatment or intensification of the oral regimen is associated with more adverse events and worse outcomes[4,5]
- If the patient is not being treated, the elevated value should be noted and follow-up guided by standard recommendations[2]
- The absence of acute end-organ damage should also be noted (eg, no evidence of acute coronary syndrome, aortic dissection, pulmonary edema, hypertensive encephalopathy, ischemic stroke, or intracranial hemorrhage).

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WHAT IS ORTHOSTATIC HYPOTENSION?

Orthostatic hypotension is sustained reduction of systolic BP of 20 mm Hg or more or diastolic BP of 10 mm Hg or more, or both, within 3 minutes of standing.[6] In the standing position, blood pools in gravity-dependent body compartments, resulting in reduced venous return, cardiac output, and BP. In healthy patients, these posture-induced hemodynamic alterations precipitate compensatory sympathetic activation to increase peripheral vascular resistance and cardiac output.[6,7]

Orthostatic hypotension may be neurogenic or nonneurogenic; the former is associated with greater morbidity and mortality.[6] Neurogenic orthostatic hypotension is often present in patients with dysfunction of the compensatory autonomic reaction. Reflexive increases in sympathetic neurocirculatory tone in these patients fail to compensate for decreased venous return to the heart, and, as a result, the postural response of the heart rate is insufficient to maintain BP.[6,7]

TABLE 1
Criteria for blood pressure (BP) measurement

Measurement steps	Criteria
Patient preparation	The patient should avoid exercise or consuming caffeine, alcohol, or nicotine for at least 30 minutes before measurement
	Ensure the patient has emptied their bladder
	Muscle tension, talking, background noise, pain, and psychological processes (eg, fear, anxiety) may impact BP measurement
Equipment	Use a BP measurement device that has been validated and is calibrated regularly
	Ensure proper cuff size is used, ideally with bladder length that is 80% of arm circumference
Patient position	The patient's back should be supported and legs uncrossed; the patient's arm should be supported
	Remove clothing covering the location of cuff placement; the middle of the cuff should be positioned on the patient's upper arm at the level of the right atrium (midpoint of the sternum)
Number of measurements	Check BP in both arms at the first examination; if there is a consistent interarm difference, use the arm with the higher pressure
	Take a minimum of 2 readings at intervals of at least 1 minute and average them to represent the patient's BP
	If there is > 5 mm Hg difference between the first and second readings, obtain additional readings and average them to represent the patient's BP

Based on information from references 1 and 2.

Neurogenic orthostatic hypotension can often be attributed to age-related degeneration of sympathetic output. It is also prominent in neurodegenerative disorders such as Parkinson disease, multiple system atrophy, and peripheral neuropathic disorders such as diabetes mellitus, amyloidosis, and human immunodeficiency virus infection.[7,8] Conversely, nonneurogenic orthostatic hypotension may be seen in patients with hypovolemia, heart failure, severe venous stasis, and chronic illness with deconditioning, or it may be related to medications.[8,9]

NEXT STEPS: 3 SCENARIOS

No history of hypertension, no confirmed orthostatic hypotension

If the patient does not have a history of hypertension and does not have orthostatic hypotension, the first step is to recheck the patient's BP in the seated position. Causes for reactive BP elevation such as pain, anxiety, urinary retention, or withdrawal from medications or substance use should be considered. Ultimately, achieving complete BP control during an acute hospitalization is not an appropriate goal, and in-hospital BP readings of 140/90 mm Hg or higher should not suffice to label a patient as hypertensive. Indeed, in the absence of acute end-organ damage, treating isolated inpatient hypertension may lead to harm.[4,5] Instead, note the elevated reading and follow current guidelines for detecting high BP in the outpatient setting.[2]

History of hypertension, on medical therapy, no orthostatic hypotension

The benefits of controlling chronic hypertension in the outpatient setting, including reduction in cardiovascular events and mortality, are well defined.[1,2] In the inpatient setting, however, there is little role for intensification of the antihypertensive regimen or use of intravenous agents. In the absence of acute end-organ damage, use of intravenous medications for inpatient BP elevation should be discouraged. Intravenous medications may precipitate sudden drops in BP and have been associated with higher risk of adverse clinical outcomes such as acute kidney injury, cardiac injury, and transfer to an intensive care unit.[5]

There is rarely an indication to intensify an established oral regimen for BP control in the inpatient setting. Observational studies suggest patients discharged with intensification did not experience better BP control in the following year.[4] However, the question of whether to treat elevated BP in the hospital setting

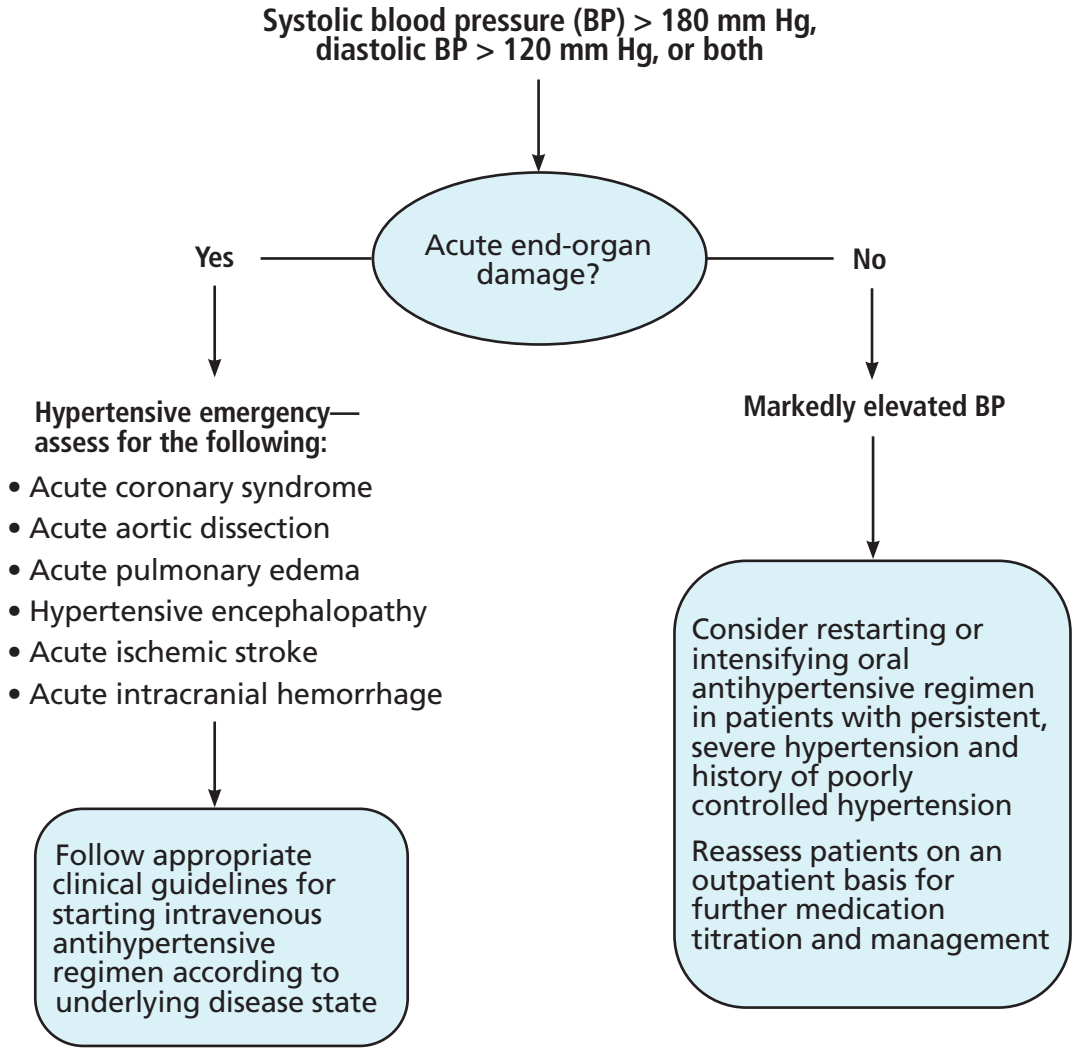

Figure 1. When to consider antihypertensive treatment in the inpatient setting.

Based on information from references 2, 4, and 5.

depends on context. **Figure 1** identifies situations in which inpatient antihypertensive treatment may be warranted.[2,4,5] Regardless, these patients require outpatient BP follow-up.

Supine hypertension, confirmed orthostatic hypotension

In established orthostatic hypotension, the next step is evaluation for reversible causes; the most common are hypovolemia and drug effects.[6] In the absence of reversible causes, the patient should be evaluated for supine hypertension with orthostatic hypotension. This hemodynamic dichotomy poses a unique therapeutic challenge, as pharmacologic treatment to normalize standing BP frequently worsens supine hypertension and vice versa.[7] Patients with autonomic dysfunction often experience supine hypertension because they lack baroreceptor function that buffers changes in BP in both directions.[6] There are no epidemiologic data on the cardiovascular consequences of isolated supine hypertension.[10]

APPROACH TO ISOLATED SUPINE HYPERTENSION

In isolated supine hypertension, BP is elevated at night and often low-normal during the day. Therefore, the

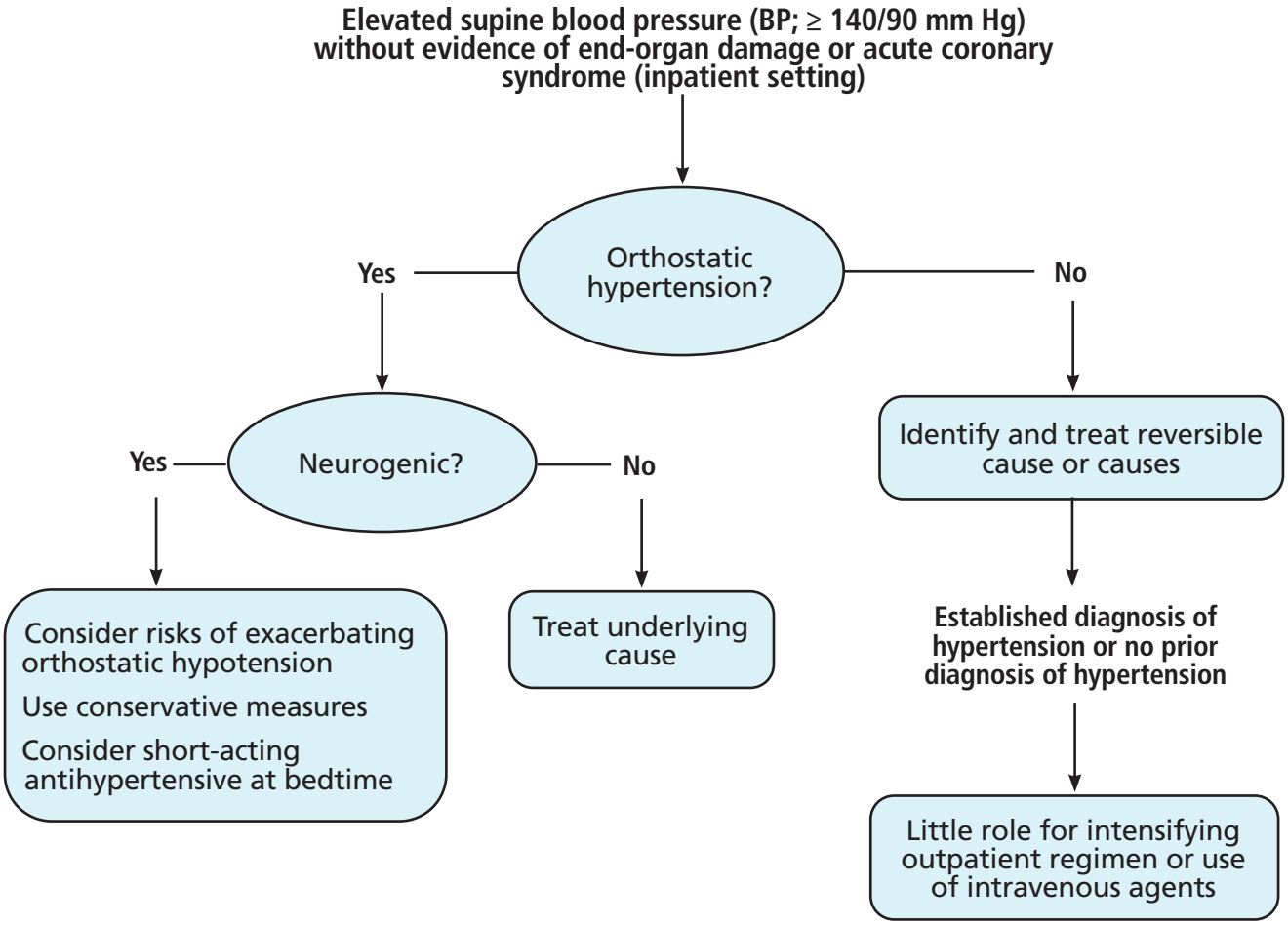

Figure 2. Approach to inpatient with asymptomatic supine hypertension and no evidence of end-organ damage or acute coronary syndrome.

Based on information from references 6–10.

average BP over a 24-hour period may be only moderately elevated, even in patients who have severe supine hypertension. Pharmacologic treatment of supine hypertension may increase fall risk during nocturnal ambulation, as many patients with autonomic insufficiency also experience nocturia. Conversely, emerging studies suggest that supine hypertension may be associated with end-organ dysfunction parameters such as left ventricular hypertrophy, increased arterial stiffness, increased carotid intima-media thickness, and microalbuminuria.[9,10] Ultimately, there is insufficient evidence to assess risk or prognostic impact associated with supine hypertension independently of the associated neurogenic orthostatic hypotension.[9]

Supine BP lower than 180/110 mm Hg in the setting of orthostatic hypotension and in the absence of acute end-organ damage should be monitored, but treatment is not warranted. It may respond to conservative measures, such as small, frequent meals to avoid postprandial hypotension and nocturnal head-of-bed elevation (6–7 cm, or 30 degrees).[9] For recurrent higher BP measurements, clinicians may consider a short-acting antihypertensive agent before bedtime, such as captopril, clonidine, hydralazine, or nitroglycerin patch.[6,8] The potential benefits of antihypertensive medications must be balanced against the risks associated with side effects on a case-by-case basis.

THE BOTTOM LINE

Supine hypertension in a hospitalized patient who is asymptomatic, has no acute end-organ damage, and was admitted with noncardiovascular diagnoses

usually does not require treatment with intravenous agents or intensification of an oral antihypertensive regimen. There is benefit to evaluating for orthostatic hypotension, however, because identifying orthostatic changes can have a major impact on the safety of acute treatment (**Figure 2**).[6–10] Persistently elevated BP in inpatient settings warrants close outpatient follow-up after the patient recovers from their acute illness.

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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New atrial fibrillation guideline: Modify risk, control rhythm, prevent progression

ABSTRACT

The latest (2023) guideline on atrial fibrillation from the American College of Cardiology, American Heart Association, American College of Chest Physicians, and Heart Rhythm Society introduces a new staging system for the disease, emphasizes risk-factor modification, prioritizes rhythm control over rate control, and clarifies which patients should be considered for catheter ablation. It also delves deeper than earlier guidelines into calculations of risk of thrombosis when deciding whether to start anticoagulant therapy.

KEY POINTS

- The new staging system helps to emphasize that atrial fibrillation is a progressive disease that can be prevented or slowed.
- Lifestyle and other risk-factor modifications should be a pillar of therapy. Patients should be encouraged to lose weight if obese, exercise, stop smoking, drink less, and keep their hypertension and diabetes under good control.
- For patients at intermediate risk of thrombosis according to their CHA_2DS_2-VASc score, other scoring systems can help with the decision whether to initiate anticoagulant therapy.
- Early in the disease course, rhythm control should be prioritized over rate control, to maintain sinus rhythm and decrease atrial fibrillation burden.
- Catheter ablation is the first-line treatment for rhythm control in select patients with atrial fibrillation.

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The new (2023) guideline for diagnosing and treating atrial fibrillation from the American College of Cardiology (ACC), American Heart Association (AHA), American College of Chest Physicians, and Heart Rhythm Society[1] has reexamined and reprioritized which treatment options take precedence, highlighting an individualized approach to management. Earlier guidelines were released in 2014[2] and 2019.[3]

See related article, page 297

Atrial fibrillation affects 37.57 million people worldwide, and its prevalence is increasing.[4] It is characterized by disorganized electrical and mechanical activation of the atria and can lead to serious health complications if left undiagnosed or untreated.[5] Notably, atrial fibrillation can lead to ischemic stroke, which can be debilitating and life-threatening. In addition, people with atrial fibrillation and preexisting heart disease face higher morbidity and mortality rates. In a study of 6,432 people, atrial fibrillation was associated with higher risks of dementia (odds ratio 2.25, 95% confidence interval 1.64–3.10) and mild cognitive impairment (odds ratio 1.28, 95% confidence interval 1.04–1.56).[6]

In view of the severe consequences of atrial fibrillation and its growing prevalence, it is crucial to understand the most recent guideline to ensure that patients receive optimal care.

WHO WROTE THE GUIDELINE?

The ACC and AHA Joint Committee on Clinical Practice Guidelines continually reviews,

TABLE 1
Stages of atrial fibrillation

Stage	Description	Explanation
1	At risk of atrial fibrillation	Modifiable risk factors: obesity, lack of fitness, hypertension, sleep apnea, excessive alcohol consumption, diabetes mellitus Nonmodifiable risk factors: genetic factors (eg, variants in *TTN, MYH7, MYH6, LMNA,* and *KCNQ1*), male sex, old age
2	Pre–atrial fibrillation	Structural or electrical conditions that can lead to atrial fibrillation (eg, atrial enlargement, frequent atrial ectopy, short bursts of atrial tachycardia, atrial flutter, heart failure, valve disease, coronary artery disease, hypertrophic cardiomyopathy, neuromuscular disorders, thyroid disease)
3A	Paroxysmal atrial fibrillation	Intermittent and terminating within 7 days of onset
3B	Persistent atrial fibrillation	Continuous and lasting longer than 7 days
3C	Long-standing persistent atrial fibrillation	Continuous and lasting longer than 12 months
3D	Successful atrial fibrillation ablation	Freedom from atrial fibrillation after ablation
4	Permanent atrial fibrillation	Not pursuing further attempts at rhythm control

Based on information from reference 1.

updates, and modifies guideline methodology as new data emerge. The Joint Committee in turn selects writing committee members who have expertise in the subject under review and who reflect the broader cardiovascular community, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives, and clinical practice settings. The writing committee includes cardiologists, electrophysiologists, pharmacists, surgeons, and patient representatives and lay stakeholders. In addition to the writing committee, evidence review committees focus on systematic reviews and literature searches.

The ACC and AHA have strict policies to ensure guidelines are developed without inappropriate influence or bias so that patient care is evidence-based. These guidelines apply to both inpatients and outpatients.

WHAT ARE THE NEW RECOMMENDATIONS?

Four stages of atrial fibrillation

The new guideline[1] keeps the old categories based on the duration of atrial fibrillation (paroxysmal, persistent, long-standing persistent, and permanent), but introduces 4 stages (**Table 1**):

- **Stage 1:** at risk of atrial fibrillation
- **Stage 2:** pre–atrial fibrillation, in which the patient has structural or electrical conditions that further predispose to atrial fibrillation
- **Stage 3A:** paroxysmal atrial fibrillation
- **Stage 3B:** persistent atrial fibrillation
- **Stage 3C:** long-standing persistent atrial fibrillation
- **Stage 3D:** freedom from atrial fibrillation after successful ablation
- **Stage 4:** permanent atrial fibrillation, at which point the patient and clinician have discussed their options and jointly decided not to pursue rhythm control any longer.

Classifying atrial fibrillation by stages drives home the concept that atrial fibrillation is a progressive disease that exists on a spectrum and requires different interventions at different stages. The guideline highlights the variety of strategies used at different stages and emphasizes a holistic and multidisciplinary approach. The new classification emphasizes the importance of early intervention, including prevention, screening, and risk-factor management.

Lifestyle and risk-factor modifications are key

The 2023 guideline[1] makes lifestyle and risk-factor modification 1 of the 3 pillars of atrial fibrillation prevention and treatment. (The other 2 are stroke prevention and symptom management.) Risk factors for atrial fibrillation are well established, and risk-factor modification reduces the risk of new-onset atrial fibrillation and the risk of complications in those who already have atrial fibrillation. Patients who have modifiable or

TABLE 2
Primary prevention of atrial fibrillation

Maintain or achieve a healthy weight
Engage in physical activity
Moderate alcohol consumption or abstain; avoid binge drinking
Stop smoking
Control hypertension
Control hyperglycemia in diabetes

Based on information from reference 1.

TABLE 3
Secondary prevention of atrial fibrillation

Lose weight if overweight or obese, ie, body mass index > 27 kg/m^2
Start a standardized exercise program
Stop smoking
Minimize alcohol consumption or abstain entirely
Optimally control comorbidities including hypertension and diabetes

Based on information from reference 1.

nonmodifiable risk factors for atrial fibrillation are now classified as having stage 1 atrial fibrillation (**Table 1**).[1] Patients with confirmed atrial fibrillation should be counseled on lifestyle and risk-factor modification to prevent progression and adverse outcomes, and those at risk of developing atrial fibrillation should be counseled to prevent its onset.

Primary prevention (**Table 2**)[1] involves counseling patients at risk of developing atrial fibrillation to lose weight if obese, exercise more if sedentary, limit their alcohol consumption to 1 or fewer standard alcoholic drinks per day, stop smoking if they smoke, and control their diabetes mellitus and hypertension if they have these diseases. Controlling hypertension is especially important—it was the leading risk factor for age-standardized atrial fibrillation death in the Global Burden of Disease Study 2017.[4] Cannabis, cocaine, and methamphetamine use also increases the risk of new atrial fibrillation.[7]

For people who already have atrial fibrillation, effective measures to prevent it from progressing (secondary prevention) include weight loss of at least 10% of body weight in overweight or obese patients, moderate-to-vigorous exercise for at least 210 minutes per week, smoking cessation, minimizing or eliminating alcohol consumption, and optimal blood pressure control (**Table 3**).[1,8–11] Both the primary and secondary prevention measures received a class 1 (strong) recommendation.[1]

Interestingly, caffeine abstinence does not prevent episodes of atrial fibrillation, though it may reduce symptoms in patients who report that caffeine triggers or worsens their symptoms.

No studies have found a correlation between good glycemic control and decreased atrial fibrillation burden. Nonetheless, optimization of glycemic control with improvement of hemoglobin A1c by more than 10% before catheter ablation decreased the likelihood of atrial fibrillation recurrence in a study in 298 patients.[12]

The new staging classifications, combined with the knowledge that risk-factor modification can reduce the incidence and worsening of atrial fibrillation, should inspire clinicians to identify patients who are at risk of developing atrial fibrillation (ie, are in stage 1), and give us yet another reason to encourage patients to lose weight, eat healthy, drink less, control their diabetes and hypertension, and stop smoking.

Starting anticoagulation and subsequent evaluation

Every year, patients with atrial fibrillation should be assessed for their risk of thromboembolic events using clinical risk scores such as CHA_2DS_2-VASc, as well as their risk of bleeding (class 1 recommendation).

CHA_2DS_2-VASc is a simple point system: 1 point each for congestive heart failure, hypertension, diabetes, vascular disease, age 65 to 74 years, and female sex; 2 points for age 75 or older; and 2 points for a prior stroke, transient ischemic attack, or thromboembolic event. Thus, possible scores range from 0 to 9. Men with a score of 0 and women with a score of 1 are at low risk and do not need anticoagulation, whereas men with a score of 2 or higher and women with a score of 3 or higher have an annual thromboembolic risk greater than 2% and do need anticoagulation (class 1 recommendation).

But what about patients at intermediate risk, ie, men with a score of 1 and women with a score of 2?

Other risk scores. For patients at intermediate risk, scores other than CHA_2DS_2-VASc can help to stratify their risk further, which can help in shared decision-making regarding anticoagulation. New risk scores such as ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)[13,14] and GARFIELD-AF (Global Anticoagulant Registry in the Field–Atrial Fibrillation)[15] may modestly improve risk discrimination by including variables such as renal disease, dementia, proteinuria, or previous bleeding.

Further risk stratification may assist with shared decision-making, especially for patients at low or intermediate risk with characteristics not accounted for in CHA_2DS_2-VASc. In the new guideline, discussing with patients factors that modify these individual stroke risks, such as extent of blood pressure control, to help in decision-making about starting anticoagulation receives a class 2a (moderate) recommendation.

Left atrial appendage occlusion

Some patients at moderate to high risk of stroke can't receive anticoagulation, and for them, percutaneous placement of a left atrial appendage occlusion device[16–18] has a class 2a recommendation.[1] This is an upgrade from the 2019 guideline,[3] in which these devices received a class 2b (weak) recommendation for this group of patients.

Prioritizing early rhythm control

The guideline recommends trying to achieve sinus rhythm early in the disease course with antiarrhythmic drugs or with catheter ablation to decrease the burden of atrial fibrillation (ie, its frequency and duration).

This is new. For decades, we thought that rate control was as good as rhythm control. Supporting this view, the 2002 Atrial Fibrillation Follow-Up Investigation of Rhythm Management trial[19] found that rhythm control conferred no survival advantage over rate control. The choice between rate and rhythm control, therefore, was based on shared decision-making between patient and clinician, taking into account the patient's age, preference, and symptoms.

More recent data now indicate that rhythm control improves quality of life by reducing symptoms, whereas patients treated with rate control continue to experience symptoms.[20] Rhythm control also decreases symptom burden and all-cause and cardiovascular mortality, stroke, and heart failure hospitalization.[20] Rhythm-control strategies can also reduce the likelihood of atrial fibrillation progression.

Therefore, the new guideline recommends rhythm control in general to reduce the risk of progression (class 2a recommendation) and the risk of dementia or worsening cardiac structural abnormalities (class 2b recommendation), and in patients with the following specific conditions.

Reduced left ventricular function and persistent or high burden of atrial fibrillation. A trial of rhythm control should be recommended to evaluate whether the atrial fibrillation is contributing to reduced left ventricular function. Studies have shown that left ventricular function improves after rhythm control is started in individuals with relatively controlled heart rates.[21]

Symptomatic atrial fibrillation. Rhythm control in symptomatic patients can be used to reduce symptoms (class 2a recommendation) or to determine if the symptoms are due to the atrial fibrillation in uncertain cases.

Recently diagnosed symptomatic atrial fibrillation (< 1 year) (class 2a recommendation). Achieving rhythm control in early-onset atrial fibrillation was associated with reduced rates of death, stroke, and hospitalizations.[22]

Atrial fibrillation and heart failure (class 2a recommendation). In these groups, rhythm control has several benefits, including improved symptoms and lower rates of hospitalizations, stroke, and death.[21,23]

Which patients are candidates for catheter ablation?

Catheter ablation is now the first-line treatment for atrial fibrillation in specific patient populations, having received a class 1 recommendation as first-line therapy for rhythm control in the following groups[24]:

- Patients with symptomatic atrial fibrillation in whom typical treatment has been ineffective, contraindicated, not tolerated, or not preferred, and who desire rhythm control
- Patients with symptomatic paroxysmal atrial fibrillation who are younger than 70, have few comorbidities, and desire rhythm control
- Patients with symptomatic or clinically significant atrial flutter who desire symptom improvement
- Patients with atrial fibrillation and concomitant heart failure with reduced ejection fraction on guideline-directed medical therapy. In this population, catheter ablation has been shown to improve quality of life, reduce symptoms and cardiovascular mortality, and improve ejection fraction.

DO OTHER SOCIETIES AGREE OR DISAGREE?

The 2024 European Society of Cardiology guidelines for the diagnosis and management of atrial fibrillation[25] largely agree with the 2023 American guideline,[1] with some minor differences.

Staging. The European guidelines classify atrial fibrillation as first diagnosed, paroxysmal, persistent, or permanent. This classification is based more on presentation and duration. The updated American guideline classifies atrial fibrillation as a continuum and emphasizes early intervention and risk-factor modification strategies throughout each stage.

Early rhythm-control strategy. Both guidelines agree on the role of an early rhythm-control strategy in symptom management and improving quality of life. The European guidelines recommend early rhythm-control strategies to reduce atrial fibrillation–related

symptoms. Even in cases in which there is uncertainty about whether symptoms are related to atrial fibrillation, a trial of early restoration of sinus rhythm is considered a reasonable step.

The updated American guideline recommends an early trial of rhythm interventions in patients with reduced left ventricular function and persistent or high-burden atrial fibrillation as a class 1 recommendation. Class 2 recommendations state that it may be helpful to implement early rhythm-control strategies in patients with symptomatic atrial fibrillation or in those with a recent diagnosis of atrial fibrillation (within the past year) to reduce hospitalizations, stroke, and mortality. Additionally, rhythm-control strategies may reduce the likelihood of atrial fibrillation progression.

Catheter ablation. In the American guideline, catheter ablation gets a class 1 recommendation as first-line therapy in select patients, such as younger patients with few comorbidities with symptomatic paroxysmal atrial fibrillation, to improve symptoms and prevent progression. The most recent European guidelines have also escalated catheter ablation to a class 1 recommendation in select patients.[25] Similar to the American guidelines, catheter ablation is now a class 1 recommendation in patients with atrial fibrillation and heart failure with reduced ejection fraction, patients with symptomatic paroxysmal or persistent atrial flutter, and patients with symptomatic atrial flutter.

HOW WILL THIS CHANGE DAILY PRACTICE?

Patients who develop atrial fibrillation acutely in the hospital after medical or surgical illness should be treated with rate and rhythm control and anticoagulation after assessing the risks and benefits. Potential triggers of atrial fibrillation, such as electrolyte abnormalities, should also be treated. Before discharge, these patients should be counseled on recurrent atrial fibrillation and lifestyle and risk-factor management. The need for continued anticoagulation and the rate and rhythm control should be reassessed at follow-up.

A multimodal approach with both rhythm and rate control is still appropriate for atrial fibrillation. Nonetheless, recommendations suggest that early rhythm-control strategies should be implemented in patients with symptomatic, recently diagnosed atrial fibrillation (< 1 year of diagnosis) and in patients with heart failure with reduced ejection fraction. Early referral to a cardiac electrophysiologist or heart rhythm specialist is warranted for aggressive rhythm-control measures. Catheter ablation is now first-line therapy in younger patients with few comorbidities and in appropriate patients with atrial fibrillation and heart failure with reduced ejection fraction on guideline-directed medical therapy, and should be pursued appropriately.

Last, the guideline emphasizes an annual assessment of thromboembolic risk by using verified scores beyond CHA_2DS_2-VASc in shared decision-making regarding anticoagulation or other treatments, such as left atrial appendage occlusion.

WHAT IS THE EXPECTED CLINICAL IMPACT?

The new guideline will lead to more efforts to prevent atrial fibrillation through aggressive lifestyle and risk-factor modification. There will be a preference for early rhythm control over rate control and for ablation as the first line of treatment in certain groups. Also, the new guidelines will involve using scoring systems beyond CHA_2DS_2-VASc and frequently assessing stroke and bleeding risk to allow better risk stratification for patients beyond just those considered at high risk.

WHEN WOULD THE GUIDELINES NOT APPLY?

The 2023 guideline[1] recommends aggressive risk-factor modification and early rhythm control. However, some patients cannot undergo risk-factor interventions, receive rhythm-control therapies (including catheter ablation), or use anticoagulants, owing to severe comorbidities or systemic disease (cardiac or otherwise). Additionally, patients who are pregnant may not be able to take antiarrhythmic drugs or certain anticoagulant drugs for stroke risk reduction.

The guideline addresses special patient groups in whom catheter ablation is first-line therapy, but it is unclear whether those who have had prior unsuccessful cardioversions or ablations are candidates for repeat ablation despite having heart failure with reduced ejection fraction on guideline-directed medical therapy.

While the guideline encourages individualized calculations of stroke risk, those at increased bleeding risk present a unique dilemma of deciding whether to use anticoagulants in the setting of increased bleeding risk or not to use anticoagulants to decrease bleeding risk. Shared decision-making between the patient and clinician to determine the best course of action and using bleeding risk scores such as HAS-BLED (hypertension, abnormal renal or hepatic function, stroke, bleeding tendency or predisposition, labile international normalized ratio on warfarin, elderly [age > 65 years], drugs [aspirin or nonsteroidal anti-inflammatories] or alcohol, or both) can be helpful. Additionally, there are no specific changes in therapy addressed in the guidelines

regarding heart failure with preserved ejection fraction as there are with reduced ejection fraction (catheter ablation being first line).

Historically, women have been underrepresented in most atrial fibrillation trials, as have minority populations and patients of lower socioeconomic status. Future research regarding differences in management strategies in these populations is necessary for guideline refinement.

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The beat goes on: Highlights from the new American and European A-fib guidelines

With a prevalence of 37.57 million known cases globally, atrial fibrillation is one of the most commonly occurring cardiac arrhythmias.[1] Atrial fibrillation diminishes quality of life, is associated with poor long-term prognosis, and has a considerable socioeconomic impact on health systems worldwide.[2]

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The updated American College of Cardiology (ACC), American Heart Association (AHA), American College of Chest Physicians (ACCP), and Heart Rhythm Society (HRS) 2023 guideline for the diagnosis and management of atrial fibrillation[3] and the recent 2024 European Society of Cardiology (European) guidelines for the management of atrial fibrillation[4] have been welcomed by cardiac societies. Recommendations in both guidelines stress the importance of a holistic patient-centered approach to atrial fibrillation and acknowledge that the increasing incidence of atrial fibrillation is linked to preventable risk factors in an aging population, such as heart failure, diabetes, hypertension, high alcohol consumption, physical inactivity, smoking, and obesity. The ACC/AHA/ACCP/HRS (American) guideline[3] recognizes the significance of preemptive treatment of risk factors in patients at risk of atrial fibrillation and highlights the need for integrative primary prevention as first-line therapy, as reflected by the introduction of atrial fibrillation stages such as "at risk of atrial fibrillation" and "pre–atrial fibrillation."

In this issue of the *Journal*, Campbell at al[5] provide a timely, expert review of the new American guideline for the diagnosis and management of atrial fibrillation.[3]

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The authors emphasize the new staging system and the inclusion of individuals at risk of atrial fibrillation, and acknowledge that atrial fibrillation is a "disease continuum." They also call attention to the need to incorporate lifestyle and risk-factor modification recommendations, including targeting obesity, encouraging reduced alcohol consumption, smoking cessation, and strict management of diabetes and hypertension, into clinical practice to reduce the risk of new-onset atrial fibrillation and the complications of clinically manifested atrial fibrillation. Further, the authors point out that the need for anticoagulation should be determined annually based on risk assessment of thromboembolic events.

PREVENTION CONSIDERATIONS

It is laudable that the European guidelines[4] recommend early intervention and aggressive treatment of cardiovascular risk factors to reduce progression and recurrence of atrial fibrillation and thereby prevent hospital admissions and exacerbations of symptoms. However, they stop short of strongly recommending preventive measures, despite results of trials such as RACE 3 (Routine Versus Aggressive Risk Factor Driven Upstream Rhythm Control for Prevention of Early Atrial Fibrillation in Heart Failure)[6] that showed early targeted therapy for underlying conditions helped maintain sinus rhythm in patients with persistent atrial fibrillation. This is particularly relevant for individuals with obesity, who, in a meta-analysis that included data from 587,372 patients in 16 studies, were found to have a 51% increased risk of new-onset atrial fibrillation, with no sex difference.[7] Progressive weight loss had a beneficial effect on long-term freedom from atrial fibrillation and arrhythmia-free survival in the LEGACY

(Long-Term Effect of Global Directed Weight Management in an Atrial Fibrillation Cohort) trial,[8] although this was only achieved if weight loss was 10% or more and maintained over time. In another study of patients with longstanding persistent atrial fibrillation undergoing ablation, weight loss had no impact on arrhythmia burden and long-term ablation outcome,[9] suggesting a possible point of no return. Further, atrial fibrillation incidence was noted to be risk-factor specific in several studies, with an increased risk of 50% for individuals with hypertension,[10] 20% for those with prediabetes, 28% for those with diabetes,[11,12] and 38% for heavy drinkers (≥ 21 alcoholic drinks per week).[13]

A study that used drug-target Mendelian randomization analyses suggested that lowering systolic blood pressure by 10 mm Hg with antihypertensive drugs had a preventive effect on atrial fibrillation development (odds ratio 0.64).[14] A recent meta-analysis found that treatment of diabetes with sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonists, and dipeptidyl peptidase-4 inhibitors reduced the risk of new-onset atrial fibrillation by 23%, 28%, and 34%, respectively, compared with insulin.[15] Absolute abstinence from alcohol, but not reduced alcohol consumption, in chronically heavy drinkers showed the greatest effect, reducing incident atrial fibrillation by 63%.[16] Preventive measures need to address all risk factors individually to achieve cumulative success.

COMPARISON OF THE GUIDELINES

Campbell and colleagues[5] highlight the changes in recommendation class regarding shared decision-making between patient and clinician to determine the best course of action in atrial fibrillation management and the option of rhythm control as first-line treatment to evaluate the impact of atrial fibrillation on heart function—with the goal to prevent symptoms; improve quality of life; and reduce mortality, stroke, and hospitalization.[3]

Guidance on anticoagulation

Both the American and European guidelines[3,4] recommend using the CHA_2DS_2-VASc score (1 point given for congestive heart failure, hypertension, age 65 to 74 years, ≥ 75 years [doubled], diabetes mellitus, prior stroke, transient ischemic attack, or thromboembolism [doubled], vascular disease, female sex) for thromboembolic risk assessment and warn against using currently available bleeding scores in isolation to determine eligibility for anticoagulation. However, the European guidelines[4] discourage the use of sex to calculate the CHA_2DS_2-VASc score, seeing it as an age-related modifier and not a risk factor per se. Anticoagulation guidance for device-detected atrial high-rate episodes is appreciably more nuanced in the American guideline,[3] with clear cut-offs for duration of atrial high-rate episodes and clear guidance on anticoagulation management.

Treatment of life-threatening bleeds with specific antidotes for direct oral anticoagulants is designated a class 1 recommendation in the American guideline,[3] whereas the European guidelines acknowledge the limited availability of these agents in some healthcare environments, giving their use a class 2a recommendation.[4]

Left atrial appendage occlusion

Campbell et al[5] point out that the American guideline recommends that percutaneous placement of a left atrial appendage occlusion device is reasonable in patients experiencing atrial fibrillation with a moderate to high thromboembolic risk and contraindication to anticoagulation; this was upgraded to a class 2a recommendation owing to updated safety data on devices for left atrial appendage occlusion.[3] This remains a 2b recommendation by the European guidelines, citing the lack of "solid" randomized controlled trial data and need for continued postprocedure antithrombotic treatment.[4] Conversely, surgical left atrial appendage closure for all patients with atrial fibrillation undergoing cardiac surgery is recommended as an adjunct to oral anticoagulation to prevent ischemic stroke and thromboembolism,[4] while the American guideline[3] does not promote this technique for patients with a CHA_2DS_2-VASc score less than 2.

Catheter ablation

Catheter ablation with pulmonary vein isolation has a clear class 1 indication as first-line therapy when compared with antiarrhythmic drugs for select patients with paroxysmal and symptomatic atrial fibrillation who are younger and have fewer comorbidities.[3] This upgrade in recommendation has been partially adopted by the European guidelines, which do not limit the procedure to a specific ablation method or to select groups and give it class 2a status. Only when atrial fibrillation is proven to cause symptoms or drive heart failure does catheter ablation receive a class 1b recommendation. Anticoagulation following catheter and surgical ablation is advocated for 3 months in the American guideline[3] and at least 2 months in the European guidelines.[4]

Pharmacologic therapy

Further differences exist regarding pharmacologic treatment of atrial fibrillation. Unlike the European

guidelines,[4] the American guideline[3] does not recommend first-line digoxin for the treatment of acute and long-term atrial fibrillation in patients with preserved left ventricular ejection fraction, owing to its slower treatment response and subsequent longer hospital stays compared with diltiazem.[17]

Dronedarone is mentioned by both guidelines[3,4] for maintenance of sinus rhythm. The European guidelines[4] suggest using dronedarone for patients with heart failure with midrange and preserved ejection fraction and ischemic or valvular disease. The American guideline[3] warns against its use in patients with risk factors for cardiovascular events and recent history of symptoms or hospitalization due to heart failure, noting the results of ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease),[18] which showed increased mortality in patients with severely symptomatic or recently decompensated heart failure.

Both American and European guidelines recommend that low-dose amiodarone is reasonable for long-term maintenance of sinus rhythm if other rhythm-control strategies are ineffective or contraindicated.[3,4] Further reversal of trigger factors and concomitant treatment of risk factors and comorbidities is encouraged as part of a complementary atrial fibrillation care pathway for patients with first-time atrial fibrillation.

Both cardiac and noncardiac surgery can trigger new-onset, incidental, acute, and recurrent atrial fibrillation, but evidence regarding preventive or therapeutic pharmacologic measures appears to be contradictory. The American guideline[3] understandably argues that evidence on pretreatment of patients at high risk of atrial fibrillation is not clear due to mixed results in prior trials, with no clinical advantage seen between rate- and rhythm-control strategies in a randomized controlled trial of 2,109 patients looking at the length of hospitalization and rates of new-onset persistent atrial fibrillation after cardiac surgery.[19]

In comparison, the European guidelines[4] introduced pretreatment with amiodarone (class 1) before cardiac surgery if prophylaxis is desired, owing to its ability to reduce the incidence of postoperative atrial fibrillation by 51% compared with placebo, with no difference in effect between pre- or postoperative initiation.[20] Conversely, pretreatment with beta-blockers is discouraged[4] owing to a lack of efficacy prior to cardiac surgery and a recorded increase in mortality in noncardiac surgery, according to a review of 23 meta-analyses comprising 89 randomized controlled trials (19,211 patients).[21]

Guidance on treatment of postoperative atrial fibrillation is similar for both guidelines[3,4] and has not changed, with rhythm and rate control equally recommended, taking into account the hemodynamic status of the patient.

Both guidelines[3,4] note that atrial fibrillation that occurs both during and after surgery has an up to 50% risk of recurrence, putting patients at high risk of stroke, heart failure, and mortality, thereby necessitating an upgrade in recommendations regarding long-term anticoagulation (class 2a). The American guideline recommends initial treatment for 60 to 90 days followed by reassessment of thromboembolic risk and rate-control strategy at 90 days, with the possibility of lifelong anticoagulation. This is mirrored in the European guidelines.

Concomitant posterior left pericardiotomy during cardiac surgery reduces pericardial effusion postoperatively and decreases risk of postoperative atrial fibrillation (odds ratio 0.49, 95% confidence interval 0.38–0.61),[22] which is similar to the reductions seen with treatment with amiodarone but without the adverse effects.

Guideline writing process

The American guideline[3] was written by the ACC- and AHA-appointed Joint Committee on Clinical Practice Guidelines, which summarizes the evidence and formulates the recommendations that are then peer reviewed, approved by the governing bodies of the ACC and AHA, and endorsed by the ACCP and HRS. European guidelines are written by consensus of an appointed clinical practice guidelines committee after all evidence is reviewed.[23] Patient-reported outcomes and experiences are also measured and evaluated. The guidelines are reviewed by all national cardiac societies, at which time revisions can be incorporated.

Considerations regarding cost-effectiveness of treatment of atrial fibrillation also differ between committees. Local multidisciplinary teams evaluate cost efficiencies for the European guidelines owing to the vast differences in healthcare provision in Europe.[4] The American guideline,[3] on the other hand, acknowledges that affordability is limited for some patients in the United States due to lack of healthcare insurance and no national consensus on cost-effectiveness.[24] They advise taking affordability into account when recommending treatment options such as warfarin in nonvalvular atrial fibrillation if direct oral anticoagulants are unaffordable for the individual.[3] These differences in procedure might explain some weighting differences in the recommendations between societies.

CONCLUSION

Both recently published guidelines represent a strong shift toward preventive medicine and a holistic patient-centered approach to the diagnosis and management of atrial fibrillation. Further clinical trials are warranted to address gaps in evidence relating to the optimal timing, technique, and target patient groups for catheter ablation, as well as uncertainty regarding anticoagulation strategies in patients with device-detected atrial fibrillation.

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REVIEW

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Managing right ventricular failure in the setting of pulmonary embolism

ABSTRACT

Pulmonary embolism (PE) has a significant impact on right-sided heart function. Clinical presentation can range from no involvement of the right ventricle to right ventricular dysfunction, cardiogenic shock, and even cardiac arrest. The authors explore the pathophysiology of PE-induced right ventricular failure, emphasizing the mechanisms by which PE contributes to dysfunction, current diagnostic tools for risk stratification, and the importance of timely diagnosis. The primary focus is on strategies for managing right ventricular failure secondary to PE, including medical, percutaneous interventional, and surgical options. Recent advances in the field are also noted, including emerging therapies and evolving treatment algorithms.

KEY POINTS

- Inpatient mortality for patients with high-risk PE is as high as 42.1% and is primarily due to right ventricular dysfunction from a sudden rise in right ventricular afterload.
- Risk of mortality is classified as low, intermediate (intermediate low-risk and intermediate high-risk), and high.
- Management of PE with right ventricular involvement of varying severity requires prompt and concomitant integration of several approaches: management of hemodynamics (preload and afterload), reperfusion, pharmacologic support, supportive care, and, in refractory cases, use of mechanical circulatory support and advanced therapy.

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Pulmonary embolism (PE) significantly impacts right-sided heart function. Clinical presentation can range from no involvement of the right ventricle to right ventricular dysfunction, cardiogenic shock, and even cardiac arrest. In a retrospective subset from the Pulmonary Embolism Response Team Consortium Registry,[1] inpatient mortality was as high as 42.1% in patients with high-risk PE with hemodynamic collapse (termed *catastrophic* PE). Management requires critical evaluation, risk stratification, and multidisciplinary care that can include medical, percutaneous interventional, and surgical options. This article predominantly discusses patients classified as having intermediate- and high-risk PE, given the associated hemodynamics and involvement of the right ventricle.

RIGHT VENTRICULAR FAILURE IN ACUTE PE

Acute PE is associated with an elevated risk of death, primarily due to acute right ventricular dysfunction resulting from a sudden rise in right ventricular afterload.[2] Vascular obstruction caused by thrombus in the pulmonary arterial circulation can lead to significant increases in pulmonary pressures and pulmonary vascular resistance, raising right ventricular afterload. In PE, hypoxemia and pulmonary vasoconstrictors also contribute to pulmonary vascular resistance. The crescent-shaped right ventricle, characterized by fine layers of myofibrils arranged in series for volume expansion and enhanced compliance compared with the left ventricle, is designed to tolerate preload

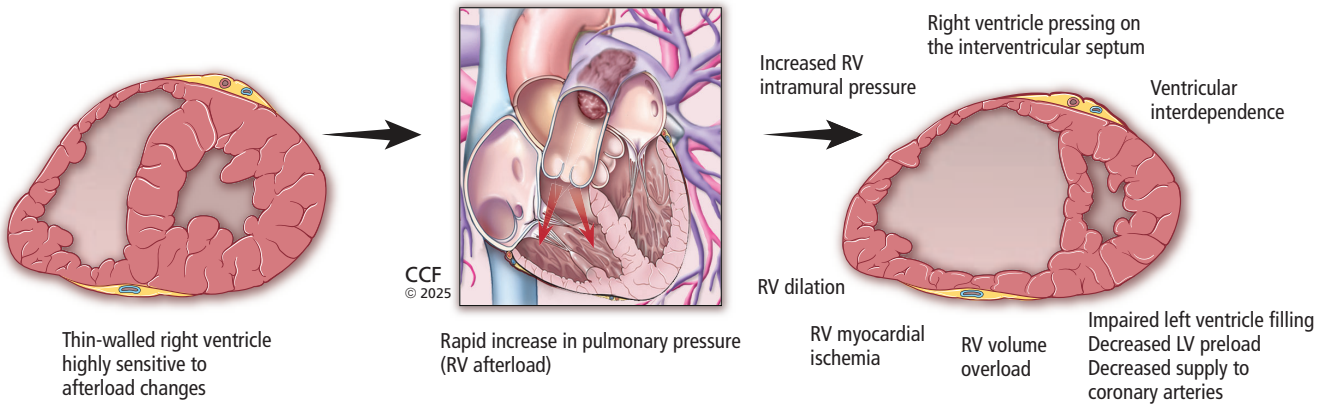

Figure 1. Illustration of the pathophysiology and development of right ventricular (RV) failure in the setting of acute increase in afterload caused by pulmonary embolism.

LV = left ventricular

Based on information from references 2 and 4.

changes and is compliant in low-pressure systems. It struggles to adapt rapidly to acute elevations in circulatory pressures and has limited capacity to adapt to sudden increases in afterload.

During an acute PE, the right ventricle attempts to preserve right ventricle–pulmonary artery coupling and maintain stroke volume and cardiac output by dilating and altering its geometry.[3] However, the right ventricle cannot endure consistently elevated pressures, which leads to further right ventricular dilation and acute septal deviation toward the left ventricle, giving rise to altered ventricular interdependence—a phenomenon where the performance of one ventricle is influenced by the other due to the shared interventricular septum. Consequently, the right ventricle exerts pressure on the interventricular septum, impairing filling of the left ventricle, decreasing left ventricular preload, and reducing blood supply to the coronary arteries.

The increase in right ventricular intramural pressure and wall tension also causes straightening of the wall of the right ventricle, leading to decreased right coronary artery perfusion and right ventricular ischemia, even in individuals without preexisting coronary disease.[2] Furthermore, with persistent right ventricular dilation and enlargement, the tricuspid valve annulus may expand, resulting in inadequate closure of the valve leaflets and subsequent secondary tricuspid regurgitation. These effects create a cycle of ischemia, compounded by decreased oxygenation from obstructive thrombotic material, resulting in a drop in blood pressure and hemodynamic changes, all of which may manifest as syncope, hypotension, cardiogenic shock, and cardiac arrest (**Figure 1**).[2,4] Moreover, this dysfunction permits retrograde blood flow into the right atrium, compromising right ventricular filling, elevating right atrial pressure, and contributing to progressive venous congestion.

DIAGNOSTIC AND PROGNOSTIC TOOLS IN ACUTE PE

Signs of right ventricular involvement can be observed through laboratory and imaging studies. Computed tomography pulmonary angiography has been a cornerstone in the diagnosis of acute PE due to its detailed contrast enhancement of pulmonary vasculature. It is also a valuable tool in assessment of the right ventricle. Per the 2019 European Respiratory Society (ERS) guidelines, an increase in the right ventricle-to-left ventricle diameter ratio greater than 1 found with computed tomography pulmonary angiography (**Figure 2**) is indicative of acute right ventricular dysfunction, and is associated with increased risk of adverse outcomes and all-cause and PE-related mortality.[5–7] Additional findings that may be supportive of acute right ventricular failure in certain clinical settings include septal straightening or bowing, reflux of contrast in the inferior caval vein, and hepatojugular reflux of contrast into the inferior caval vein. Thrombus load and central location have not shown a consistent association with all-cause mortality.[6]

Echocardiography is invaluable in the assessment of right ventricular dysfunction in acute PE as it can identify numerous findings suggestive of right ventricular dysfunction[5,7]:

- Enlarged right ventricle
- Dilated right ventricle with right ventricle-to-left ventricle ratio (> 1.0)

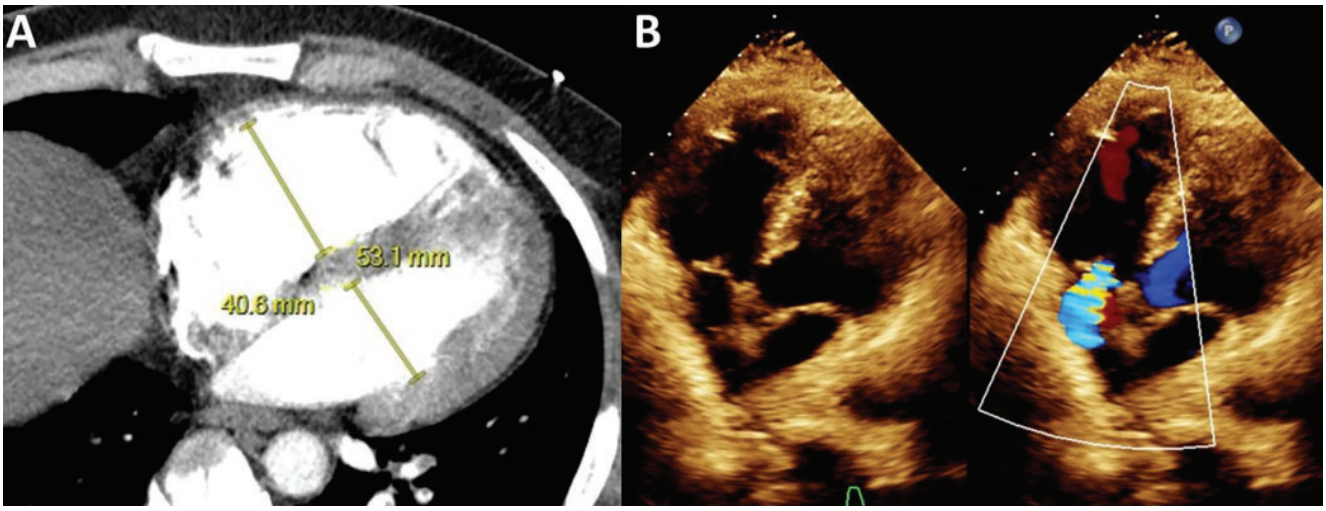

Figure 2. (A) Computed tomography and (B) echocardiogram showing an increased right ventricle–to–left ventricle ratio, which is used to assess right ventricular strain and dysfunction for risk stratification of pulmonary embolism.

- McConnell sign (right ventricular free wall akinesis with the apex spared)
- Flattened intraventricular septum
- Distended inferior caval vein with decreased inspiratory collapsibility
- Decreased tricuspid annular plane systolic excursion (< 16 mm)
- Decreased peak systolic velocity of tricuspid annulus
- Right heart mobile thrombus or clot in transit
- 60/60 sign (coexistence of acceleration time of pulmonary ejection less than 60 ms and midsystolic notch with mildly elevated [< 60 mm Hg] peak systolic gradient at the tricuspid valve).

Low left ventricular outflow tract velocity time integral of 15 cm or less and right ventricular outflow tract velocity time integral less than 9.5 cm have also been associated with adverse outcomes.[8,9]

Biomarkers that have been proposed as tools for diagnosis and prognosis of patients with acute PE include troponins (marker of myocardial injury) and natriuretic peptides (marker of right ventricular dysfunction).[7]

TRIAGING AND RISK STRATIFICATION

Initial management of patients with PE begins with triaging and risk stratification using clinical assessment tools including the Pulmonary Embolism Severity Index (PESI) score or its simplified version (sPESI), cardiac biomarkers, and imaging (**Figure 3**).[1,7]

Severity of PE and risk of early death are stratified as high, intermediate (intermediate low-risk and intermediate high-risk), and low. Patients classified with high-risk PE are hemodynamically unstable, as defined by cardiac arrest, shock, or hypotension. Patients classified with intermediate-risk PE have signs of right ventricular involvement, while patients classified as low risk do not. Patients with intermediate high-risk PE are hemodynamically stable but have abnormalities in all 3 indicators of risk—clinical (PESI III–V or sPESI ≥ I), laboratory (elevated troponin), and imaging parameters indicative of right ventricular dysfunction (shown on computed tomography pulmonary angiography or echocardiography). Patients classified with intermediate low-risk PE have at least clinically severe presentation and 1 or none of the other parameters.[7] In the registry study noted earlier, the term *catastrophic* PE was introduced as a further classification of patients with high-risk PE and hemodynamic collapse, particularly those requiring vasopressors or experiencing cardiac arrest.[1]

ESSENTIALS OF MANAGEMENT

Management of PE with right ventricular involvement of varying severity requires prompt, concomitant integration of clinical care focused on hemodynamics (preload and afterload), reperfusion, pharmacologic support, supportive care, and, in refractory cases, use of mechanical circulatory support and advanced therapy (**Table 1**).[7,10]

Preload

Management of preload, particularly fluids and diuresis, has been studied sparsely. In a study of hemodynamically

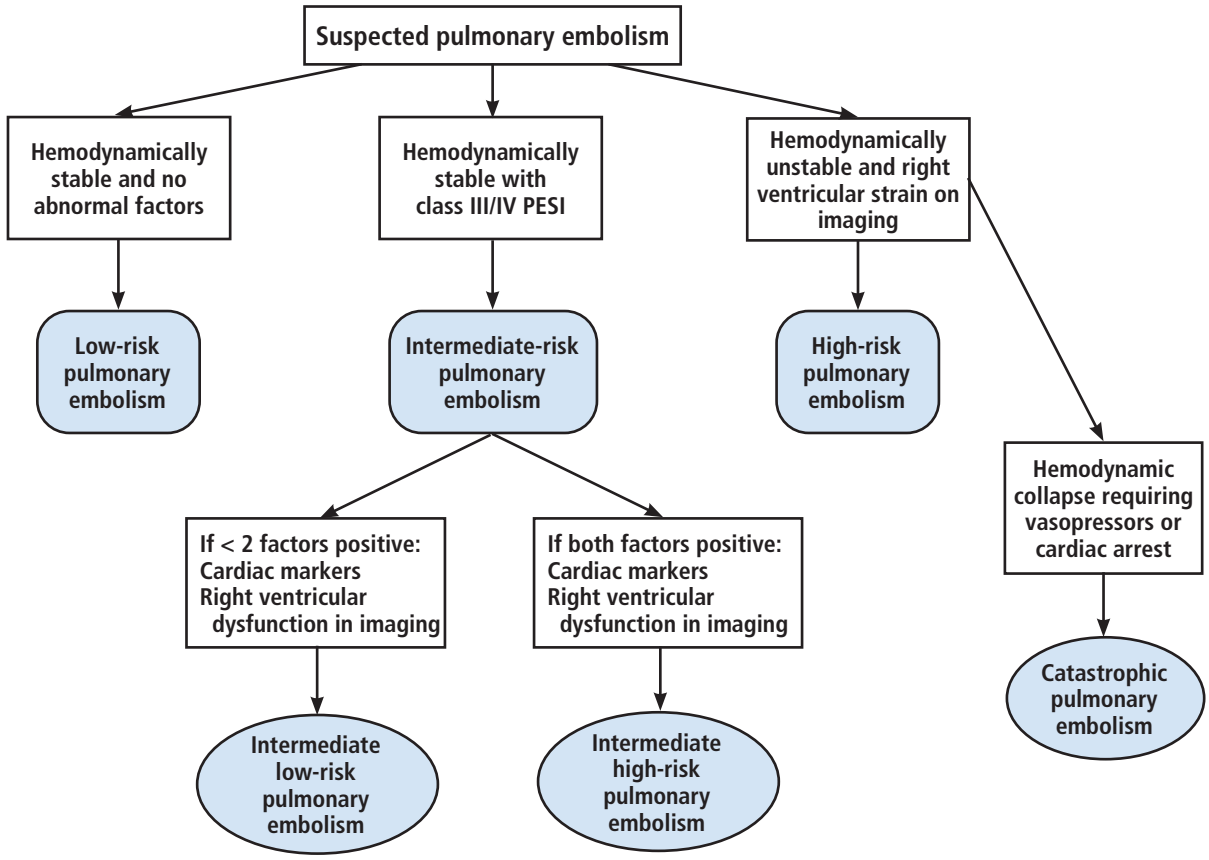

Figure 3. Algorithm of our initial assessment and risk stratification of pulmonary embolism based on Pulmonary Embolism Severity Index (PESI) score, cardiac markers (troponin or brain natriuretic peptide), right ventricular strain on imaging (transthoracic echocardiography or computed tomography pulmonary angiography), and hemodynamic instability (cardiac arrest, obstructive shock, or persistent hypotension). Note the addition of a subcategory of high-risk pulmonary embolism, termed *catastrophic* pulmonary embolism (those with hemodynamic collapse).

Based on information from references 1 and 7.

stable patients with submassive PE (defined as a normotensive patient with PE and evidence of right ventricular dysfunction), the cohort receiving intravenous furosemide bolus experienced earlier improvements in parameters of right ventricular function compared with the cohort receiving volume expansion.[11] More recently, in a randomized controlled trial targeting normotensive patients with intermediate-risk PE, a single high-dose bolus of furosemide improved the primary outcomes of normalization of sPESI items and reduced oligoanuria in the first 24 hours (a critical symptom of low cardiac output), and maintained stable renal function compared with placebo.[12] In another trial, right ventricular dysfunction parameters did not differ between patients with intermediate high-risk PE treated with diuresis compared with volume loading; however, diuretics were tolerated safely, and brain-type natriuretic peptide was normalized earlier in the diuretic group.[13]

Although supporting evidence is limited, reducing the preload of an overloaded right ventricle during acute PE with diuresis would be expected to decrease right ventricular load and stress, and fluids could be detrimental. However, if a patient with acute PE has low central venous pressure (by ultrasonography of the inferior caval vein), a modest fluid challenge (≤ 500 mL) may improve the cardiac index.[7] When volume overload is evident, diuresis with concomitant support from vasopressors can be pursued despite hypotension, to target improvement in cardiac output while reducing right ventricular dilation.

TABLE 1
Principles of management options of right ventricular failure in pulmonary embolism

Management of the thrombus	Management of the preload	Pharmacologic support	Mechanical support
High-risk pulmonary embolism: intravenous thrombolytics vs surgical embolectomy	Volume assessment	First line: norepinephrine	Venoarterial extracorporeal membrane oxygenation
Intermediate-risk pulmonary embolism: catheter-guided therapies (thrombolysis or thrombectomy) vs anticoagulation alone	Fluid challenge vs intravenous furesomide	Second line: dobutamine	Right ventricular assist device
Inferior caval vein filter placement as an adjunct to above, especially if contraindications to anticoagulation			

Based on information from references 7 and 10.

Afterload and reperfusion therapy

Because the thrombus drives the acute increase in right ventricular afterload that is the primary cause of right ventricular dysfunction, it is essential to plan reperfusion early in the course of care.

High-risk PE. Primary reperfusion with systemic thrombolysis remains the treatment of choice for patients with high-risk (or massive) PE (defined as syncope, systemic arterial hypotension, cardiogenic shock, or resuscitated cardiac arrest), and, together with anticoagulation initially with unfractionated heparin, readily improves pulmonary vascular resistance, pulmonary artery pressure, and obstruction.[7,14] Absolute contraindications to intravenous thrombolysis include the following[7]:

- A history of hemorrhagic stroke or stroke of unknown origin
- Ischemic stroke in the previous 6 months
- Central nervous system neoplasm
- Major trauma, surgery, or head injury in previous 3 weeks
- Bleeding diathesis
- Active bleeding.

For systemic thrombolysis, lower doses of recombinant tissue–type plasminogen activator (50 mg over 2 hours compared with 100 mg over 2 hours) showed similar efficacy and possibly better safety in patients with acute PE.[15]

The ERS guidelines define the classes of PE treatment recommendations, with surgical embolectomy being recommended (class I indication: evidence or agreement of the benefit of treatment) for patients with high-risk PE who have contraindications to systemic thrombolysis or in whom thrombolysis has failed.[7] Bayiz et al[16] demonstrated the safety and efficacy of percutaneous mechanical aspiration thrombectomy in patients with massive or high-risk PE, who, at follow-up, had decreased pulmonary clot burden and improved hemodynamic parameters, pulmonary artery pressure, right ventricular end-diastolic pressure, and right ventricle-to-left ventricle ratio. Currently, percutaneous catheter-directed treatment is a class IIa indication (weight of evidence favors usefulness of treatment) and should be considered for patients with massive or high-risk PE when thrombolysis is contraindicated or has failed.[7]

Low- and intermediate-risk PE. Anticoagulation is recommended (class I indication) for patients with low- to intermediate-risk PE. When oral anticoagulation is initiated, direct oral anticoagulants are preferred over vitamin K antagonists,[7] as these agents have a lower risk of bleeding complications and similar efficacy.[17]

Intermediate-risk (or submassive) PE has been a focus of research in recent years, given the risk for decompensation and subsequent right ventricular strain and dysfunction. Patients with intermediate-risk PE vary in clinical presentation,[1] making management of the clot a crucial part of clinical decision-making. Thrombolysis can prevent hemodynamic decompensation and death in patients with intermediate-risk PE, but it also carries an increased risk of major hemorrhage and stroke.[18] In the PEITHO (Pulmonary Embolism Thrombolysis) trial,[19] thrombolysis in patients with intermediate-risk PE did not affect long-term mortality

and did not reduce right ventricular dysfunction or clinical symptoms, compared with anticoagulation alone. In patients with contraindications or in whom thrombolysis has failed, surgical embolectomy was reported to have a high survival rate.[20]

Another modality for thrombus management is placement of an inferior caval vein filter to prevent a clot from reaching the right side of the heart and pulmonary circulation. Routine use of inferior caval vein filters is not recommended, but they should be considered in patients with absolute contraindications to anticoagulation or recurrent PE despite therapeutic anticoagulation.[7]

In conclusion, strategies for reperfusion treatment of intermediate-risk PE remain a gray area. The ERS guidelines[7] determined that anticoagulation is the only class I recommendation for initial treatment of patients with intermediate or high clinical probability of PE. However, promising studies with a focus on emerging techniques are currently taking place.

Percutaneous interventions for clot management

Catheter-directed therapies have emerged over recent years as safe and effective options.

Catheter-directed thrombolysis. In the ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism) trial,[21] ultrasonography-assisted catheter-directed thrombolysis in patients with intermediate-risk PE, in addition to anticoagulation, resulted in reversal of right ventricular dilation and decreased mean right ventricle-to-left ventricle ratio at 24 hours compared with anticoagulation alone, without an increase in bleeding complications.

SEATTLE-II (A Prospective, Single-Arm, Multicenter Trial of EkoSonic Endovascular System and Activase for Treatment of Acute Pulmonary Embolism)[22] studied 150 patients with right ventricular dysfunction (79% had submassive PE and 21% had massive PE) who underwent catheter-directed low-dose fibrinolysis. This therapy resulted in a significant decrease in mean right ventricle-to-left ventricle ratio 48 hours after the procedure ($P < .0001$) and reduced mean pulmonary artery systolic pressure, with a safe bleeding profile and no intracranial hemorrhage at 72 hours.[22] In the OPTALYSE-PE (Optimum Duration of Acoustic Pulse Thrombolysis Procedure in Acute Pulmonary Embolism) trial,[23] catheter-directed therapy with low-dose tissue plasminogen activator administered using a shorter duration of delivery improved clot burden and right ventricular function.

More recent studies have explored outcomes of catheter-directed therapies in patients with intermediate high-risk PE. The CANARY (Catheter-Directed Thrombolysis vs Anticoagulation in Patients With Acute Intermediate-High-Risk Pulmonary Embolism) randomized clinical trial[24] showed significantly lower right ventricle-to-left ventricle ratio at the 3-month echocardiography follow-up after catheter-directed thrombolysis ($P = .01$) compared with anticoagulation monotherapy, although the study was prematurely terminated due to the COVID-19 pandemic.There is an ongoing study comparing catheter-directed thrombolysis vs anticoagulation alone in patients with intermediate high-risk PE.[25]

Catheter-directed percutaneous mechanical thrombectomy is an emerging effective treatment option in patients with high- and intermediate-risk PE, without thrombolytic complications and their associated bleeding adverse events. FLARE (FlowTriever Pulmonary Embolectomy Clinical Study)[26] showed significant improvement in the right ventricle-to-left ventricle ratio 48 hours after the procedure, with minimal major bleeding, in patients with intermediate-risk PE. The recent FLAME (FlowTriever for Acute Massive PE) study[27] compared peripheral mechanical thrombectomy with other contemporary therapies (systemic thrombolysis or anticoagulation alone) in patients with high-risk PE and found a lower rate of in-hospital adverse outcomes and 1.9% all-cause mortality in the thrombectomy group. These studies are an important step forward in management options other than systemic thrombolysis for hemodynamically unstable patients with high-risk PE.

Furthermore, a study using data from the largest US National Inpatient Sample database noted that catheter-based therapy (thrombolysis or mechanical thrombectomy) for patients with cancer and intermediate- or high-risk PE was associated with a lower risk of in-hospital mortality or cardiac arrest but had a high risk of bleeding.[28]

In the PERFECT (Pulmonary Embolism Response to Fragmentation, Embolectomy, and Catheter Thrombolysis) multicenter registry,[29] 101 patients with massive (high-risk) and submassive (intermediate high-risk) PE were treated with catheter-directed therapy, including mechanical or pharmacomechanical thrombectomy or thrombolysis. Clinical success—defined as hemodynamic stability, improvement in pulmonary artery pressure and right heart strain, and survival to hospital discharge—was achieved in 85.7% of patients with massive PE and 97.3% of patients with submassive PE. These therapies were found to be safe, with improved right-sided heart function.

PHARMACOLOGIC SUPPORT

Inotropes and vasopressors

In patients with high-risk PE and shock, vasopressors are often needed to maintain systemic blood pressure and improve end-organ and coronary perfusion.[7] In cases of persistently low cardiac output despite vasopressor therapy, it is advisable to consider contractility support with inotropes. Norepinephrine and dobutamine are currently recommended as class IIa options for patients with high-risk PE. However, dobutamine should be used cautiously to enhance right ventricular and cardiac output, as it may worsen ventilation-perfusion mismatch and increase the risk of arrhythmias. Additionally, using dobutamine without a vasopressor can exacerbate hypotension.

Pulmonary vasodilators

The role of pulmonary vasodilation has also been explored in right ventricular dysfunction in patients with PE. In a randomized clinical trial with 20 patients who had acute intermediate high-risk PE, a single-dose of sildenafil (in 10 patients) did not significantly improve the cardiac index and instead lowered blood pressure compared with placebo.[30] In another randomized clinical trial, patients with severe acute submassive (intermediate high-risk) PE who received treatment with nitric oxide did not achieve the primary composite end point of normal right ventricle on echocardiogram and normal plasma troponin T.[31] However, a preplanned post hoc analysis showed that 29% more patients treated with nitric oxide had resolution of right ventricular dilation or hypokinesis at 24 hours.[31] In a randomized clinical trial of 14 patients with acute PE (hemodynamically stable with high clinical probability of right ventricular dysfunction), epoprostenol compared with placebo did not result in improvement of right ventricular dilation or other parameters.[32]

While pulmonary vasodilators can be beneficial in specific types of pulmonary hypertension, their effectiveness in right ventricular failure associated with pulmonary vascular issues may be limited. This is likely due to the unique pathophysiology of PE, particularly the acute increase in afterload resulting from a substantial clot burden. Overall, pulmonary vasodilators are not encouraged, as they can aggravate hypoperfusion of organs and systemic hypotension, despite efforts to decrease blood pressure and pulmonary vascular resistance.[7]

SUPPORTIVE CARE

For hypoxemic patients, prompt administration of supplemental oxygen therapy is essential. Intubation and mechanical ventilation are reserved for select patients with refractory hypoxemia and unstable hemodynamics, with careful use of anesthetic agents to avoid hypotension and cautious monitoring given the detrimental effects of positive end-expiratory pressure.[7]

In recent years, an integrated approach involving multidisciplinary teams, early risk stratification, and prompt decision-making in patients with intermediate-risk PE has led to lower rates of all-cause mortality,[33] reduced intensive care unit and overall hospital length of stay,[34] and high survival-to-discharge rates.[35] A multidisciplinary team approach in patients with high-risk PE and certain patients with intermediate-risk PE is a class IIa recommendation.[7] In the long term, if patients develop pulmonary hypertension as a complication, referral to a pulmonary hypertension center is highly recommended.

MECHANICAL CIRCULATORY SUPPORT AND ADVANCED THERAPY

Extracorporeal membrane oxygenation

Some patients may experience clinical deterioration that is resistant to treatment, including cardiac arrest or worsening hemodynamic shock requiring increased vasopressor support. In these cases, extracorporeal membrane oxygenation (ECMO) can be used as a bridging or rescue therapy; the ERS classified this as a class IIb recommendation (efficacy of treatment is less well established).[7] Venoarterial ECMO can bypass blocked pulmonary circulation by providing sufficient cardiac output to sustain systemic and coronary blood flow until the thrombus is effectively managed. However, using ECMO for an extended period, typically more than 5 to 10 days, can result in complications.[7]

Another detailed analysis from the National Inpatient Sample database of patients with high-risk PE revealed that use of ECMO in patients with massive PE increased from 0.07% to 1.1% from 2005 to 2013 and its use was not associated with a change in in-hospital mortality (61.6%).[36] ECMO was performed in 0.3% of hospitalized patients with high-risk PE for a duration of 1.9 ± 4.1 days from the index admission date, and the median hospital length of stay was 10 days. In patients with high-risk PE using ECMO for hemodynamic support, independent predictors of mortality included age, female sex, obesity, congestive heart failure, and chronic pulmonary disease.[36]

A handful of studies have looked at using ECMO as a bridge to ultimate clot management in patients with high-risk PE. In a cohort of 20 patients with high-risk PE who were managed with venoarterial

ECMO for a median 5.1 days, 94.7% had normal right ventricular function at discharge.[37] Another group of 16 patients with acute high-risk PE, 12 of whom were in cardiac arrest, underwent venoarterial ECMO for a mean duration of 1.5 days and had an overall 30-day mortality rate of 43.8%; treatment was mainly with ECMO alone, ECMO with thrombolysis, and ECMO with embolectomy.[38] While a meta-analysis on venoarterial ECMO and acute massive PE did not show significantly different in-hospital mortality between patients treated with or without ECMO,[39] another meta-analysis of venoarterial ECMO showed low-quality evidence of higher survival rates in patients 60 years or younger and in those who underwent surgical embolectomy.[40] There was evidence that venoarterial ECMO improves short-term survival of patients with acute PE.[40]

The 2022 American Heart Association guidelines maintain their earlier statement on cardiopulmonary resuscitation, which suggests that extracorporeal cardiopulmonary resuscitation for cardiac arrest from PE can be considered as a bridge to reperfusion therapy in select patients when it can be implemented and conventional cardiopulmonary resuscitation is failing.[41]

Right ventricular assist devices

Right ventricular assist devices have been explored for refractory shock related to PE. The devices can be placed surgically, with cannulation performed in the right atrium or right ventricle and pulmonary artery while connected with an extracorporeal flow pump.[4] They also can be placed percutaneously with lower flow than surgical right ventricular assist devices. Right ventricular assist devices, while offloading the right atrium and right ventricle from excessive preload, ultimately increase right ventricular afterload by generating constant flow and pressure in the pulmonary artery.[4] The percutaneous right ventricular assist device Impella RP, when used in hemodynamically unstable patients with PE, can lead to shock reversal with improvement in cardiac index and hemodynamic stability.[10]

Overall, there is a lack of sufficient evidence on outcomes of patients with acute high-risk PE undergoing treatment with ECMO, Impella RP, or other right ventricular assist devices. The decision to bridge with mechanical circulatory support should be made on a case-by-case basis, using a multidisciplinary team approach that involves intensivists, cardiologists with expertise in heart failure, pulmonologists, and cardiothoracic surgeons.

CONCLUSION

The incidence and burden of PE have risen in recent decades. Mortality, particularly in patients at high-risk with significant right ventricular involvement, is alarmingly high. An integrated approach to risk stratification and prompt implementation of therapies are critical to manage acute, life-threatening and long-term sequelae of PE, given PE's relationship with right-sided heart dysfunction. There are evidence gaps in the management of right ventricular failure due to PE, and further studies are warranted to aid in decision-making.

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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REVIEW

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Alpha-gal syndrome: Recognizing and managing a tick-bite–related meat allergy

ABSTRACT

Alpha-gal syndrome is an emerging condition characterized by an immunoglobulin (Ig) E–mediated reaction to galactose-alpha-1,3-galactose (alpha-gal) after consumption of mammalian-derived food products. Identified in the early 2000s, the syndrome is linked to sensitization through tick bites; in the United States, the lone star tick (*Amblyomma americanum*) is the main vector. Symptoms range from pruritus and hives to severe systemic reactions like anaphylaxis, and typically occur 3 to 8 hours after eating meat. Diagnosis involves a history of consistent symptoms, positive alpha-gal IgE serology, and dietary exclusion trials. Management focuses on avoiding foods and products that contain alpha-gal and preventing tick bites.

KEY POINTS

- Alpha-gal syndrome should be considered when a patient from a region where lone star ticks are prevalent has unexplained gastrointestinal symptoms and a history of a recent tick bite and meat consumption.
- Reactions can vary among patients and are influenced by exogenous and endogenous factors.
- The characteristic delayed reaction makes an oral food challenge difficult for routine clinical practice, but it can be considered if serologic testing is unclear.
- There is no cure, but avoiding alpha-gal exposure and future tick bites can lead to symptom resolution.

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A 37-year-old woman from Virginia with a history of asthma presents with hives and diarrhea. She reports that 1 week prior, she experienced generalized pruritus, cramping abdominal pain, and diarrhea 3 hours after having a beefsteak for dinner. After a visit to urgent care, diphenhydramine 25 mg and dicyclomine 20 mg 4 times daily provided symptomatic relief. Notably, she reports having had a similar episode at night 1 month earlier but does not recall eating red meat that day. She notes that she is an avid hiker and has a history of several spider and tick bites.

Laboratory tests show a serum galactose-alpha-1,3-galactose (alpha-gal) immunoglobulin (Ig) E level of 41.2 kU/L (reference < 0.1 kU/L) and a total IgE level of 475 kU/L (< 130 kU/L). A presumed diagnosis of alpha-gal syndrome is made.

The patient is advised to abstain from eating mammalian meat. She reports another episode of abdominal pain after having a milkshake, despite adhering to a non–mammalian meat diet. She is advised to avoid consuming dairy products. After following an elimination diet for 3 years, her alpha-gal IgE level declines from 41.2 kU/L to 0.82 kU/L.

Because of the gradual decline in alpha-gal IgE levels, an oral challenge with 100 grams of ground beef is performed in the clinic. After 5 hours of observation, the patient remains asymptomatic. Due to a successful oral challenge, she resumes consuming mammalian meat and does not have any further reactions.

Figure 1. The lone star tick (*Amblyomma americanum*).

Reprinted from US Centers for Disease Control and Prevention. Lone Star Tick Surveillance. www.cdc.gov/ticks/data-research/facts-stats/lone-star-tick-surveillance.html.

WHAT IS ALPHA-GAL SYNDROME?

Alpha-gal syndrome, also known as alpha-gal allergy, mammalian meat allergy, or tick-bite–related meat allergy, is an emerging allergic condition that triggers IgE-mediated anaphylaxis, gastrointestinal symptoms or skin reactions, or both, a few hours after an affected person consumes mammalian meat, such as beef, pork, goat, rabbit, venison, or lamb, or mammalian-derived products.[1] Another phenotype, gastrointestinal alpha-gal syndrome, presents with symptoms such as abdominal pain, diarrhea, and nausea or vomiting, but without any skin, respiratory, or circulatory complaints.

Alpha-gal syndrome mostly occurs in adults and was first identified in the early 2000s.[2,3] Between 2010 and 2022, more than 100,000 cases of presumed alpha-gal syndrome were identified in the United States[4]; however, the exact prevalence of alpha-gal syndrome is unknown.

Many clinicians are not aware of alpha-gal syndrome. A nationwide survey of 1,500 healthcare professionals by the US Centers for Disease Control and Prevention showed that 42% were unaware of the condition, and 35% lacked confidence in diagnosing or treating patients with alpha-gal syndrome.[5] Because cases continue to increase and symptoms overlap with other gastrointestinal illnesses and allergies, gastroenterologists and primary care clinicians must be aware of alpha-gal syndrome for timely diagnosis and intervention.

HOW TICK BITES CAN INDUCE A MEAT ALLERGY

Alpha-gal, the allergen identified in alpha-gal syndrome, is an oligosaccharide found in the cells and tissues of all nonprimate mammals. Sensitization to alpha-gal is thought to occur through parasitic infections, most commonly tick bites, when the immune system produces IgE antibodies directed against alpha-gal present in the parasite's saliva.[6,7] According to Commins et al,[8] 80% of patients with suspected alpha-gal syndrome report being bitten by ticks, and these individuals have higher alpha-gal IgE levels than those who have not been bitten.[9]

In the United States, the lone star tick (*Amblyomma americanum*; **Figure 1**), which primarily parasitizes deer and is responsible for 90% of all tick bites in the southern United States,[3,10] has been identified as the vector responsible for alpha-gal syndrome.[11] This tick is unique because it is the only tick that bites humans during its larval stage, positioning it as the primary source of alpha-gal sensitization in the United States.[3] Other tick species that have been identified as carriers of alpha-gal in their saliva include the blacklegged tick (*Ixodes scapularis*), also known as the deer tick, in the United States; the Cayenne tick (*Amblyomma cajennense*) in Central America and Brazil; and the Asian long-horned tick (*Haemaphysalis longicornis*) in Asia.[11–13]

Glycolipid hypothesis

Although the exact pathogenesis of alpha-gal syndrome is unknown, it involves IgE-mediated activation of mast cells after mammalian meat is consumed.[13] The current "glycolipid hypothesis" describes the mechanism for the delay in response to ingestion of meat products containing alpha-gal and subsequent development of symptoms.

After individuals sensitized to alpha-gal consume mammalian meat or its derivatives, lipid micelles are formed from glycolipids containing alpha-gal.[14] Enzymes in the small intestine, mainly pancreatic lipase, break down triglycerides within the micelles into free fatty acids, monoglycerides, and diglycerides, which are absorbed by intestinal cells. The intestinal epithelium then converts the fatty acids and monoglycerides into triglycerides and bundles them into lipoprotein particles, or chylomicrons, that display alpha-gal molecules. The chylomicrons enter the lymphatic system via lacteals and reach the bloodstream about 4 hours after a meal,[1] where the alpha-gal molecules bind to alpha-gal–specific IgE antibodies on the surface of basophils or mast cells.[14] This triggers an allergic reaction or anaphylaxis as mast cells release a cascade of allergic mediators, which stimulate sensory nerves, inducing visceral pain through the contraction of intestinal smooth muscles, and activate excessive mucous secretion by the mucous glands.[3]

RANGE OF SYMPTOMS AND TRIGGERS

Alpha-gal syndrome can present with various symptoms, and the intensity of symptoms can vary over time.

Symptoms usually occur 3 to 8 hours after exposure to alpha-gal, but can also happen immediately.[15] Common symptoms include pruritus, erythema, hives, and angioedema, or severe systemic manifestations such as anaphylaxis with cough, wheezing, shortness of breath, and hypotension.

In some instances, patients can have localized gastrointestinal symptoms. A recent study showed that, among 91 individuals with alpha-gal allergy, 40.7% experienced gastrointestinal symptoms exclusively.[16] The predominant symptoms reported in the gastrointestinal phenotype are abdominal pain, nausea, vomiting, diarrhea, and heartburn.[16–18] These patients are frequently misdiagnosed with functional gastrointestinal disorders, commonly irritable bowel syndrome, owing to both the lack of awareness of alpha-gal syndrome and the lack of testing for IgE antibodies to alpha-gal.[1,3]

Notably, most sensitized individuals do not experience any symptoms after ingesting mammalian meat.[3] In regions where ticks are prevalent, 15% to 35% of the population may be sensitized to alpha-gal, but clinical alpha-gal syndrome occurs in only 1% to 8%.[15] It is crucial to recognize that, even if a person is allergic to alpha-gal, reactions may not always occur after they consume mammalian meat,[3] and a sensitized individual who has tolerated meat previously is still prone to allergic reactions in the future.

The likelihood and intensity of these reactions can be exacerbated by multiple exogenous and endogenous factors. Alcohol, nonsteroidal anti-inflammatory drugs, and exercise can enhance intestinal food absorption, potentially raising the concentration of alpha-gal allergens in the body and lowering the threshold for allergic reactions.[13] Additionally, consuming fatty cuts of meat can enhance an allergic reaction because they contain higher levels of glycolipids containing alpha-gal.[19,20] When digested, these fats form the alpha-gal–coated chylomicrons that can trigger allergic reactions by activating mast cells, as discussed above.

Individuals who have a personal or family history of food or insect allergies are more likely to have alpha-gal syndrome and experience more severe symptoms due to cross-reactivity between oligosaccharides. Those with blood type A or O are also at higher risk of developing alpha-gal syndrome.[21]

MEDICAL PRODUCTS THAT CONTAIN ALPHA-GAL CAN TRIGGER ALLERGIC REACTIONS

Medications and medical products containing alpha-gal may trigger reactions more frequently in patients with alpha-gal antibodies.[22] Chung et al[23] observed that antibodies to alpha-gal were present in patients with severe hypersensitivity to cetuximab, a therapeutic monoclonal antibody containing alpha-gal in the fragment antigen-binding portion of the heavy chain. (This led to the first observation of alpha-gal syndrome and its association with higher prevalence in regions where the lone star tick is located; see next section.)

The risk of reaction to other medical products that contain alpha-gal such as vaccines with gelatin (especially the live attenuated zoster vaccine), porcine-derived heparin or pancreatic enzymes, equine-derived antivenins, and bioprosthetic heart valves is not known, but cases of such reactions have been reported.[24–28] Heparin products are well tolerated in 98.3% of patients with a documented alpha-gal allergy.[26] On the other hand, positive skin prick tests to both antivenins and cetuximab have been seen in patients sensitized to alpha-gal, suggesting a potentially high risk of anaphylaxis with therapeutic doses of antivenin.[29]

Additionally, medical devices derived from animal materials, such as bioprosthetic cardiac valves, pose risks to those with alpha-gal sensitivity.[27] Despite anecdotal evidence of hives and anaphylaxis after porcine or bovine valve replacement, conclusive research on valve failures due to alpha-gal reactions is lacking.[25]

The probability of a clinically significant reaction is relatively low and may be influenced by the animal source, processing methods, purity level, and administered dose, as well as the patient's serum alpha-gal antibody titers.[24,26,27,29]

WHEN TO CONSIDER ALPHA-GAL SYNDROME

Patients should be tested for alpha-gal IgE antibodies if they are experiencing unexplained gastrointestinal symptoms that awaken them at night, as this reflects the characteristic delay from ingestion to reaction observed in individuals sensitized to alpha-gal.[2] These patients may also report a history of tick bites and frequent engagement in outdoor activities. However, clinicians should be cautious about testing patients exhibiting "red flag" symptoms like anemia, gastrointestinal bleeding, or significant weight loss because these are not typically caused by alpha-gal syndrome.[3] The presence of skin symptoms, including urticaria and angioedema, may also vary among patients.

Clinicians should consider alpha-gal syndrome as a potential diagnosis if patients with unexplained gastrointestinal symptoms live or have lived in regions where alpha-gal syndrome is common (**Figure 2**).[4] These regions are also where the lone star tick is found, and include the southern, midwestern, and mid-Atlantic

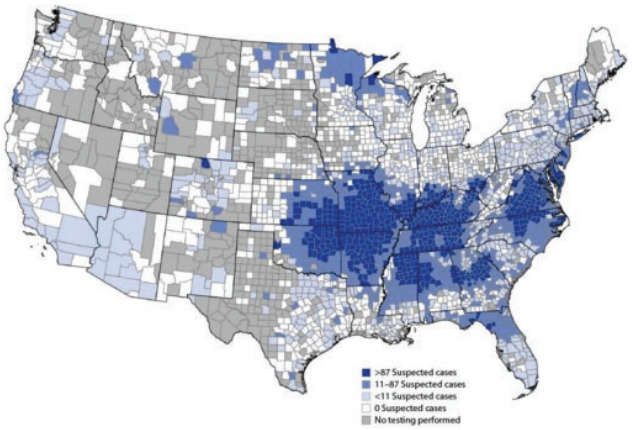

Figure 2. US Centers for Disease Control and Prevention data on the geographic distribution of suspected cases of allergy to galactose-alpha-1,3-galactose (alpha-gal syndrome) per 1 million population per year in the United States (2017–2022).

Reprinted from reference 4.

United States—particularly parts of Oklahoma, Kansas, Arkansas, Missouri, Mississippi, Tennessee, Kentucky, Illinois, Indiana, North Carolina, Virginia, Maryland, and Delaware, and Suffolk County in New York (**Figure 3**).

DIAGNOSIS IS A CHALLENGE

Alpha-gal syndrome is difficult to diagnose: the presenting symptoms can be vague, and reactions in sensitized individuals are delayed—typically happening late in the evening or in the middle of the night—or may not always occur, unlike other food allergies. Therefore, alpha-gal syndrome, especially gastrointestinal alpha-gal syndrome, may be underdiagnosed.

Alpha-gal syndrome is primarily identified through clinical evaluation and supported by laboratory testing. A history of tick bites, including larval tick bites (such as seed ticks) or "chigger" bites, and frequent engagement in outdoor activities can support a diagnosis of alpha-gal syndrome; however, tick bites are often painless, and around half of patients who develop a tick-borne illness don't remember being bitten.[15]

Serum IgE testing

An alpha-gal IgE level of 0.1 kU/L or greater confirms the diagnosis of alpha-gal syndrome, as it has a reported specificity of 92.3% and a sensitivity of 100%.[15] Laboratory testing for IgE antibodies against alpha-gal should be considered when clinical evaluation and patient history confirm 2 or more of the following:

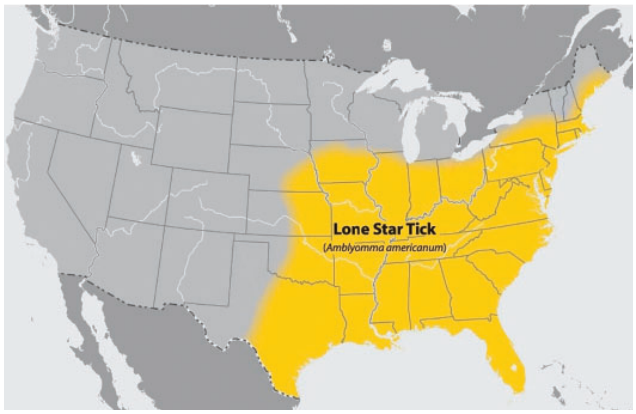

Figure 3. Distribution map of the lone star tick (*Amblyomma americanum*) in the United States.

Reprinted from US Centers for Disease Control and Prevention. Lone Star Tick (*Amblyomma americanum*). stacks.cdc.gov/view/cdc/25414.

- Timing: nighttime symptoms, starting with itching
- Ticks: history of tick bites, history of avid outdoor activities in tick-prevalent areas, prolonged irritation at the site of the tick bite
- Diet: consumes mammalian meats and high-fat dairy.

Diagnosis can be particularly difficult in patients who have reactions to mammalian products but test negative for alpha-gal IgE, which occurs in approximately 2% of patients referred for evaluation of alpha-gal syndrome.[15] Because patients with alpha-gal syndrome are also found to have elevated IgE antibodies against beef, pork, and lamb, serum IgE testing for these alternative markers can help establish the diagnosis.[8]

Skin testing

Skin prick tests with mammalian meat extracts are unreliable because of false negatives and should not be used to establish an alpha-gal syndrome diagnosis.[15] The presence of IgE antibodies to beef can indicate a primary beef allergy, and IgE antibodies to pork (porcine and cat albumin) may signify pork-cat syndrome. Occasionally, skin testing for reaction to alpha-gal–containing drugs like cetuximab and basophil activation testing can be performed in those who test negative for alpha-gal IgE antibodies.

Oral food challenge

Although food allergies are generally diagnosed through food challenges, the delayed reaction characteristic of alpha-gal syndrome renders such challenges cumbersome and infeasible for routine clinical practice. However, if the initial serologic testing does not lead to a clear diagnosis, an oral food challenge may help.[15]

Given the unpredictable nature of alpha-gal food challenges, discussing the risks and benefits with patients is essential. According to Commins,[15] 15% to 20% of patients with alpha-gal syndrome undergoing food challenges required epinephrine, emergency medical transport, or both. As a result, alpha-gal food challenges should only be conducted by clinicians skilled in identifying and managing anaphylaxis, and should always be done in a controlled clinical environment where lifesaving treatments, such as epinephrine, are readily available.

These challenges should be performed when clinically appropriate in certain specific cases[15]:

- Unclear cause of an allergic episode and patient tests positive for alpha-gal IgE (≥ 0.1 kU/L) but continues to consume mammalian meat without any symptoms
- History of tick bites or significant exposure and patient tests positive for alpha-gal IgE and has been advised to avoid mammalian meat based solely on test results, despite not having symptoms
- Alpha-gal IgE level less than 2.0 kU/L in a patient who can tolerate high-fat ice cream made from cow's milk and a small amount of pepperoni (about 12 g) without any reactions and has no history of tick bites for 1 year
- History of alpha-gal syndrome in patient who tests negative for alpha-gal IgE (< 0.1 kU/L) and has been followed over time
- Symptoms suggest alpha-gal syndrome but patient tests negative for alpha-gal IgE and additional diagnostic tests have been inconclusive.

An oral mammalian meat challenge may be performed with 2 pork sausage patties (70 g) or 3 patties in patients weighing greater than 70 kg.[15] Pork is used for oral challenges due to its fatty composition, which increases the likelihood of allergic reactions.[19] After an oral challenge, these patients must be monitored for up to 6 hours due to the risk of delayed reactions.

MANAGEMENT OF ALPHA-GAL SYNDROME

Currently, there is no cure for alpha-gal syndrome. The primary management strategy is eliminating foods and products that contain alpha-gal for a minimum of 30 days.[3] Promising data show that extended avoidance of alpha-gal can lead to symptom resolution in many patients. According to a 2021 study of 16 patients with alpha-gal IgE antibodies, three-quarters reported significant improvement or resolution of symptoms after following a strict alpha-gal–free diet over a median follow-up of 13 months.[30]

TABLE 1
Food and product safety for patients with alpha-gal syndrome

Contain alpha-gal
Foods
Meat: beef, pork, lamb, venison, rabbit, goat, buffalo, bison horse
Animal viscera: kidney, liver, heart, intestine, lung
Gelatin from beef and pork: marshmallow, gummy bears, other gelatin-based items
Lard and tallow
Cow's milk and cow's milk–based items: butter, cheese, yogurt, cream, cream cheese, ice cream
Nut milks
Medical products
Gelatin-containing vaccines: measles, mumps, and rubella; yellow fever; live attenuated zoster
Glycerol
Magnesium stearate
Porcine-sourced heparin
Monoclonal antibodies
Thrombin
Bovine-derived pancreatic enzymes
Porcine and bovine heart valves
Equine-derived antivenin
Personal care products
Lanolin
Collagen
Glycerin
Do not contain alpha-gal
Meat: chicken, turkey, duck
Seafood
Fish
Eggs
Fruits
Vegetables

Alpha-gal = galactose-alpha-1,3-galactose.

Based on information from references 15 and 24.

Avoiding dairy products is not part of our standard recommendation because 80% to 90% of patients with alpha-gal syndrome do not have reactions to cow's milk or cheese.[15] That said, published research and expert advice suggest that patients still symptomatic despite avoiding mammalian meat might benefit from eliminating dairy.[24] Poultry, fish, and seafood, however, are safe for consumption because they do not contain alpha-gal.

Foods and products to avoid

Mammalian-derived products should be avoided. Gelatin, which is made from collagen in pig or cow bones,

TABLE 2
Recommended medications

Indication	Medication and dose
Frequent travel	Fexofenadine 180 mg daily[32] Levocetirizine 5 mg daily in the evening[32] Montelukast 10 mg daily in the evening[33]
Predominant gastrointestinal symptoms	Oral cromolyn solution 100 to 200 mg, 2 to 4 times daily, 20 to 30 minutes before meals[15]
Refractory symptoms	Omalizumab (dose based on weight and immunoglobulin E levels)[31]
Severe symptoms[a]	Self-injectable epinephrine[3]

[a]Respiratory compromise, hypotension, severe angioedema.

is present in foods such as marshmallows, gummy bears, and gelatin-based desserts, which should be avoided if previous allergic reaction episodes have occurred after exposure. Similarly, lanolin, collagen, and glycerin in personal care products are derived from mammals and should be avoided in instances of previous reactions. Because reactions have been reported with exposure to the monoclonal antibody cetuximab, it is reasonable to avoid it or to consult an allergist before starting this medication. Carrageenan, an additive made from seaweed and used to thicken and stabilize yogurt, nut milks, and processed meat products, also contains alpha-gal and may provoke an allergic reation.[15]

A summary of foods and products that do and do not contain alpha-gal is provided in **Table 1**.[15,24]

Medical therapies

Medical therapy can be considered for patients with continued symptoms or with a high exposure risk (**Table 2**).[3,15,31–33] Options include using long-lasting oral antihistamines such as fexofenadine or levocetirizine, which are effective for 22 to 28 hours after intake.[32] An oral cromolyn solution may also be prescribed to stabilize mast cells, particularly to address gastrointestinal symptoms.[13] Moreover, for refractory cases, the anti-IgE monoclonal antibody omalizumab may be helpful.[34] In cases of severe allergic symptoms and anaphylaxis, patients must have access to self-injectable epinephrine for emergencies.

Alternative therapies to treat alpha-gal syndrome, such as acupuncture, currently have no scientific evidence to support their use.

Referral to an allergist

Managing alpha-gal syndrome extends beyond simple dietary restrictions and involves a multidisciplinary approach with gastroenterologists, dietitians, and allergists to ensure comprehensive patient care. An allergist referral should be placed when patients have symptoms such as facial or throat swelling, voice changes, breathing difficulties, hives, or fainting after eating. These symptoms suggest a high risk of anaphylaxis and the need for epinephrine autoinjectors. Allergists can also assist with oral food challenges, especially when there is a potential risk of anaphylaxis.

Figure 4 is our algorithmic approach to the diagnosis and management of presumed alpha-gal syndrome.

PREVENTING TICK BITES

Primary prevention for alpha-gal syndrome involves avoiding tick bites and taking appropriate action if a tick is detected. Areas where ticks are common, such as tall grass, bushes, shrubs, and leaf litter, should be avoided. Moreover, ankles and legs should be covered while hiking, ideally with clothes and boots treated with permethrin to deter ticks, and N,N-diethyl-meta-toluamide should be applied to the skin.[3,35]

Tick checks should be conducted after outdoor activities in wooded areas. The lone star tick is considerably larger than the blacklegged tick, which is the vector for Lyme disease, making it much more visible. If a tick is found, it should be removed immediately with the help of tweezers, grasping the tick near its head or mouth to ensure complete removal without crushing. An antiseptic can then be applied to the area.

ADVICE FOR PATIENTS WITH ALPHA-GAL SYNDROME

Patients with alpha-gal syndrome should be cautioned to prevent future tick bites, as repeated bites can sustain

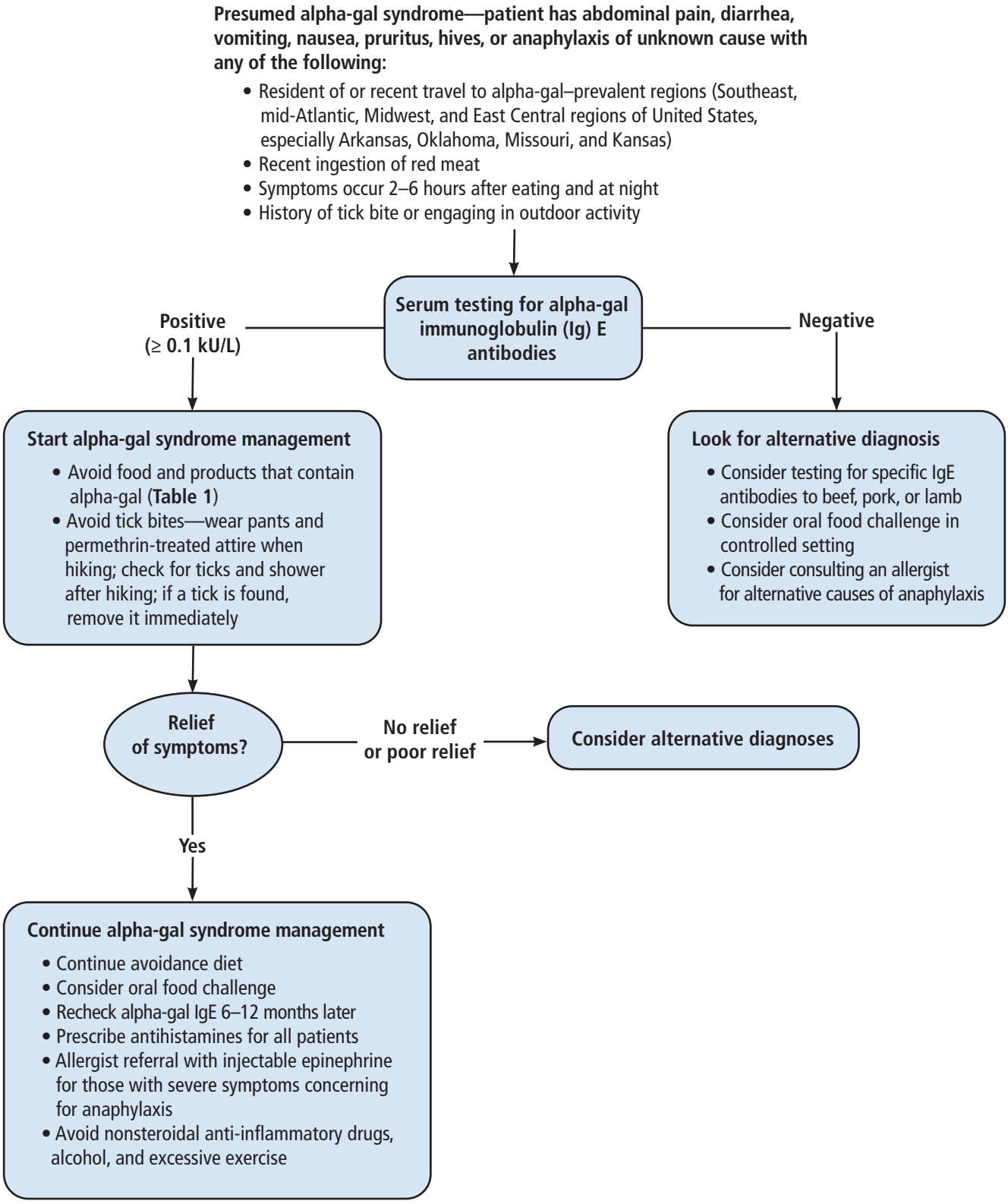

Figure 4. Algorithm for the diagnosis and management of presumed allergy to galactose-alpha-1,3-galactose (alpha-gal syndrome).

or increase alpha-gal IgE levels, which could exacerbate their allergy and symptoms.[6,11] Most patients (89%) who avoid tick bites tend to see a decline in their alpha-gal IgE levels.[36] While the rate of decrease varies, and it is uncertain what level of reduction is necessary to restore tolerance, Commins[15] found that nearly 12% of patients tracked for more than 5 years had negative alpha-gal IgE titers (< 0.1 kU/L) and were able to reintroduce mammalian meat into their diets.

In addition, if patients with alpha-gal syndrome are still consuming red meat, they should be advised to use alcohol and nonsteroidal anti-inflammatory drugs with caution and to limit their consumption of fatty meats. It is also crucial to educate these patients about the potential risk of accidental exposure to alpha-gal through processed foods, restaurant meals, and inhalation of aerosolized alpha-gal from cooking bacon or beef products.

RESEARCH GAPS AND FUTURE IMPLICATIONS

There is a lack of research on alpha-gal syndrome, and comprehensive studies are needed. Research should focus on evaluating the symptoms and immune responses in patients sensitized to alpha-gal through blinded food challenges with both alpha-gal–free and conventional mammalian meat, which would deepen our understanding of the clinical spectrum of gastrointestinal alpha-gal syndrome. Additionally, exploring the timeline to symptom resolution while following an alpha-gal–free diet and identifying factors that might further improve symptoms would be valuable. Investigating sensitized individuals who do not have symptoms, the mechanisms responsible for the spectrum of symptoms among patients with alpha-gal syndrome, and whether alpha-gal syndrome can cause chronic systemic inflammation and contribute to coronary artery disease could provide valuable insights into potential health consequences.

Moreover, further geographic studies on the regions where alpha-gal syndrome is prevalent should be conducted to identify individuals at a higher risk who might benefit from stricter preventive measures. Clear guidelines for risk stratification and desensitization protocols in patients with alpha-gal syndrome are also needed.

TAKE-HOME POINTS

- Alpha-gal syndrome has emerged as a significant and increasing contributor to anaphylaxis and severe allergic responses to mammalian meat.[1]
- Gastroenterologists need to be aware of alpha-gal syndrome, particularly because some patients exhibit gastrointestinal symptoms without skin or anaphylactic reactions.[3]
- An alpha-gal syndrome diagnosis is presumed when a symptomatic patient is from a region where lone star ticks are prevalent and has a history of a recent tick bite and mammalian meat consumption.[15]
- Definitive diagnosis requires laboratory testing that reveals increased serum alpha-gal IgE antibodies in patients with gastrointestinal distress who then show improvement on a diet that avoids alpha-gal.[15]
- The primary management strategy is eliminating alpha-gal exposure and preventing future tick bites to mitigate the risk of escalating IgE titers and worsening allergy symptoms.[3,6]
- Referral to an allergist is recommended for patients experiencing severe reactions.

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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