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Polymyalgia rheumatica
Thoracic aortic aneurysm
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Trying to get ahead of Alzheimer disease

Current data from the Alzheimer’s Association indicate that 1 in 10 people age 65 and older has Alzheimer dementia; almost two-thirds are women. Since the disease process begins decades before the recognized features of the illness appear, the numbers are even more striking.

While I often struggle to characterize features of specific early dementias and distinguish them from mild cognitive impairment or from sleep disruption and the effects of stressors of an underlying medical illness, my geriatrics and neurology colleagues who diagnose and manage Alzheimer disease patients still rely greatly on the clinical history provided by patients and their companions. Loss of ability to accurately recall recent specific events or places seems to be more specific than word-finding challenges. Executive functions and multitasking may deteriorate relatively early in some, without visual hallucinations and parkinsonian features that characterize some patients with Lewy body disease. But the early clinical features of patients with different dementias often overlap. Sorting out patients destined to have Alzheimer disease from those with mild cognitive impairment, vascular dementia, and other disorders remains a challenge.

Routine magnetic resonance imaging, even with focal volume measurement, does not seem to reliably detect early Alzheimer disease. Functional fluorodeoxyglucose positron emission tomography (FDG-PET) is expensive and also not ideally specific in distinguishing Alzheimer patients from others with mild cognitive impairment. Specialized PET using probes to identify the amyloid beta plaques is not uniformly available and also is not perfectly specific when sorting out patients with mild cognitive impairment, but this technology is rapidly advancing.

Moreover, at present, despite the growing understanding of the pathophysiology of Alzheimer disease, we have no specific proven treatment for it. Hence, one can put forth the question of whether early diagnosis actually matters. The counter argument is that it may matter a great deal to the patient and family as they make personal and family plans and decisions. And there are relevant clinical issues as well. Perhaps the reason we have no proven effective therapies, despite development of sophisticated targeting agents based on the known pathophysiology of Alzheimer disease, is that we are limited in our ability to recognize early disease and its subtypes. The lack of readily available, affordable, practical, and accurate biomarkers hampers not only our ability to provide guidance to (potential) Alzheimer patients and their families, but also our ability to easily and accurately recruit the most appropriate patients for clinical trials.

There are useful diagnostic biomarkers in the cerebrospinal fluid (eg, decreased amyloid beta 1–42 and increased specific phosphorylated tau proteins), but obtaining these can be cumbersome, and while they can generally distinguish Alzheimer patients from otherwise healthy elder adults, there has still been some concern about their ability to discriminate this disease from other dementias. The logistics of obtaining a lumbar puncture and concern regarding the specificity of these tests combine to make
cerebrospinal fluid biomarkers less than ideal in general practice.

In this issue of the Journal (page 537), Bekris and Leverenz summarize recent advances in the development of blood-based biomarkers for Alzheimer disease. While there has been some hype over potential “new tests” for this disease, the current status and associated caveats are outlined in their commentary.

A question for another day remains: If a very sensitive test became available to diagnose preclinical Alzheimer disease, would you request it for yourself?

BRIAN F. MANDELL, MD, PhD
Editor in Chief
2020

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CLEVELAND CLINIC EPILEPSY UPDATE AND REVIEW COURSE September 21–24 LIVE STREAM
INTENSIVE REVIEW FOR THE GI BOARDS: INFLAMMATORY BOWEL DISEASE AND SMALL-BOWEL DISEASE PANEL DISCUSSION AND Q & A September 23 LIVE STREAM
INTENSIVE REVIEW FOR THE GI BOARDS: PANCREAS, BILIARY, ENDOSCOPY PANEL DISCUSSION AND Q & A September 30 LIVE STREAM

OCTOBER
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PAIN MANAGEMENT SYMPOSIUM March 27–31 Orlando, FL

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SARS-CoV-2 and myocardial injury: Few answers, many questions

ABSTRACT
Acute cardiac injury, defined as an elevated high-sensitivity troponin I or troponin T upon admission or during hospitalization, is common in patients with COVID-19, occurring in 10% to 35% of patients depending on the assay used and the population studied. Even though the mechanisms of SARS-CoV-2 myocardial injury are not well defined, type 1 myocardial infarction and fulminant myocarditis are rare. Often, acute cardiac injury occurs in patients with elevated inflammatory markers, and both are associated with worse outcomes. However, the extent to which treatments should differ for patients with acute cardiac injury, heightened systemic inflammation, or both, is unknown.

KEY POINTS
The mechanisms of acute cardiac injury in COVID-19 are still being defined but include oxygen supply-demand imbalance, microvascular and endothelial dysfunction, and micro- and macrothrombosis. In some patients, these manifestations may be driven by an inappropriate inflammatory response.

Like other patients, COVID-19 patients with ischemic ST-segment elevation need emergency reperfusion therapy.

Patients with elevated troponin and elevated inflammatory markers may possibly benefit from immunosuppressive therapy, although further studies are needed.

What is the mechanism of SARS-CoV-2–associated myocardial injury?
To what extent are SARS-CoV-2 patients with myocardial injury a distinct population?
What are possible treatment options for myocardial injury associated with SARS-CoV-2 infection?

WHAT IS THE MECHANISM?
With regard to mechanism, the primary question is whether SARS-CoV-2 infection precipitates myocardial infarction with an oxygen supply-demand imbalance, either with or without acute coronary plaque pathology (type 1 and 2 myocardial infarction), or conversely,
causes myocardial injury mediated by the virus itself or the cytokine response to it.

Viral infections are well known to lead to adverse cardiovascular events, either by increased metabolic demand in the setting of limited cardiac reserve or by precipitating plaque rupture in the setting of inflammation and a prothrombotic state.9 Of note, influenza vaccination has been shown to reduce hospitalizations for cardiac disease.10 In addition, certain viruses (eg, parvovirus B19 and influenza) commonly cause myocarditis.

Although myocardial injury has not been prominent with other coronaviruses, unfortunately, SARSCoV-2 appears to be behaving differently. Despite an overall case-fatality rate of approximately 10% in symptomatic patients in the previous SARS-CoV outbreak that resulted in severe acute respiratory syndrome (SARS), cardiac complications were anecdotal and limited to case reports or series.11 Similarly, despite an even higher case-fatality rate in Middle East respiratory syndrome due to MERS-CoV, cardiac complications were limited.9,12

In contrast, in an initial report of causes of death in COVID-19, one-third were considered secondary to respiratory failure with myocardial damage, and nearly another tenth were considered secondary to myocardial damage alone.13 Furthermore, perimyocarditis from SARS-CoV-2 infection has been reported in the absence of symptomatic respiratory disease,14 though fulminant myocarditis—generally defined as sudden and severe inflammation of the myocardium resulting in myocyte necrosis, edema, and cardiogenic shock—seems to be a rare presentation with SARS-CoV-2.

Of note, SARS-CoV-2 enters respiratory and cardiac cells via angiotensin-converting enzyme 2 (ACE 2), a membrane-bound protein.15 Yet this potential cardiac tropism offers an incomplete explanation for the seemingly disproportionate cardiac manifestations of COVID-19, given that SARS-CoV also uses ACE 2 as a functional receptor.15,16

Alternatively, myocardial injury may be exacerbated by an inappropriate activation of type 1 T-helper cells and cell-mediated immunity with associated cytokine storm.7 A recent autopsy study17 is consistent with this hypothesis. Among 39 patients, SARS-CoV-2 cardiac infection was documented in 61.5%, and patients with higher viral loads had greater expression of proinflammatory genes. However, inflammatory cell infiltrates typical of active myocarditis were not observed.

■ A DISTINCT POPULATION?
These putative mechanisms of injury are integrally entwined with the second question of whether patients with SARS-CoV-2-associated myocardial injury represent a distinct population. For one, COVID-19 patients with elevated troponins are older and have more cardiovascular comorbidities, such as coronary artery disease, chronic heart failure, hypertension, and diabetes mellitus.5,6,8 These findings support the concept of myocardial oxygen supply-demand mismatch with resultant ischemia in a vulnerable population.

However, in patients who succumb to COVID-19, troponin levels may continue to rise throughout the illness, a pattern distinct from the typical rise and fall after an ischemic insult.6 Moreover, about a third of patients may demonstrate an increase in troponin over time, and these patients have a higher mortality rate.9 Importantly, patients with elevated troponins have higher levels of inflammatory markers such as C-reactive protein (CRP).8 The increases in troponin and CRP appear to parallel each other, and the overall correlation is similar in magnitude to the correlation between troponin and N-terminal probrain natriuretic peptides. These observations, though nascent, suggest that some patients may develop a hyperinflammatory state that perpetuates nonischemic myocardial injury.

Given that elevated troponin is associated with a high mortality rate and that the mechanism of injury could be related to increased systemic inflammation, as more data are emerging, consideration should be given to checking troponin upon admission, with surveillance testing during the initial days of hospitalization. Further considerations in this initial clinical approach include assessing cardiac risk factors and the magnitude of the inflammatory response.

A rise and fall of cardiac markers in the presence of signs and symptoms of myocardial injury has not been prominent with other coronaviruses, but SARS-CoV-2 appears to be behaving differently.
dial ischemia, such as new ischemic changes on electrocardiography or imaging evidence of regional myocardial dysfunction in a pattern compatible with ischemia, diagnoses a myocardial infarction. The absence of these features defines myocardial injury, and substantial elevations in CRP may point toward cytokine-mediated damage.

Traditionally, cardiac imaging would feature prominently in the distinction between acute myocardial infarction and injury. Given limited resources and the need to minimize exposure to COVID-19 patients, this decision will be individualized, though it will involve selective use of focused echocardiography.

In patients who have convalesced from COVID-19, studies have shown that myocardial damage and inflammation may be evident in a majority of patients when assessed with cardiac magnetic resonance imaging. However, the cross-sectional design of these studies precludes any assessment of causality, and the clinical implications are unclear. Therefore, in the absence of another indication, cardiac magnetic resonance imaging is currently not clinically recommended in asymptomatic patients who have recovered from COVID-19.

Of note, the overlap between acute myocardial infarction, myocardial injury, and heightened systemic inflammation continues to be defined, though these considerations do aid in risk stratification. An elderly patient with coronary artery disease, diabetes mellitus, and elevations in troponin and CRP will have among the poorest prognoses. However, even in the absence of these risk factors, a patient with elevated troponin and inflammatory markers is at increased risk. In evaluating patients with an elevated troponin, we are well accustomed to risk stratification according to cardiovascular comorbidities, but with COVID-19, we should also risk-stratify based on the degree of heightened inflammation.

**WHAT ARE THE POSSIBLE TREATMENTS?**

Finally, the consideration of treatment options in a patient with a positive troponin test is informed by the presumed answers to the first 2 questions. Specifically, does the mechanism of injury seem more likely related to myocardial infarction with oxygen supply-demand mismatch, or to direct myocardial injury? And is this a patient with underlying cardiac conditions, increased systemic inflammation, or both?

Treatment strategies for type 1 myocardial infarction are well delineated, and treatment of type 2 myocardial infarction includes addressing the underlying cause and providing therapies to improve the myocardial oxygen supply-demand mismatch, especially in the setting of known fixed coronary stenosis. Importantly, therapies such as beta-blockers and vasodilators must be used judiciously to avoid precipitating decompensated heart failure or shock. In this setting, revascularization is rarely indicated, and the benefit of antiplatelet and anticoagulant therapy is unknown.

With COVID-19, treatment is supportive, and directed therapies are urgently required. Remdesivir has been shown to shorten the time to recovery, and in hospitalized patients who are hypoxic, dexamethasone improves survival. In severe disease, the success of dexamethasone suggests that morbidity and mortality may be driven by heightened inflammation. This increased inflammation may progress to secondary hemophagocytic lymphohistiocystosis and resultant fatal hypercytokinemia with multiorgan failure. In this inflammatory state, further immunosuppression may improve outcomes.

In cardiac disease, promising immune treatments target autoinflammation, a process driven by endogenous danger signals and perpetuated by inflammasome-induced cytokine production. Such therapies have demonstrated efficacy and include colchicine, rilonacept, and anakinra in pericarditis and colchicine and canakinumab in atherosclerotic disease. Colchicine inhibits tubulin polymerization and inflammasome activity, whereas anakinra, rilonacept, and canakinumab inhibit interleukin 1, a cytokine that is central to the inappropriate innate immune response. In open-label case-control studies, anakinra and canakinumab have shown promise in treating severe COVID-19 pneumonia, and a small randomized trial suggested a potential benefit of colchicine. Accordingly, larger randomized studies with these therapies are currently enrolling patients.
For troponin-positive COVID-19 patients, we currently have few answers and many questions. With COVID-19, typical acute coronary syndromes and classic myocarditis occur rarely. The mechanisms of acute cardiac injury are still being defined, but include oxygen supply-demand imbalance, microvascular and endothelial dysfunction, as well as micro- and macrothrombosis. In some patients, these manifestations may be driven by an inappropriate inflammatory response.

In general, for the practicing clinician, we can consider 3 broad categories of patients with COVID-19 and abnormal troponins:
- Patients with ischemic ST elevation, who need emergency reperfusion therapy
- Patients with troponin elevation without systemic heightened inflammation, who need supportive care
- Patients with elevated troponin and inflammatory markers, who may possibly benefit from immunosuppressive therapy, although further studies are needed (Figure 1).

**REFERENCES**

13. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 pa-

Address: Paul Cremer, MD, Cardiovascular Medicine, J1-5, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; cremerp@ccf.org
Management of patients with COVID-19 in the MICU

ABSTRACT

COVID-19 management practices devised for the medical intensive care unit are centered on 2 main goals: ensuring caregiver safety and providing the highest quality patient care through adherence to evidence-based best practices. Rapid, sweeping changes for successful management are based on creating an educational platform to introduce and then further cement these concepts through a unified approach to clinical care. Creating a culture change in a short period of time requires overcoming a host of challenges; however, the result is a more unified and focused approach.

KEY POINTS

- Use personal protective equipment based on the risk of transmission when in contact with patients who are potentially COVID-19-positive.
- Evaluate patients often to avoid delaying intubation.
- If intubation is required, modify procedures to ensure caregiver safety.
- On admission, obtain electrocardiography, troponin levels, ferritin levels, and select serologic tests.
- Bundle all care (eg, medications, laboratory samples, and procedures) to limit traffic into the room.
- To minimize information overload, create a team to review available literature and develop an easily accessible and up-to-date educational resource.

As the COVID-19 pandemic continues, it is essential for healthcare providers to follow updated literature and adapt these to individual institutions. In this review, we describe the COVID-19 management practices devised for the medical intensive care unit (MICU) in the Respiratory Institute at Cleveland Clinic.

The foundation of our MICU operations is centered on 2 main goals: ensuring caregiver safety, and providing the highest quality patient care through adherence to evidence-based best practices.

ENSURING CAREGIVER SAFETY

We need to preserve our workforce for the health of the community and the functioning of the institution. Identifying the appropriate situations for personal protection equipment (PPE) is essential, so we adapted evolving standards of care (Figure 1) that outline when and how PPE should be used based on the risk of transmission when in contact with potential COVID-19-positive patients, either confirmed or under investigation for infection. Equipment includes a surgical mask, gown, protective eyewear, and gloves for all caregiver interactions. An N95 respirator or a powered air-purifying respirator (PAPR) is used for encounters with patients undergoing therapies at high risk for aerosolization (eg, high-flow nasal cannula [HFNC], noninvasive ventilation [NIV]) or procedures at high risk for disease transmission (eg, intubation, tracheostomy, endoscopy).

In addition, to reduce the high risk of transmission during the process of donning or doffing PPE, especially when doffing, we instituted a “buddy” system to create an additional layer of caregiver safety (Figure 2). This per-
son provides direct observation and feedback during the process of donning and doffing PPE to ensure caregiver safety.

We also adjusted respiratory practices to enhance safety by minimizing aerosolization. For hospitalized patients with COVID-19 who develop hypoxemia, oxygen is supplemented with a target oxygen saturation (SpO2) range of 90% to 96%, and the patients are transferred to the MICU on escalating requirements for closer observation, as they can quickly deteriorate. In patients with increasing oxygen requirements, we prefer HFNC with a surgical mask placed on the patient, as tolerated, to minimize aerosolization. In patients with concomitant comorbid conditions that indicate the use of NIV with either continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP), such as chronic obstructive pulmonary disease or congestive heart failure, we use expiratory-port high-energy particulate air (HEPA) filters.

**Personal Protective Equipment (PPE) Recommendations for Patient Care (Inpatient & Ambulatory)**

Use standard precautions in the care of all other patients based on anticipated exposure to blood & body fluid. Standard precautions may be used in addition to required PPE in patients in transmission-based precaution. PPE to consider based on exposure may include some or all of the following:

- Gloves
- Gowns
- Face Mask
- Eye Protection

<table>
<thead>
<tr>
<th>Guidelines for Care of SUSPECTED OR CONFIRMED COVID-19 patients:</th>
<th>Inpatient setting: Patients are immediately placed in appropriate isolation precautions (Droplet/Contact + Eyewear)</th>
</tr>
</thead>
</table>
| - Confirmed positive COVID-19  
- Signs or symptoms of respiratory illness  
- Pending respiratory viral testing  
- Presumed positive | N95² (fit-tested respirator)  
Face Mask² (surgical or ear-loop mask)  
Protective Eyewear (goggles or face shield)  
Gown & Gloves |

**Table 1.** Cleveland Clinic recommendation for personal protective equipment for COVID-19 (updated July 28, 2020).

**Figure 1.** Cleveland Clinic recommendation for personal protective equipment for COVID-19 (updated July 28, 2020).

1 Powered Air Purifying Respirator (PAPR) indicated for caregivers for whom an N95 mask does not fit.

2 Face mask usage:
- Masks should always be worn covering nose & mouth
- Handle used mask by ear loops or strings ONLY
- Never touch front of the mask

- Perform hand hygiene after handling used mask
- Fabric and cloth masks ARE NOT considered PPE
We integrate objective criteria into clinical judgment to identify patients with potential deterioration while on NIV or HFNC (Table 1). Although we do not advocate early intubation, these patients are evaluated often to avoid delaying intubation. In patients who are intubated, we use inline nebulizers. In those not on mechanical ventilation, we use metered-dose inhalers.

Procedures for intubation, if required, have also been modified to ensure caregiver safety. Preoxygenation is achieved with delivery of 100% oxygen via a nonrebreather mask or HFNC. Bag mask ventilation is not recommended. We have our most experienced operators use video laryngoscopy to perform intubation to minimize the duration of the procedure and to ensure maximum distance from the patient’s oropharynx. After successful intubation, we put patients directly on mechanical ventilators with continuous capnometr monitoring.
Chest radiography is performed at admission to ensure placement for necessary procedures such as nasogastric tube and central line. However, we avoid daily chest radiography unless clinically indicated, such as when changing location of the endotracheal tube or changing ventilation parameters (eg, increasing resistance, hypoxemia). We developed a process for performing portable radiologic studies from outside the room.

**MAINTAIN BEST PATIENT CARE**

It is challenging to maintain our standards of care when isolation practices increase. We have 5 distinct MICUs and we dedicated 2 of these units (with plans to expand further based on patient volume) to the COVID-19 patient population. Each patient has his or her own room with distinct walls.

To ensure the safety of other patients and our caregivers, we created a cohort unit in which we place all confirmed COVID-19 patients, while all MICU admissions were tested for COVID-19 regardless of the diagnosis.

Given that there is no curative therapy for COVID-19 and that therapeutic considerations have been extrapolated from limited experience and evolving literature, we developed multidisciplinary teams to help develop consistent clinical practice strategies. These teams include MICU providers, infectious disease specialists, and pharmacists.

For hypoxic respiratory failure, our mechanical ventilation strategy includes low-tidal-volume ventilation with a goal end-inspiratory plateau pressure of 30 cm H$_2$O or below and allows for permissive hypercarbia (pH ≥ 7.15). We titrate the fraction of inspired oxygen and positive end-expiratory pressure (Fio$_2$/PEEP) according to established protocols.$^1$ It is often easier to use existing evidence-based protocols in a pandemic when unfamiliar teams may be caring for these patients. Early proning and neuromuscular blockade are recommended as adjuvant therapy in patients. For patients who are refractory to conventional mechanical ventilation, trials of salvage therapy with inhaled vasodilator and extracorporeal life support can be considered. After initial volume resuscitation, as patients often come with evidence of volume depletion, we are vigilant in preventing and decreasing volume overload. In patients with acute lung injury, diuresis with the Fluid and Catheter Treatment Trial lite protocol should be implemented.$^2$ Dexamethasone is given to COVID-19 patients requiring mechanical ventilation or oxygen supplementation if there is no contraindication.$^3$

Although uncommon, bacterial co-infections have been reported in patients with COVID-19.$^3$ As a preventive measure, we start coverage with antibiotics in critically ill patients presenting with severe respiratory distress, basing it on their risk factors for community vs drug-resistant organisms (eg, MRSA, *Pseudomonas*). Procalcitonin is ordered on admission and followed to help with de-escalation of antibiotic therapy.

Critically ill patients with COVID-19 experience a sequelae of manifestations from activation of the innate inflammatory cascade, which increases the incidence of cardiomyopathy/heart failure, disseminated intravascular coagulation, venous thromboembolism (VTE), and the cytokine-release syndrome. Although there are currently no accepted standardized therapies for the prevention or treatment of these phenomena, we perform screening modalities that include electrocardiography, troponin levels, ferritin, and select serologic tests on admission with follow-up based on the patient’s

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**TABLE 1**

**Signs of respiratory failure despite noninvasive ventilation or a high-flow nasal cannula**

<table>
<thead>
<tr>
<th>Patients on noninvasive ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume &gt; 9.5 mL/kg ideal body weight consistently over the first 4 hours</td>
</tr>
<tr>
<td>Fraction of inspired oxygen (Fio$_2$) &gt; 60% to maintain target oxygen saturation (SpO$_2$)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients on high-flow nasal cannula</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROX index (ratio of SpO$_2$/Fio$_2$/respiratory rate) ≥ 4.88 at 2, 6, and 12 hours is a good predictor of no need for intubation, and &lt; 3.85 predicts high risk of need for intubation</td>
</tr>
</tbody>
</table>
COVID-19 AND MICU CARE

TABLE 2
Cleveland Clinic MICU COVID-19 workup checklist (updated 7/25/2020)

All patients under investigation or with confirmed COVID-19 on admission: procalcitonin, full respiratory viral panel, 2 sets of blood cultures, human chorionic gonadotropin (females of reproductive age)

Patients with confirmed COVID-19 or strongly suspected

On admission:
- Complete blood cell count (CBC) with differential, complete metabolic panel, liver function tests, lactate dehydrogenase, C-reactive protein (CRP), fibrinogen, D-dimer, high-sensitivity troponin, N-terminal pro-B-type natriuretic peptide, creatine kinase (CK), CK-MB, procalcitonin, ferritin, activated partial thromboplastin time, international normalized ratio, interleukin 6
- Chest radiography (bundle with other care)
- Electrocardiography
- Point-of-care ultrasonography
- Echocardiography if shock or suspicion for cardiomyopathy
- Deep vein thrombosis scan if D-dimer > 3,000 ng/mL

Daily monitoring:
- CBC, complete metabolic panel, magnesium, phosphate
- CRP daily; if elevated along with hemodynamic instability or persistent fever, consider checking triglyceride, ferritin, fibrinogen, and liver function tests; daily CRP can be discontinued at discretion of providers
- Troponin every day for 3 days or if change in hemodynamics
- No routine chest radiography
- Corrected QT interval from cardiac monitor

and performing procedures at the same time) to limit traffic into the room to only what is essential. Our nursing and respiratory therapy teams have placed medication administration pumps and ventilator screens outside of patient rooms, which has decreased our PPE use by about 50% to 60%. This placement also allows for more efficient titration of medications and ventilator settings, resulting in decreased sedative use and easier adjustment of ventilator support.

To further limit room traffic, we delegate 1 caregiver to perform a daily comprehensive physical examination with a dedicated single-use stethoscope that remains in the room. The results are documented and shared with all other care and consulting teams to limit entrance. They are repeated based on changes in the patient’s clinical condition.

Neurologic assessment and skin examination are performed by bedside nurses every 2 to 4 hours with other bundled care. All other practices including daily routine lab draws and ancillary support such as physical therapy continue on an essential-only basis.

Family visitation is limited as an infection-control method, but the team has placed special emphasis on maintaining communication with patients and their supporting members. Updates are amended in various fashions based on the provider and patient’s preference to be done outside of the rooms. This involves phone calls, videoconferencing, and in some instances communicating by writing on the glass doors.

Be aware of information overload. Not a minute goes by without a new post, tweet, e-mail, or letter from caregivers at the front lines with new disease manifestations or unproven therapies. At times, this generates an overwhelming amount of anxiety. We have created an educational team that is responsible for reviewing all available literature and developing an educational platform that serves our teams. This is done through an easily accessible, shared toolkit that allows our caregivers to rapidly find protocols and up-to-date educational resources (eg, webinars, simulations, checklists), especially with rapidly updated guidelines. This resource becomes the source of truth for the institution, aligns caregivers, and decreases anxiety from misinformation.

clinical course (Table 2). In patients at high risk of VTE (ie, those with D-dimer > 3,000 ng/mL fibrinogen equivalent units), we perform point-of-care ultrasonography to assess the presence of thromboembolism over extremities. Therapeutic anticoagulation is indicated for patients with conclusive evidence of VTE.

As with any new disease that has unproven therapies, our approach is to develop the best evidence-based guidelines for our teams to follow and to engage in clinical trials to form better guidance.

We also have developed bundle care practices to preserve PPEs while maintaining our standards of care. We bundle all care (eg, giving medications, obtaining laboratory samples,
SUMMARY

To manage COVID-19, we have developed best practices for the MICU to maintain the highest quality patient care while ensuring the safety of all caregivers. This requires rapid, sweeping changes to the system. Success is based on creating an educational platform to introduce and then further cement these concepts through a unified approach to clinical care. Creating a culture change in a short period of time requires overcoming a host of challenges. However, the result is a more unified and focused approach.

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Address: Eduardo Mireles-Cabodevila, MD, Pulmonary Medicine, A90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; MIRELEE@ccf.org
A 40-year-old woman presented with altered mental status, having been found by her family after she had been in the bathroom for more than 7 hours. She was on chemotherapy with mFOLFOX6 for metastatic rectal cancer. Her regimen consisted of 5-fluorouracil (5-FU) in a 400-mg/m² bolus and 2,400 mg/m² by continuous infusion for 3 days, levofolinate 200 mg/m², and oxaliplatin 85 mg/m². She was currently on her 10th course and had been experiencing general malaise and appetite loss. At the onset of her current symptoms, her cumulative dose of 5-FU was 40.2 g. She had no known metastasis to the liver, nor did she have a history of liver disease.

Her Glasgow Coma Scale score on arrival was 10 on a scale of 15, with the following elements:

- Eye opening 3 of 4 (opens eyes to sound)
- Verbal response 1 of 5 (no response)
- Motor response 6 of 6 (obeys commands).

Her eyes were deviated upward. She had urinary incontinence.

On arterial blood gas analysis, oxygen and carbon dioxide levels were normal; lactate was elevated (4.1 mmol/L) without acidemia (pH 7.445, bicarbonate 24.8 mmol/L).

Results of a complete metabolic panel revealed elevated serum ammonia (109 μg/dL) and blood urea nitrogen (23 mg/dL) levels, and normal levels of electrolytes, glucose, hepatobiliary markers, serum creatinine, and serum thiamine (27 ng/mL). A urine drug screening test was negative.

Electroencephalography showed diffuse slow and triphasic waves without epileptiform patterns.

Diffusion-weighted brain magnetic reso-
nance imaging (MRI) showed symmetrical, bilateral high-intensity areas in the insular cortex, cingulate gyrus, and thalamus (Figure 1a).

5-FU was discontinued. Her mental status recovered, and MRI findings normalized by hospital day 2 (Figure 1b). Her symptoms were diagnosed as 5-FU–induced encephalopathy, and she was discharged on day 5. Her chemotherapy regimen was changed, and no mental status changes recurred.

### 5-FU–INDUCED ENCEPHALOPATHY

5-FU is one of the most widely used anticancer drugs. It can induce encephalopathy that presents with altered mental status or seizures, although this effect is rare, with an incidence of 0.6%. The encephalopathy can present as hyperammonemic encephalopathy, leukoencephalopathy, or Wernicke encephalopathy. Risk factors include azotemia, dehydration, cephalopathy, or Wernicke encephalopathy.2

**Main mechanisms**

Krebs cycle suppression, caused by fluoracetate, a 5-FU catabolite, inhibits the adenosine triphosphate-dependent urea cycle, leading to hyperammonemia.3 This mechanism also produces lactic acid, causing hyperlactatemia.

Dihydropyrimidine dehydrogenase (DPD) deficiency. DPD is an enzyme involved in 5-FU catabolism. DPD deficiency leads to 5-FU accumulation, with neurotoxic effects such as demyelination.4 5-FU also increases cellular thiamine metabolism, thereby causing Wernicke encephalopathy.5

Although the DPD level was not measured in this case, the mechanism likely involved Krebs cycle suppression rather than DPD deficiency because serum ammonium and lactate levels were elevated.

### Diagnosis and prognosis

The diagnostic criteria for 5-FU–induced encephalopathy include development of encephalopathy during or shortly after 5-FU administration, along with exclusion of other metabolic, somatic, and drug-related causes.6 The differential diagnosis includes stroke, nonconvulsive status epilepticus, other encephalopathy (eg, uremic, hepatic, drug-induced), infection, and psychogenic disorders. However, the history of recent 5-FU administration is crucial.

This disorder has a diverse MRI presentation. In the leukoencephalopathy type, the lesions are found in the deep white matter and corpus callosum.1 The gray matter, including the bilateral basal ganglia, thalamus, and parasagittal frontal cortices can occasionally be involved, as in our patient.7 Regardless of the presentation, abnormal MRI findings improve after 5-FU is stopped.1,7 Bilateral, symmetrical lesions in the insular cortex and cingulate gyrus, as in our patient, are characteristics of hyperammonemic encephalopathy.8

Discontinuing 5-FU and providing supportive therapy usually lead to rapid symptom resolution,8 although fatal outcomes have been reported.9 Uridine triacetate, the antidote for 5-FU, has been proposed as a treatment for severe 5-FU toxicity and should be considered for severe cases.10

Acknowledgment: The authors would like to sincerely thank Ms. Ryoko Yoshida for editing the figure.
A 30-year-old man presented with a 6-month history of an exophytic mass growing on the lower mid-back (Figure 1). It was initially suspected to be verruca vulgaris, and he had been referred to a specialty clinic for sexually transmitted infections to confirm it. The lesion was occasionally tender to palpation and bled spontaneously.

Physical examination revealed a 1.5-cm ulcerated, violaceous-to-erythematous polypoid nodule with overlying serous crust on the lower back. No pigmentation was noted within the mass or adjacent to the base of the lesion.

Histopathologic examination of a shave biopsy specimen revealed:
• An exophytic polypoid lesion with broad ulceration, composed of markedly atypical melanocytes in a sheet-like pattern throughout the dermis (Figure 2A)
• Focal epidermal contiguity with atypical melanocytes arranged in single cells and nests in the epidermis (Figure 2B)
• A mitotic rate of greater than 30 mitoses/mm² (Figure 2C)
• Lymphovascular invasion (Figure 2D)
• Melanocytes highlighted by S-100 protein on immunohistochemical staining.

These findings were diagnostic of melanoma, specifically the polypoid variant, with a tumor thickness of 5 mm.

The patient was referred for wide local excision with sentinel lymph node biopsy, which demonstrated inguinal node involvement and BRAF mutation on immunostaining. Positron-emission tomography–computed tomography, magnetic resonance imaging, and computed tomography of the head, chest, abdomen, and pelvis were unrevealing. The formal diagnosis was stage IIC disease (T4bN1M0). The patient began immunotherapy with nivolumab. He was treated with this drug for 1 year and now is on active surveillance.

**IMPORTANCE OF ACCURATE DIAGNOSIS**

Polypoid melanoma is a rare clinical variant of nodular melanoma characterized by an exophytic mass with frequent ulceration, young age at onset (20 to 39 years), and poor prognosis.¹,² It has been reported to account for 2% to 43% of all melanomas, with the wide variability attributed to discrepancies in clinico-pathologic criteria used in different reports.¹

Lesions can affect the mucosa of the upper respiratory tract, esophagus, and anorectal junction, although cutaneous lesions are most frequently on the back.²-⁵ Polypoid melanoma...
mas have a propensity for ulceration, rapid progression over several weeks to months, and early metastasis to the lymph nodes, followed by possible metastasis to distant sites such as the skin, brain, liver, and subcutaneous soft tissue.\(^2,4\)

Of the melanoma variants, polypoid melanoma has the poorest prognosis, given the risk of regional lymphatic and distal micrometastatic involvement, often attributed to increased tumor thickness and ulceration at presentation.\(^3,4\) The 5-year survival rate for the polypoid nodular variant ranges from 32% to 42%, compared with 57% for nonpolypoid nodular melanoma and 77% for superficial spreading melanoma.\(^2,5\)

**Potential for misdiagnosis**

Polypoid melanoma is often misdiagnosed, as it may be confused with benign skin conditions such as verruca vulgaris, leading to inappropriate treatment with cryotherapy or electrodessication and curettage. Other conditions to consider in the differential diagnosis include pyogenic granuloma, keratoacanthoma, and infarcted intradermal nevi or acrochordons, as these lesion types may similarly present with small protruding or dome-shaped papules.

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**Figure 2.** Histopathologic images show (A) an exophytic polyp with ulceration and atypical melanocytes arranged in a sheet-like pattern throughout the dermis (hematoxylin and eosin [H&E] stain, original magnification × 2) and (B) focal epidermal contiguity with atypical melanocytes arranged in single cells and nests in the epidermis (H&E stain, original magnification × 20). High-power images (H&E stain, original magnification × 40) show (C) confluent, atypical melanocytes with conspicuous mitoses and focal cytoplasmic melanin, and (D) lymphovascular invasion at the periphery of the lesion.
Although these lesions often have distinguishing features, such as central hyperkeratosis in keratoacanthomas or the characteristic collarette of acanthotic epidermis at the base of pyogenic granulomas, polypoid melanomas may still be difficult to diagnose clinically, given that both pedunculated and sessile forms exist, as well as both pigmented and amelanotic variants. Additionally, ulceration may have many causes and can be seen in both benign and malignant growths. It may also obscure clinical presentation of cutaneous neoplasms, and tissue biopsy with histopathologic review should be considered for diagnostic guidance in such cases.

Given the highly aggressive clinical behavior and poor prognosis of polypoid melanoma, clinicians should maintain a low threshold for removal of rapidly growing pedunculated lesions with histopathologic evaluation, especially if the patient is relatively young and the lesion has progressed quickly or has ulcerated.

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**CME/MOC**

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Emerging blood-based biomarkers for Alzheimer disease

Emerging blood-based biomarkers for Alzheimer disease are an exciting new development in the dementia field, since they may offer a broadly accessible and relatively inexpensive screening tool. Looking to the future, when disease-modifying or prevention treatments will be available, investigators are focused on how to detect the earliest biological signals of Alzheimer disease, perhaps even years or decades before clinical symptoms appear.

The current standard workup for a patient with dementia symptoms focuses on disorders that may look like dementia or aggravate the early symptoms of Alzheimer disease, or a related dementia (eg, metabolic disorder, structural abnormality, vitamin deficiency). Currently, patients and their families want to know, Is this Alzheimer disease, or something that can be reversed? Current diagnostic testing can be challenging due to complexity, cost, or level of intervention. A validated blood test that could be widely utilized would be a step forward for diagnosing and, hopefully, intervening before a patient becomes clinically impaired.

DEMENTIA’S TOLL

An astonishing 5.8 million Americans age 65 and older have Alzheimer disease or a related dementia, and this number is expected to increase to 13.8 million by 2050.1 The impact on families is both financial and emotional. More than 16 million Americans currently provide unpaid care for family members or friends with dementia. The projected national cost of caring for those with Alzheimer disease and other dementias is currently $305 billion, which is unsustainable. As the aging population increases, so does the population with Alzheimer disease. The burden of caring for the increasing aging population with dementia is exacerbated by a shortage of dementia care specialists and the increasing burden on primary care clinicians to identify and provide care for these patients.1

EARLY CHANGES IN THE BRAIN ARE HARD TO DETECT

The pathologic hallmarks of Alzheimer disease are the accumulation in the brain of extracellular amyloid beta plaques and intraneuronal inclusions (neurofibrillary tangles) consisting of phosphorylated tau, a microtubule-associated protein. Also present are dystrophic neurites, loss of synapses, neuronal death, and gliosis. These pathologic changes can begin 10 to 20 years before the onset of clinical symptoms.2

Current validated biomarkers of Alzheimer disease pathology include:

- Amyloid beta and tau positron emission tomography (PET)
- The ratio of the concentrations in the cerebrospinal fluid of 2 amyloid beta peptides: the 1–42 peptide and the 1–40 peptide
- The concentrations of total tau and phosphorylated tau (specifically, phosphorylated at amino acid 181) in the cerebrospinal fluid.3,4

The memory specialist is faced with a multitude of nuanced and mixed pathologies underlying a dementia syndrome.3 Biomarkers of Alzheimer disease pathology in combination with cognitive assessment and structural brain imaging can be valuable diagnostic tools in these circumstances. However, cerebrospinal
BLOOD TESTS FOR ALZHEIMER DISEASE

fluid analysis and PET are not easily utilized by the primary care clinician due to access, comfort with the testing or interpretation, and expense. Furthermore, the bedside cognitive testing currently used by primary care providers does not easily identify patients with early cognitive changes.

Therefore, for the primary care clinician, less-invasive and less-specialized screening tools, such as a blood test, would be a significant development. These screening tools could help determine who should be referred for more in-depth testing. Recent developments in the field are bringing us closer to blood tests that primary care clinicians can use as screening tools. This trend is promising, since it also will help in developing therapies targeting early-stage Alzheimer disease-specific pathology in larger and more diverse populations. Blood testing could fit into a diagnostic algorithm, similar to testing for certain cancers, that the primary care clinician could utilize for those at high risk of Alzheimer disease, such as the elderly and those with a strong family history.

■ SEARCHING FOR A BLOOD-BASED BIOMARKER

A major barrier to developing new drugs for Alzheimer disease is that it is hard to identify patients who are in the early stage of the disease, soon after the pathologic changes in the brain have begun but before cognitive impairment has become apparent, especially in the primary care setting. Given that an inexpensive and sensitive blood-based biomarker would enhance the ability of the primary care clinician to screen for possible Alzheimer disease, many researchers have focused significant effort on developing one.

Circulating amyloid beta
In early studies, plasma levels of amyloid beta lacked a consistent association with Alzheimer disease.6 This was most likely due to assay-related difficulties, since plasma measurements of this protein may be influenced by matrix effects whereby other proteins in plasma bind it. However, later studies using more sensitive assays indicated that the plasma ratio of the amyloid beta-1–42 and 1–40 peptides was lower in amyloid PET-positive individuals, as it is in the cerebrospinal fluid,7–11 strongly suggesting that a plasma 1–42-to-1–40 ratio may be a feasible blood-based biomarker of Alzheimer disease. The only missing piece was a blood-based measure of tau.

Plasma total tau
Initial studies of blood-based tau suggested that the plasma total tau concentration is higher in patients with Alzheimer disease than in cognitively normal controls. Unfortunately, the difference was not as clear or as well replicated as in cerebrospinal fluid.6 Subsequent studies also reported elevated plasma total tau in Alzheimer disease12,13 and an association with faster clinical disease progression,12 supporting the idea that plasma tau is indeed significantly elevated in Alzheimer disease.

Plasma phosphorylated tau 181, tau 217
Since cerebrospinal fluid phosphorylated tau 181, a key component of neurofibrillary tangles, adds better diagnostic accuracy than tau alone, researchers developed a new assay for phosphorylated tau at amino acid 181 in plasma. An association between this new phosphorylated tau 181 test and amyloid beta, as well as tau PET, was even stronger than those obtained using the plasma total tau test,14–16 strong evidence that plasma-phosphorylated tau 181 is a feasible blood-based biomarker of Alzheimer disease. However, since tau is phosphorylated at many sites, other phosphorylated sites may be better circulating biomarkers of Alzheimer disease. Most recently, intriguing new findings suggest that the plasma tau phosphorylated at amino acid 217 differs in patients with Alzheimer disease compared with cognitively normal controls and people with other neurodegenerative disorders.17,18 Plasma phosphorylated tau 217 is an intriguing finding, since it appears to outperform plasma phosphorylated tau 181 and imaging markers in terms of diagnostic accuracy.17,18

■ STUDIES UNDER WAY

While these new findings are encouraging, they are early results. These blood-based tests need further testing in large-scale studies over the long term to refine and verify them, especially in the general population.

There is as yet no gold standard biomarker for Alzheimer disease (or for vascular demen-
tia) before clinical symptoms arise. Definitive diagnosis is done at autopsy, based on neuropathologic amyloid and tau findings.

The Alzheimer’s Association Global Biomarker Standardization Consortium was established more than a decade ago to bring together key researchers, clinicians, industry, regulatory bodies, and government leaders in Alzheimer disease and other dementias. The goal is to achieve consensus on the best way to standardize and validate biomarker tests for use in clinical practice. Promising biomarkers have spurred several method-comparison and standardization studies across multiple laboratory sites, both nationally and internationally, under Consortium guidance. Future method-comparison and standardization studies will bring us closer to plasma amyloid and tau biomarkers as effective screening tools in the primary care setting.

This is an exciting time, since blood-based biomarkers for Alzheimer disease are a potentially important step forward for both research and clinical care. As we move toward disease-modifying therapies for Alzheimer disease and related dementias, they will be crucial for enhancing further clinical trial strategies, supporting primary care practice diagnosis and management, and, hopefully, moving to an era of better interventions for these devastating disorders.

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Q: Should women with HPV-related noncervical cancers be considered at high risk for cervical cancer?

A: Yes. Human papillomavirus (HPV) infection causes cancer in more than just the cervix, and the incidence of high-grade cervical lesions is higher for women with noncervical HPV-related cancers. Currently, however, no guidelines exist for screening for cervical cancer in women who have other HPV-related cancers. Nevertheless, screening and early diagnosis reduce the risks of cancer-related comorbid conditions and death, so until clear guidelines are available, the current evidence suggests that these women should be considered at high risk and offered closer surveillance.

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15 HIGH-RISK HPV GENOTYPES

HPV is the most common sexually transmitted infection in the United States, with greater than half the population infected at least once during their lifetime. Of the more than 100 known HPV genotypes, there are 15 high-risk oncogenic types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82.

Persistent infection with high-risk HPV causes most cases of squamous cell carcinoma of the cervix, vulva, vagina, oropharynx, penis, and anal canal. This causation is supported by epidemiologic and molecular studies, and high-risk HPV DNA can be found in most of these carcinomas. Infection with low-risk genotypes (HPV-6 and HPV-11) can result in benign anogenital warts and respiratory papillomatosis but not cancer.

Most HPV infections are transient and resolve or become dormant within 2 years, but a few women with persistent high-risk HPV infection develop cervical cancer. With improved screening, early diagnosis, and treatment of precancerous lesions, the incidence and mortality rates of cervical cancer have decreased, and these rates are expected to decrease further with adequate HPV vaccination.

The only HPV vaccine currently available in the United States protects against 9 HPV serotypes, including HPV-16 and HPV-18, which cause more than 60% of HPV cancer cases in men and women, including most cervical, anal, and oropharyngeal cancers. In particular, HPV-16 causes more cases of cancer than any other HPV serotype. Around the world, vaccination provides the opportunity to decrease the burden of high-risk HPV infections in future generations.

The HPV Vaccine Impact Monitoring Project (HPV-IMPACT) study collected data on cervical lesions attributable to HPV-16 and HPV-18 and also examined vaccination rates in women ages 18 to 39. The vaccinated women had fewer lesions than those who were not vaccinated.

For men and women, the incidence rates of high-risk HPV at multiple anatomic sites are increasing. Without effective screening programs, the incidence of high-risk HPV-mediated oropharyngeal, vulvar, and anal squamous cell carcinoma likewise is steadily increasing. Certain sexual behaviors (eg, unprotected oral sex, receptive anal sex) and other factors such as impaired local mucosal and systemic immunity increase the risk of

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HPV infection and subsequent cancer.

Anal cancer is slightly more common in women than in men. However, the rate of anal cancer is especially high in men positive for human immunodeficiency virus (HIV) who have sex with men, and it is elevated to a lesser extent in immunosuppressed individuals. The anus and cervix, which share embryologic and anatomic characteristics, may respond similarly to malignant changes induced by persistent high-risk HPV infection, and a clear majority of cancers at both these sites are attributable to HPV, as evidenced by detection in tumor specimens.

In addition, according to the US Centers for Disease Control and Prevention, oropharyngeal squamous cell carcinoma is now the most common HPV-associated cancer, with incidence rates increasing by 2.7% per year in men and 0.8% per year in women. Oropharyngeal cancers are known to be caused by tobacco and alcohol use, but recent studies show that about 70% of these cancers are HPV-positive, with non-Hispanic White males having the highest risk.

HPV AND CANCER SCREENING

Cervical cancer screening guidelines for HIV-positive women also apply to immunosuppressed women without HIV

Cervical cancer screening guidelines for immunocompetent females are based on data from 1.5 million women. However, with their increased risk of cervical cancer, HIV-positive women have different screening guidelines based on HIV-specific data. Other women with suppressed immune function or immune dysfunction due to solid-organ transplant, bone marrow transplant, or disease-modifying therapy for autoimmune disease, as well as women with inflammatory bowel disease who are receiving immunosuppressive therapy, also have increased risk of high-grade squamous intraepithelial lesions of the cervix and squamous cell carcinoma.

Primarily based on expert opinion but also on available data, cervical cancer screening guidelines for HIV-positive women (noted below) also apply to immunosuppressed women without HIV:

- Cotesting (HPV and cervical cytology) every 3 years, if preferred, for women 30 years of age and older.
- If HPV testing is unavailable or if the woman is age 21 to 29, cervical cytology is indicated annually for 3 years, and then once every 3 years thereafter if initial results are negative.
- Screening continues (past age 65) as long as the patient’s health supports continued screening.

Women who were exposed to diethylstilbestrol in utero have an increased risk of clear-cell adenocarcinoma of the cervix, a rare cancer unrelated to HPV. For these women, annual cervical cytologic examination is currently recommended.

Screening women with lower genital tract cancers for anal dysplasia, cancer

The progression from HPV acquisition to persistent HPV infection to precancerous and cancerous cervical lesions is well established. Other noncervical HPV-related cancers have not been studied as extensively, but an event progression similar to that of cervical cancer has been hypothesized.

Patients with HPV infection at a single anatomic site have a higher risk of infection at other HPV-related sites through autoinfection. For some women with concurrent cervical and anal high-risk HPV infections, the genotypes have shown a high degree of concordance. High-risk HPV infection and coexisting abnormal anal and cervical cytologic findings are common in women receiving immunosuppressive therapy. Women who have been treated for high-risk HPV-positive anal cancer have high rates of persistent anal HPV infection, which can lead to infection of other genital sites.

Likewise, the prevalence of anal intraepithelial lesions is increased in women with HPV-related high-grade squamous intraepithelial cervical lesions, and this prevalence is greater in women with cervical cancer and greater still in women with HPV-mediated vulvar cancer. Cervical, vulvar, vaginal, and anal dysplasia and cancers can be considered parts of a multicentric disease of the lower anogenital tract.

Women with cervical, vulvar, and vaginal cancer have a higher risk of anal cancer. Screening recommendations for anal cancer...
in these women, at a minimum, should include annual symptom query, visual inspection, and digital anorectal examination. Anal cytology can be considered, depending on the degree of anal cancer risk and the availability of colorectal surgeons who can perform the high-resolution anoscopy required after abnormal cytologic results. The annual anal cytology that some recommend for women with HIV could benefit women with high-grade vulvar dysplasia and cancer because their anal cancer rates are similar. Limited data on the natural course of anal dysplasia in women with HPV-mediated cancers hinders the creation of evidence-based guidelines.

Cervical cancer screening for women with noncervical HPV-related cancers

Evidence suggests that the risk of cervical cancer may increase for women with other HPV-related cancers, but currently, we lack specific data and guidance about screening for cervical cancer in women with other HPV-related cancers. This area of ambiguity needs further research. Until then, on the basis of currently available evidence, these women should be considered at high risk and offered cervical cancer screening similar to that of women with HIV infection, as previously detailed.

Because most cases of cervical cancer in the United States are in women who are unscreened or underscreened, we recommend reviewing results of any prior cervical screening. Cervical HPV testing with genotyping and reflex cytologic testing (ie, primary HPV screening) or HPV and cytologic testing (ie, cotesting) should be performed if these tests are available and prior results are not current or cannot be reviewed. Negative HPV test results provide strong evidence of reduced risk of cervical cancer.

Prevention and treatment of precancerous cervical lesions reduce the rate of cervical cancer. In one study, treatment of cervical intraepithelial neoplasia grade 3 reduced cancer risk from 30% to 1%. Thus, the recommended follow-up for abnormal cervical cancer screening results must occur in a timely manner.

A PRUDENT STRATEGY

The global burden of HPV-related cancers is increasing, but the incidence of these cancers can be reduced by broadly increasing HPV vaccination rates for both sexes worldwide. Because HPV is a multicentric disease, women with lower genital tract cancers should be considered to have higher risk for anal cancers, and women with noncervical HPV-related cancers should be considered to have a higher risk for cervical cancer.

A prudent strategy would be to offer these women closer surveillance, and the suggested screening guidelines are summarized in Table 1. More research is needed to provide clear guidelines for cervical cancer screening for women with other HPV-related cancers.

TABLE 1

<table>
<thead>
<tr>
<th>Suggested screening guidelines</th>
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<tbody>
<tr>
<td><strong>Cervical cancer screening for women with other HPV-related cancer</strong></td>
</tr>
<tr>
<td>Cotesting HPV and cervical cytology every 3 years; preferred for women age 30 and older</td>
</tr>
<tr>
<td>Annual cervical cytology for 3 years, then every 3 years if negative; preferred for women under age 30, or if HPV testing is unavailable</td>
</tr>
<tr>
<td><strong>Anal cancer screening for women with other HPV-related high-grade anogenital dysplasia or cancer</strong></td>
</tr>
<tr>
<td>Annual symptom query, visual inspection, and digital anorectal examination</td>
</tr>
<tr>
<td>Anal cytology can be considered, depending on the availability of high-resolution anoscopy (high-grade vulvar dysplasia and cancer are associated with higher risk than at other sites)</td>
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HPV AND CERVICAL CANCER


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The HPV vaccine: Understanding and addressing barriers to vaccination

In this issue, Drs. Vegunta and Long present an excellent review of conditions related to human papilloma virus (HPV), including cervical, vaginal, anal, oropharyngeal, and penile cancers.1

See related article, page 541

Cancers related to HPV have a major impact on a patient’s life; even for those lucky enough to be cured, the morbidity associated with treatment can be considerable. Anatomic changes due to surgery may cause chronic pain and body image concerns, chemotherapy often leads to symptomatic premature menopause, and radiation treatment can cause anatomic changes to the genital tract, contributing to painful intercourse and sexual dysfunction. Treatment not only affects the patient physically, but impacts both the patient and partner psychologically, including plans for future childbearing.

It is not surprising that a clinician who cares for patients affected by HPV-related disease will be passionate about preventive efforts, especially encouraging HPV vaccination to healthy individuals during routine visits. We know that the HPV vaccine works. In 2018, a meta-analysis of 26 randomized controlled trials (including more than 70,000 women and girls) showed that the vaccine not only is well tolerated but significantly decreases the risk of preinvasive cervical disease in young women.2,3 Additionally, there has been an 86% decrease in infection with the HPV subtypes causing cancers and genital warts among teenage girls and a 40% decrease in cervical precancers among vaccinated women.4

By decreasing infection with carcinogenic HPV strains, the hope is that the HPV vaccine may decrease the incidence of other HPV-related cancers, although there is not yet sufficient evidence to show this possible benefit.

We have a safe and effective cancer-prevention vaccine, but widespread vaccination remains a challenge in the United States. Patients may have concerns about vaccine safety and efficacy due to mixed messages from the media and other sources, but other common reasons for not vaccinating are provider discomfort in discussing sexuality, not receiving a strong recommendation from the clinician, and the belief by both the patient and provider that the patient is not at high risk.5

Similarly, a survey of guardians in a Texas school district (a state where the vaccination rate is < 50%) identified scheduling conflicts and the lack of vaccine recommendation from a healthcare provider as significant hurdles to vaccination.6 Even in a New York school district that permitted adolescent vaccine self-consent, scheduling and returning for the appointment were significant challenges affecting the vaccination rate.7

Key steps to implementing successful HPV vaccination in practice include understanding the individual patient’s risk, following recommended vaccination timelines (which allow some flexibility with scheduling), and optimizing clinician-patient communication.

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■ UNDERSTANDING HPV RISKS

Any patient who is sexually active is at risk for HPV-related cancer. Approximately 80% of individuals will become infected with HPV at some point in their life, and HPV is the most common sexually transmitted disease in the United States. Yet despite how common HPV infection is, many women do not think that they are at risk. According to a survey of more than 900 unvaccinated females age 15 to 24, this belief was a main reason for forgoing vaccination (both in women who were and were not sexually active).9

For women who have sex with women, HPV can live on sexual devices for more than 24 hours. In addition to discussing the importance of vaccination, they should be counseled to use a barrier method over any shared sexual devices and clean the devices appropriately after each use.10

■ WHO SHOULD RECEIVE THE VACCINE?

In the United States, HPV vaccination is routinely recommended to all adults until age 26, although the vaccine can be offered until age 45 in select patients who are not immunized. However, the vaccine is most likely to be beneficial when the series is completed before sexual debut; thus, guidelines recommend starting vaccination at age 11 to 12, with the option to start as early as age 9.11

■ COMMUNICATING EFFECTIVELY

Clinicians may not feel comfortable discussing topics related to sexuality, especially in the field of pediatrics. A survey of members within 4 California chapters of the American Academy of Pediatrics showed that 71% of pediatricians would feel more comfortable discussing vaccination if the conversation also included education about HPV-related head and neck cancers.12

California Chapter 3 of the American Academy of Pediatrics created a 22-minute clinician training video that includes clinical vignettes of pediatricians counseling families who had concerns about vaccination (available at: https://aapca3.org/hpv-videos-education-promotion-project/). After watching this video, surveyed clinicians were shown to have improved their knowledge of vaccine safety, HPV disease burden (especially for males), and the importance of not delaying vaccination beyond preadolescence.13 This brief video intervention also led to more providers feeling “very comfortable” advising families.13

Another study looked at the most effective way to educate patients. A randomized controlled trial of 3 patient counseling strategies—an 8-minute educational video (n = 87), an educational handout with the same information written at an eighth-grade reading level (n = 84), and usual care (n = 85)—was performed to assess vaccine acceptance. More patients in the educational video arm agreed to have the HPV vaccine (51.7%) than in the handout or control arms (33.3% and 28.2%, respectively, P < .01). Interestingly, both the video and handout helped increase knowledge similarly, although the video helped most for the patient’s decision to be vaccinated.14

In my practice, I start by notifying the patient that they are due for their HPV vaccine, just as I would do with any other preventive recommendation (eg, need for blood testing, cancer screening). Many patients will agree to this simple approach without a need for a long discussion about risks vs benefits, which may, paradoxically, lead to a greater hesitation to be vaccinated.15,16

Next, I clarify that the goal of HPV vaccination is to prevent cancer, and I remind the patient that everyone who engages in sexual activity is at risk. For those who have more concerns, it is important to first understand what the specific barriers are before trying to address them.

Despite our best efforts to educate, some patients may decline vaccination. It is important to avoid thinking of this as “losing a battle,” as respecting patient autonomy ensures not only a trusted partnership in the patient’s future healthcare, but also helps to minimize clinician frustration. Patients may opt to go against our recommendations in multiple situations, and they will make their own life decisions no matter how hard we try to provide optimal care.
COMPLETING THE VACCINATION SERIES

Given that scheduling conflicts seem to play a prominent role in nonadherence to vaccination schedules, some flexibility with appointments is key. Anyone age 15 or older will need 3 doses of the HPV vaccine, typically with the second dose given 1 to 2 months after the first, and the third within 6 months of the first (at 0, 1–2, and 6 months). To accommodate a patient’s schedule, the second HPV vaccination can be scheduled at 4 weeks after the first dose, and the third dose 12 weeks after the second.17 There should be at least 5 months between the first and third dose (referred to as the “minimal interval”).

If repeat vaccination has occurred any earlier than these minimal intervals, then the patient will need another dose after the appropriate minimal interval has passed. Caution with interval dates is needed only when patients wish to come in earlier than recommended; if the vaccine schedule is interrupted or delayed, then a patient can continue with the remainder of the routine recommended schedule; no additional boosters or schedule adjustments are required (no maximum interval).

SHOULD VACCINATION BE MANDATED?

In Australia, where the HPV vaccine was made available for free in a national school program, vaccination rates of more than 70% have been achieved nationally in girls ages 12 to 13, with resultant clinical benefits in preventing both warts and precancerous lesions.18 A meta-analysis of 9 high-income countries suggested that HPV infections decreased most when there is at least 50% coverage of the female population.19 In addition to Australia, Denmark, Canada (Quebec province), and New Zealand have offered widespread vaccination to multiple age cohorts, leading to optimized population immunity and the maximum impact on clinical outcomes.19,20

Vaccination rates vary greatly among US states. In contrast to the 78% vaccination rate in Washington, DC, which has a mandate for school entry, the Mississippi rate is only 29%.20 As of 2019, only 3 states provide free HPV vaccination through their health departments, although 25 states have laws requiring some funding for HPV education and vaccination.20

Of note, in the United States, there has been a higher uptake of the HPV vaccine among minority patients (higher in Hispanic and Black vs White populations) and also in those within a lower socioeconomic status group (income below federal poverty level, and having Medicaid coverage as opposed to private insurance). Because these populations of women historically have been at higher risk for HPV-related disease and cancer, it is hoped that this may lead to reversing some of these healthcare disparities.20

In the United States, significant controversy surrounds the idea of mandating vaccination prior to starting school, limiting vaccine exemptions, and the perceived loss of an individual’s autonomy. Although a rise in vaccine-preventable illnesses has been seen primarily in communities with lower rates of vaccination, asking school administrators and nurses to “police” who is allowed to return to school adds an extra layer of complexity to this heated debate.

Although many may disagree with me, I suspect the best path to improving vaccination rates will not be achieved by adding more laws and rules, but by improving the education of both patients and caregivers, establishing a trusting patient-doctor relationship, simplifying office workflows (empowering nursing teams to educate patients, and then prompting clinicians that the vaccine order is needed), and by lifting financial barriers to vaccination, including copays, prior authorization, and coverage ambiguity.

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HPV VACCINE


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Polymyalgia rheumatica: An updated review

**ABSTRACT**

Polymyalgia rheumatica should be suspected in older patients with bilateral shoulder and hip stiffness that is worse in the morning and improves with use. An array of nonspecific musculoskeletal complaints, constitutional symptoms, and elevated serum inflammatory markers may be present, so other conditions should also be considered. Prolonged glucocorticoids with patient-tailored dosing and duration are the mainstay of treatment. Corticosteroid-sparing therapy with adjunctive methotrexate may benefit select patients.

**KEY POINTS**

- Rheumatoid arthritis, late-onset spondyloarthritis, and RS3PE (remitting seronegative symmetrical synovitis with pitting edema) are important mimics of polymyalgia rheumatica.

- Diagnostic usually requires either an elevated erythrocyte sedimentation rate (> 30 or 40 mm/h) or C-reactive protein level (> 6 mg/dL).

- Ultrasonographic evidence of inflammation, especially subacromial bursitis, increases diagnostic specificity.

- Patients should be evaluated at diagnosis and periodically for the development of giant cell arteritis.

- To help avoid relapse, therapy should continue until symptoms resolve, followed by slow tapering.

- Preliminary studies show possible benefit from tocilizumab, an interleukin-6 receptor antibody, as monotherapy or for refractory cases.

Polymyalgia rheumatica (PMR) is easily recognized when it presents classically, ie, in an older woman with pelvic girdle stiffness that improves over the day, elevated inflammatory markers, and a rapid response to prednisone therapy. But its presentation often overlaps with that of other rheumatologic and inflammatory syndromes.

This article provides guidance on the evaluation and management of PMR and discusses current and emerging therapies.

**OLDER ETHNIC EUROPEANS MOST AFFECTED**

PMR typically presents in people over age 50, with incidence increasing with age. Annual incidence varies from 12 to 60 cases per 100,000 in different populations, with the highest rate in those of Northern European descent. Women are more often affected than men.

PMR’s etiology is not well understood. Genetic and infectious associations have been investigated without conclusive results. Studies in various geographic regions have revealed increased numbers of certain polymorphisms for genes involved in the immune system, but they have not been consistently found across different populations of patients with PMR.

**PROXIMAL BILATERAL MORNING STIFFNESS**

The cardinal feature of PMR is proximal girdle pain associated with restricted range of motion and stiffness. Shoulders are affected in up to 95% of cases; the neck and pelvic girdle can also be involved. Patients often report being unable to stand up from a chair, get out of bed without assistance, or lift their arms to comb their hair.
POLYMYALGIA RHEUMATICA

Bilateral symptoms should particularly raise suspicion for PMR. In some cases, symptoms are unilateral at onset, but quickly become bilateral and often develop rapidly over a few days.

Symptoms are characteristically worse in the morning and with inactivity. Morning stiffness tends to last an hour or more. Pain can also be strikingly severe at night and can affect sleep.

■ INFLAMMATION MAY BE WIDESPREAD

Symptoms are related to inflammation of the articular and extra-articular structures, causing synovitis and bursitis of the shoulder, hip, and neck.

Distal joint arthritis may also occur. It is often asymmetric and most commonly affects the knees and wrists, with the feet usually unaffected. Inflammation may also involve periarticular structures, causing distal tenosynovitis and carpal tunnel syndrome. Pitting edema affecting the distal extremities due to regional tenosynovitis can occur and occasionally is a presenting feature.

Constitutional symptoms (ie, low-grade fever, anorexia, fatigue, and asthenia) are also common, occurring in up to half of patients. However, persistent high fever is uncommon with isolated PMR and may signal the con- currence or development of giant cell arteritis (GCA).

■ PHYSICAL EXAMINATION:

PAIN, LIMITED RANGE OF MOTION

On physical examination, active range of motion is restricted due to pain, without actual weakness, while passive range of motion may be normal. Muscle tenderness may also be present.

■ LABORATORY TESTS FOR INFLAMMATION

Laboratory studies are helpful, as they may indicate an inflammatory state consistent with PMR or, alternatively, suggest or help rule out another diagnosis.

Primary tests: ESR and CRP

Most established diagnostic criteria for PMR require either elevated erythrocyte sedimentation rate (ESR) (> 30 or 40 mm/h) or elevated C-reactive protein (CRP) (> 6 mg/dL), indicating an ongoing inflammatory process. While uncommon, it is possible for levels to be normal; in such cases, rheumatology referral is indicated if PMR is otherwise suspected.

Conversely, elevated levels alone do not establish the diagnosis, as ESR and CRP increase with a variety of conditions, including normal aging.

Other tests may be abnormal

Other laboratory findings consistent with an ongoing inflammatory process and commonly seen in PMR include normochromic anemia, thrombocytosis, and leukocytosis. Liver enzymes, particularly alkaline phosphatase, may also be elevated.

■ PMR HAS MANY MIMICS

Symptoms of PMR may be nonspecific, and many diseases present similarly (Table 1).

Rheumatoid arthritis and spondyloarthritis, which may be late-onset, are important considerations. Both can present with distal arthritis, seen in up to half of patients with PMR. As in PMR, joint involvement in rheumatoid arthritis is usually bilateral and symmetric. However, serologic tests for rheumatoid factor and anticitrullinated peptide antibody tend to be positive in rheumatoid arthritis and spondyloarthritis, but not in PMR. Spondyloarthritides are associated with low back pain and stiffness, as well as evidence of sacroiliitis on imaging, which are rare in PMR.

RS3PE (remitting seronegative symmetrical synovitis with pitting edema) involves pitting edema in the distal extremities caused by extensor tendon synovitis, most commonly involving the dorsal surfaces of the hands and wrists. Lower-extremity involvement is much less common. Like PMR, RS3PE responds rapidly to glucocorticoids except when associated with a paraneoplastic syndrome, in which case the underlying malignancy must be treated.

Other medium-to-large-vessel vasculitides, including GCA, may also present with unexplained fever and constitutional symptoms. Patients with symptoms of PMR should always be evaluated for signs and symptoms of GCA, including new-onset headache, scalp tenderness, tongue or jaw claudication, and
vision changes. If GCA is suspected, temporal artery biopsy should be pursued.

GCA is diagnosed in 16% to 21% of patients with PMR, and between 35% and 50% of patients with GCA have coexisting PMR.20,21 A number of studies have explored genetic features that might link these diseases. Both are associated with certain genetic polymorphisms, particularly those related to the immune system, including genes for human leukocyte antigen and tumor necrosis factor (TNF). However, these associations have not been found consistently.22

Noninflammatory syndromes, such as osteoarthritis, spinal stenosis, Parkinson disease, and paraneoplastic asthenia should particularly be suspected if inflammatory markers are absent.4

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Key features of polymyalgia rheumatica mimics</th>
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<tr>
<td><strong>Disease</strong></td>
<td><strong>Features</strong></td>
</tr>
<tr>
<td>Inflammatory diseases</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Symmetrical joint involvement, autoantibody-positive, may see erosions on imaging in advanced disease</td>
</tr>
<tr>
<td>Spondyloarthritis</td>
<td>Low back involvement, sacroiliac joint tenderness, sacroilitis on imaging</td>
</tr>
<tr>
<td>RS3PE (remitting seronegative symmetrical synovitis with pitting edema)</td>
<td>Peripheral edema, extensor synovitis on imaging, may be paraneoplastic</td>
</tr>
<tr>
<td>Crystalline arthropathy</td>
<td>Usually involvement of medium to large joints, intermittent symptoms, characteristic radiography and ultrasonographic findings, synovial fluid analysis positive for crystals</td>
</tr>
<tr>
<td>Autoimmune myositis</td>
<td>Muscle weakness and tenderness, elevated muscle enzymes</td>
</tr>
<tr>
<td>Other connective tissue diseases</td>
<td>Multiorgan involvement, specific autoantibodies may be positive, hypocomplementemia</td>
</tr>
<tr>
<td>Noninflammatory diseases</td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>Pain exacerbated with use, normal inflammatory markers, degenerative changes on imaging</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Fatigue, chronic pain with more generalized involvement</td>
</tr>
<tr>
<td>Spinal spondylosis and stenosis</td>
<td>Numbness, paresthesias, muscle weakness, normal inflammatory markers</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>Muscle stiffness primary complaint, other symptoms typical of Parkinson disease including tremor and rigidity</td>
</tr>
<tr>
<td>Infection</td>
<td>Fever, heart murmur, leukocytosis, positive blood cultures</td>
</tr>
<tr>
<td>Malignancy and paraneoplastic syndromes</td>
<td>Weight loss, diffuse symptoms usually not limited to shoulder or pelvic girdle, lack of response to low-dose glucocorticoid therapy</td>
</tr>
<tr>
<td>Drug-induced myopathy (eg, statin, glucocorticoid, colchicine)</td>
<td>Lack of systemic symptoms, muscle weakness and tenderness, improvement with discontinuation of drug, elevated muscle enzymes, positive anti-HMG-CoA reductase antibody</td>
</tr>
<tr>
<td>Thyroid and parathyroid disease</td>
<td>Systemic symptoms typical of endocrinopathy; abnormal thyroid markers; abnormal calcium, phosphorus, or parathyroid levels</td>
</tr>
</tbody>
</table>
Statin-induced muscle toxicity is associated with myalgias and muscle weakness that are usually symmetric, involving the large proximal muscles, particularly of the lower extremities. Muscle enzymes are frequently elevated, and 3-HMG-CoA reductase antibodies may be positive. In most cases, discontinuing the drug is sufficient, but if symptoms and muscle enzyme elevation persist, further evaluation for other causes of myopathy and assessment for immune-mediated myopathy are indicated. If the latter is suspected, specialist consultation should be sought, as immunosuppressive treatment may be indicated.

AN EMERGING ROLE FOR ULTRASONOGRAPHY

Interest has been growing in the use of ultrasonography to help diagnose PMR. Studies have primarily used radiologists and rheumatologists for image acquisition. A number of intra- and extra-articular ultrasonographic findings have been associated with PMR, including biceps tenosynovitis, bursitis (subacromial-subdeltoid, ischiogluteal, iliopsoas, and trochanteric), and synovitis (glenohumeral, coxofemoral, and intervertebral). However, not all of these findings are specific to PMR or are readily identified. A meta-analysis reported the superior accuracy of diagnosing PMR based on subacromial bursitis vs other areas of inflammation, with unilateral subacromial bursitis having an 80% sensitivity and 68% specificity and bilateral subacromial bursitis being 66% sensitive and 89% specific. The PMR classification criteria proposed in 2012 by the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) include optional ultrasonographic criteria, allotting a point for either bilateral shoulder pathology or concomitant shoulder and hip findings. Use of ultrasonographic criteria increases the specificity of the EULAR/ACR classification system from 81.5% to 91.3%. Power Doppler ultrasonography allows better assessment of increased blood flow in small blood vessels compared with conventional color Doppler, making it suitable for detecting soft tissue inflammation, as in tendinitis and bursitis. A prospective study of 57 patients with PMR found that a positive power Doppler signal associated with inflammatory shoulder findings at the time of diagnosis was associated with a significantly greater risk of disease relapse than if such findings were absent. However, the same study reported that 60% of patients continued to have ultrasonographic signs of shoulder inflammation at 6-month follow-up despite being clinically in remission or having low disease activity status, indicating a limited ability of ultrasonography for detecting disease relapse.

TREATMENT OF CHOICE: STEROIDS

The mainstay of treatment of PMR is oral prednisone therapy. According to the latest EULAR/ACR guidelines, prednisone therapy should be within the range of 12.5 to 25 mg, using the minimum effective dosage to achieve remission. Tapering should be individualized once remission is achieved.

Induction dosing should be based on symptom severity, body mass index, and comorbidities. Suggested initial dosing for an average patient is 15 mg/day. Smaller doses (7.5–10 mg daily) can be considered for patients with smaller body habitus, milder symptoms, uncontrolled diabetes, or risk of significant drug adverse effects. For patients with a larger body size or severe symptoms, oral prednisone at 20 to 25 mg per day should be considered. Treatment should have the goal of symptom remission, as well as improvement and eventual normalization of ESR and CRP levels. ESR and CRP levels typically normalize within 2 to 4 weeks of starting treatment, and normalization is often associated with symptom resolution. If improvements are not evident within 1 to 2 weeks of starting therapy, prednisone should be escalated and alternate diagnoses considered.
Twice-daily dosing of prednisone (which has a half-life of about 4 hours) has been anecdotally reported to achieve better symptom relief. For patients with difficult-to-control symptoms, this may be helpful, but careful consideration should be taken before recommending this option, given the potential for overdosing and adverse effects.

Dasgupta et al.34 explored treating PMR with oral vs intramuscular glucocorticoids in a double-blind study. Both regimens had comparable remission rates. However, because intramuscular therapy has been evaluated only by a single randomized controlled trial, its routine use is discouraged.30

Rapid symptomatic improvement in response to low-dose prednisone (< 15 mg) historically was regarded as diagnostic for PMR.4 However, this response is likely not specific to PMR, as other inflammatory arthritides (eg, rheumatoid arthritis, inflammatory osteoarthritis, crystal arthropathies) may also improve with low-dose prednisone. Conversely, higher dosage requirements may signal another diagnosis, so specialist consultation should be sought if parenteral therapy or twice-daily dosing is being considered.

**TREATMENT DURATION AND TAPERING**

Another debated issue is treatment duration, which should generally be patient-specific and symptom-driven. The glucocorticoid dosage that controls symptoms is typically maintained for 2 to 4 weeks after pain and stiffness have resolved. Dosage is then decreased by about 20% every 2 to 4 weeks, as tolerated, to the minimum amount needed to maintain symptom suppression.35 Once a daily prednisone dosage of 10 mg is reached, tapering should be slowed to a rate of 1 mg every 1 to 2 months until discontinuation.35,36 Typical treatment lasts 1 to 2 years. Attempting to taper steroids before symptoms resolve or too quickly after symptoms have resolved may result in a higher rate of relapse and decreased success with treatment cessation.36

**MANAGING RELAPSES**

Relapses and flares should prompt reevaluation of symptoms and laboratory studies for alternate diagnoses. Subsequently, if the patient is still on glucocorticoids, the dosage should be increased by 10% to 20%.35 For patients whose steroids were successfully discontinued before relapse, induction therapy should be restarted at the lowest effective dose with subsequent taper as tolerated. If symptoms are severe, a single dose of intramuscular methylprednisolone 120 mg can be used to assist with induction therapy.37 After 2 relapses, a steroid-sparing agent such as methotrexate, azathioprine, a TNF inhibitor, or an interleukin 6 (IL-6) receptor blocker can be tried.

**MANAGING CHRONIC STEROID THERAPY**

Adverse effects of chronic glucocorticoid use include skin changes, body composition changes, ocular disorders, cardiovascular disorders (eg, premature atherosclerosis and arrhythmias), gastrointestinal disorders, osteoporosis, mood changes, and renal effects (eg, hypertension).38

Patients treated with corticosteroids long-term (> 7.5 mg daily for more than 3 months)39 should optimize their vitamin D intake, with supplementation as necessary. Supplementation should be considered for those who cannot tolerate adequate dietary calcium. Bisphosphonate therapy (alendronate or zoledronic acid) should be started as a preventive measure in patients at high risk of fragility fractures, such as elderly patients and patients with a history of fragility fracture.37 Others should have their risk factors assessed, and bisphosphonate therapy should be considered for those expected to receive high cumulative glucocorticoid doses, eg, patients who receive a large initial dose.

**GLUCOCORTICOID-SPARING THERAPY FOR SOME CASES**

Multiple adjunctive treatments have been explored for PMR.

**Methotrexate is standard**

Methotrexate, usually at a starting dosage of 10 to 15 mg per week, is the most commonly used glucocorticoid-sparing therapy for PMR.40 A double-blind, randomized controlled trial in 40 patients reported no steroid-sparing effect of methotrexate at a dose of 7.5 mg per week.41 However, another double-blind randomized
Polyarthralgia Rheumatica

Persistent high fever is uncommon with isolated PMR and may signal giant cell arteritis.

Controlled trial, in 72 patients, showed the addition of methotrexate at 10 mg per week was associated with shorter prednisone treatment, suggesting this approach may be useful for patients at high risk of steroid-related toxicity. Additionally, a randomized prospective trial in 24 patients reported that the use of subcutaneous methotrexate in a dosage of 10 mg per week allowed for a smaller cumulative prednisone dose over the course of 1 year without loss of efficacy.

Although limited by small sample sizes, these studies suggest that methotrexate can be useful in conjunction with prednisone for specific patient populations, such as the elderly or patients with osteoporosis. The EULAR/ACR guidelines recommend the early introduction of methotrexate therapy in addition to glucocorticoids in patients at high risk for relapse or prolonged therapy and for those who develop glucocorticoid-related adverse effects.

Azathioprine: A possible alternative

While less studied than methotrexate, azathioprine may also be useful. A double-blind randomized controlled trial evaluated the use of azathioprine 150 mg daily as adjunctive therapy. The trial enrolled 31 participants diagnosed with PMR, GCA, or both, taking at least 5 mg of daily oral prednisolone to manage symptoms. At the end of 1 year, the group receiving azathioprine were on a lower dose of prednisolone than the placebo group. However, patients with PMR were not separately analyzed, precluding recommending the routine use of azathioprine based on this study.

TNF blockers not recommended

Tumor necrosis factor (TNF) blockers have been evaluated for PMR as an adjunctive or stand-alone therapy. A 2012 review noted promising results, but the only randomized controlled trials included (evaluating infliximab and etanercept) failed to meet their primary end points. Hence, TNF blockade is not recommended for managing PMR.

IL-6 blockade is promising

IL-6 plays a major role in sustaining disease activity in PMR, so IL-6 blockade has been explored as a possible treatment, with promising results. Devauchelle-Pensec et al performed a prospective longitudinal study of 20 patients with recent-onset PMR treated with intravenous tocilizumab 8 mg/kg infusions 3 times at 4-week intervals without glucocorticoids. After week 12, patients were treated with oral prednisone for 12 weeks. This regimen was found helpful, but the authors concluded that randomized controlled trials are necessary to evaluate it further.

Lally et al, in an open-label trial in 10 patients who were newly diagnosed with PMR and had been treated with glucocorticoids for less than 1 month, evaluated the efficacy of monthly intravenous tocilizumab 8 mg/kg for 1 year concurrent with rapid tapering of glucocorticoids. One patient withdrew from the study, but the remaining 9 achieved the primary end point of relapse-free remission at 6 months without glucocorticoids.

Izumi et al treated 13 patients who had intractable PMR (significant relapses or little or no response to glucocorticoid treatment) with tocilizumab in addition to their current treatment of prednisolone or methotrexate. They noted significant improvement in PMR symptoms, including morning stiffness, despite decreasing dosage of prednisolone, with no severe adverse effects.

The double-blind, randomized controlled Safety and Efficacy of Tocilizumab Versus Placebo in Polymyalgia Rheumatica With Glucocorticoid Dependence (SEMAPHORE) trial is currently under way with more than 100 patients. Although data are still being accumulated, tocilizumab appears to be a promising glucocorticoid-sparing option for treating patients with PMR. However, there are poorly understood risks of long-term use, including possible increases in infections and cardiovascular events. Therefore, careful consideration is advised before starting IL-6 inhibitors in patients with PMR until more evidence is available.

Close Clinical Monitoring

Regardless of the medication regimen used, patients should be followed closely in the first year after starting treatment, at 0, 1 to 3, and 6 weeks, and at 3, 6, 9, and 12 months. Additional visits should be arranged as needed for new or worsening symptoms.
Monitor for GCA development and aortitis

During follow-up visits, patients should be monitored for symptoms of GCA, including headache, tenderness over temporal arteries, jaw claudication, acute vision loss, and low-grade fever.\textsuperscript{57} GCA and PMR may present together or may be separated in time by long intervals.\textsuperscript{56} Treatment of PMR may not prevent the development of clinical GCA, as the prednisone dosage for PMR is much lower than for GCA, though this is probably rare.\textsuperscript{57}

For patients who exhibit signs of GCA, prednisone 40 to 60 mg daily should be promptly started for treatment.\textsuperscript{58}

Atypical symptoms, such as unexplained low back pain or symptoms isolated to the lower limbs in association with elevated inflammatory markers should prompt further evaluation for aortitis.\textsuperscript{59} Measurement of bilateral blood pressures and auscultation for bruits should be routinely performed at follow-up.

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POLYMYALGIA RHEUMATICA


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Thoracic aortic aneurysm: Optimal surveillance and treatment

ABSTRACT
Aneurysm of the thoracic aorta is less common than in the abdominal aorta, but it is clinically important because of the risk of rupture and death. Cases are often found incidentally. Indications for surgical or endovascular repair are based on aneurysm location and risk factors for rupture such as aneurysm size, rate of growth, and associated conditions, while medical management is also important. Surveillance with various imaging tests is critical before and after intervention to guide treatment.

KEY POINTS
Patients with aortic aneurysm require multidisciplinary care, including a cardiologist and possibly a cardiovascular surgeon and genetic counselor.

Medical care includes traditional cardiovascular risk factor management. Beta-blockers are often used to control blood pressure but should be used with caution in those with acute aortic valve regurgitation.

WHAT IS THE CLINICAL IMPORTANCE OF TAA?
TAA is clinically important because of the risk of devastating complications—acute aortic syndromes such as aortic dissection and rupture.1,2

Type A aortic dissection (ie, originating in the ascending aorta) is a fatal condition with dismal in-hospital mortality rates of 57% without emergency surgery and 17% to 25% with emergency surgery in national and international registries despite advances in management.3,4

The mortality rate is much lower but still significant in expert aortic centers of excellence,
THORACIC AORTIC ANEURYSM

such as the 4% to 7% reported by Cleveland Clinic.3 The incidence of combined TAA and aortic dissection has been reported to be 6 to 13 per 100,000 per year,6–8 although this would underestimate clinically silent TAA.3

There are no effective preventive strategies for TAA to date; thus, early detection, surveillance, and treatment are critical to improving outcomes. Guidelines are available.1,2,9

WHO IS AT RISK?

Risk factors for TAA (Table 1) are abundant in modern society and include older age, male sex, hypertension, smoking, and atherosclerosis. No wonder, then, that the incidence of TAA and the number of surgical repairs are increasing.3,10

Genetic conditions associated with TAA such as Marfan syndrome are less common but nevertheless important because the prognosis and management are different.1,2,9 Some risk factors or conditions increase wall stress, while others increase medial degeneration.10 Although only 5% of cases of TAA are associated with genetic syndromes, another 20% are in patients who have a family history of TAA, which has important implications for assessment, management, and counselling.11 And many cases are idiopathic, lacking obvious causes or risk factors.

HOW IS TAA DISCOVERED?

Most cases of TAA are asymptomatic and are discovered either incidentally on imaging or as part of dedicated screening for those at risk.1 That said, possible symptoms include chest, abdominal, or back pain, dyspnea, cough, dysphagia, hoarseness, claudication, and cerebrovascular events.

The clinical history should be directed at symptoms, risk factors, and family history.

Physical examination should focus on the cardiac, neurologic, and peripheral vascular systems and should include blood pressure (and how it differs in different limbs), pulses, murmurs, and bruits, and other signs specific to associated conditions.1

Basic investigations that can detect possible abnormalities associated with TAA include electrocardiography (showing ischemic changes or myocardial hypertrophy), chest radiography (showing a widened mediastinum or prominent aortic shadow), and blood tests, including complete blood cell count, metabolic profile, and markers of inflammation, coagulation, and myocardial injury, many of which help in the differential diagnosis of TAA vs acute aortic syndromes.1,9

WHAT IS A NORMAL-SIZE AORTA?

Although aneurysm is generally defined as an increase of more than 50% of the normal arterial diameter, cardiac imaging guidelines have clear dimension thresholds for different severities of TAA dilation.9,10

<table>
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<td>Thoracic aortic aneurysm: Risk factors, associations, and causes</td>
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<table>
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<tr>
<th>Risk factors</th>
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<tbody>
<tr>
<td>Older age</td>
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<tr>
<td>Male sex</td>
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<tr>
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<td>Marfan syndrome</td>
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<td>Loëys-Dietz syndrome</td>
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<td>Ehlers-Danlos syndrome</td>
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<tr>
<td>Turner syndrome</td>
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<tr>
<td>Autosomal-dominant poly cystic kidney disease</td>
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<tr>
<td>Shprintzen-Goldberg (craniosynostosis) syndrome</td>
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<table>
<thead>
<tr>
<th>Inflammatory causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takayasu arteritis</td>
</tr>
<tr>
<td>Giant-cell arteritis</td>
</tr>
<tr>
<td>Behçet arteritis</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infective causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycotic aortitis</td>
</tr>
<tr>
<td>Syphilis</td>
</tr>
</tbody>
</table>

| Idiopathic |

The risk of rupture or dissection decides who requires prophylactic intervention.
The aorta is larger in men and in larger people generally, and therefore sex and body size are taken into account when determining the normal ranges and severity thresholds.\(^9\) The aorta also tends to increase in size with age. The upper limit of normal for aortic dimensions is 2 standard deviations above the mean diameter in a population of healthy adults.

Aortic dimensions are measured at right angles to the direction of blood flow. On echocardiography, the standardized aortic measurements are taken in the end-diastolic frame and from leading edge to leading edge for reproducibility. On CTA and MRA, measurements are from inner edge to inner edge, from aortic sinus to sinus, or from sinus to commissure (often about 2 mm smaller than from sinus to sinus; Figure 1).\(^{12,13}\) The full thoracic aortic study should include measurement of all segments: aortic sinus; sinotubular junction; proximal, mid, and distal ascending aorta; aortic arch; and descending aorta, as well as the maximal dimensions, branch involvement, and surgical anastomoses.\(^9\) The aortic walls should be examined for calcification, thrombus, dissection, hematoma, and infection.

**WHAT IMAGING MODALITIES ARE USED?**

Aortic imaging remains central to TAA diagnosis and surveillance.\(^{1,2,9}\) Three-dimensional multiplanar reconstruction software for CTA and MRA has revolutionized measurement of the aorta, recon-

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**Figure 1.** Computed tomography angiography aortic root measurements on (A) axial source image and (B–D) 3-dimensional multiplanar reconstruction (3-D-MPR) double-oblique planes. Note that without 3-D-MPR, the aortic root size is underestimated (A). Also note that sinus-commissure measurements are often slightly less than sinus-sinus measurements in (B).

---

3-D CTA and MRA have revolutionized measurement of the aorta
structing source images into double-oblique planes to ensure measurements are taken perpendicular to the lumen (Figure 1).

Echocardiographic aortic root measurement has the strongest evidence base for guiding intervention, and its thresholds have been extrapolated to other modalities and aortic locations. Clinicians need to be aware of these concepts and limitations to select the best imaging modality, perform measurements, and interpret the results. Table 2 lists the uses and limitations of 5 imaging modalities for TAA, modified from American Society of Echocardiography guidelines.9

Transthoracic echocardiography (TTE) has the advantages of portability, accessibility, and low cost. The operator should interrogate the aortic root and ascending aorta in the parasternal long-axis views, parts of the arch and descending thoracic aorta in the suprasternal view, and a segment of the abdominal aorta in the subcostal view.

Transesophageal echocardiography (TEE) has a limited role in the primary assessment of TAA unless concurrent structural cardiac disease is suspected. It can visualize a greater extent of the thoracic aorta than TTE and with superior spatial resolution, including with 3-dimensional techniques. It can also be used for intraoperative evaluation as well as a contrast-free imaging option for diagnosing acute aortic syndromes.9 The aortic root and ascending aorta can be visualized in the midtransesophageal long-axis view at 100 to 140 degrees; the aortic valve and root in the short-axis view at 45 to 60 degrees; and the descending thoracic aorta up close at 0 degrees in the short-axis view and 90 degrees in the long-axis view, where atheroma and dissection flaps can be visualized up to the aortic arch with probe withdrawal.1,14

CTA is the recommended first-line imaging for assessing TAA, having high spatial resolution and a short scan time (3–4 seconds for the thoracic aorta, < 10 seconds for thoracoabdominal and iliofemoral vessels), enabling assessment of all segments and walls of the thoracic aorta with a 3-D dataset. Radiation and contrast use are limitations. Electrocardiographic gating of CTA is recommended to reduce motion artifacts (Figure 2).

Noncontrast CT of the aorta may add value if assessing for intramural hematoma or vascular calcification, or if contrast is contraindicated.15

### Table 2

<table>
<thead>
<tr>
<th>Considerations</th>
<th>TTE</th>
<th>TEE</th>
<th>CTA</th>
<th>MRA</th>
<th>Aortography</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy of measurement</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Extent of aortic assessment</td>
<td>Limited</td>
<td>Medium</td>
<td>Entire</td>
<td>Entire</td>
<td>Limited</td>
</tr>
<tr>
<td>Detecting acute aortic syndromes</td>
<td>Poor</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
<td>Poor</td>
</tr>
<tr>
<td>Aortic regurgitation and grading</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Limited</td>
</tr>
<tr>
<td>Portable</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Contrast</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Radiation</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Cost</td>
<td>Low</td>
<td>Medium</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Invasive procedure</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Recommended line of investigation</td>
<td>Second</td>
<td>Third</td>
<td>First</td>
<td>Second</td>
<td>Third</td>
</tr>
</tbody>
</table>

CTA = computed tomography angiography; MRA = magnetic resonance angiography; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

Based on information in reference 9.
MRA also provides a high-resolution 3-D dataset for aortic assessment without the use of radiation, but has longer scan time, higher cost, and lower availability than echocardiography and CT, and so it is a second-line modality. Relevant magnetic resonance techniques include contrast-enhanced MRA, cine bright-blood sequences such as steady-state free precession and black-blood spin-echo sequences with or without inversion recovery. MRA can further assess aortic physiology, for example, measuring flow by phase-contrast velocity-encoded imaging, aortic stiffness and elasticity, and shear stress.

Both CTA and MRA can also assess for other cardiac and thoracic diseases. CTA or MRA should be performed in every patient diagnosed with TAA to confirm the maximal dimensions and assess the entire length of the aorta.

Other methods for aortic imaging include invasive aortography with fluoroscopy, positron-emission tomography, and intravascular ultrasonography, although they are never used solely for assessing TAA.

Examples of TAA pathologies are shown in Figure 3.

**Figure 2.** Computed tomography of thoracic aortic aneurysm without (A) and with (B) electrocardiographic gating. Note that the motion artifact indicated by the white arrow in (A) is not seen in (B).

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**WHEN SHOULD TAA BE FIXED?**

Table 3 summarizes the American 2010 and European 2014 guidelines and our recommendations on indications for TAA repair. The main determinants include aneurysm dimensions, rate of expansion, and associated conditions. The patient’s overall estimated risk of acute aortic syndrome also needs to be balanced with the hospital’s expertise and procedural risks for TAA repair. Surgical evaluation is necessary when there are symptoms thought to be related to the TAA, irrespective of other factors.

TAAs grow by 0.7 to 1.9 mm per year in undilated aortas, but growth can be faster in patients with a dilated aorta or associated conditions.

TAAs grow by 0.7 to 1.9 mm per year in undilated aortas, but growth can be faster in patients with a dilated aorta or associated conditions. Absent other conditions, intervention is indicated if the ascending aorta is ≥ 5.5 cm or the descending aorta is 6.0 cm.

TAA size is the strongest predictor of acute aortic syndromes. In patients who have no other conditions, the guidelines recommend surgery when the aortic root, ascending aorta, or aortic arch reaches 5.5 cm and when the descending aorta reaches 6.0 cm (≥ 5.5 cm with endovascular stenting). This is based on a sharp rise in the risk of aortic dissection when the ascending aorta reaches 6 cm and the descending aorta reaches 7 cm.
Another indication for intervention is a maximal cross-sectional area $\pi r^2/H > 10$

Factors that lower the threshold include associated conditions, faster rate of growth (measured by the same modality and exceeding the margin of error of 3–5 mm/year), and the need for adjacent aneurysm or aortic valve surgery.\textsuperscript{1,2}

The American guidelines further emphasize measuring the maximal TAA cross-sectional area. If the maximal TAA cross-sectional area (in cm$^2$) divided by height (in meters) is greater than 10, this would be another indication for intervention.\textsuperscript{2} This threshold was derived from studies from Cleveland Clinic originally applied to patients with bicuspid aortic valves and Marfan syndrome,\textsuperscript{19,20} and more recently in all TAA patients,\textsuperscript{21} with major prognostic implications (Figure 4).

Lower thresholds in associated conditions

Lower thresholds for intervention are recommended when patients have associated conditions that increase the risk of dissection at smaller dimensions and increase the rate of growth.\textsuperscript{1,2}

\textbf{Bicuspid aortic valve.} Recent guidelines have shifted the thresholds for intervention back up to $\geq 5.5$ cm, or $\geq 5.0$ cm with risk factors for patients with bicuspid aortic valves, which occur in 1% to 2% of the population.\textsuperscript{1,22} (Previously, the threshold was 4.5 cm or greater.) These patients have a risk of aortic dissection up to 8 times higher than that of the general population.\textsuperscript{23} A Cleveland Clinic study found the risk of aortic dissection in bicuspid aortic valve patients to be elevated at 4.7 to 5.3 cm, but the risk further accelerates beyond

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{aortopathology.png}
\caption{Range of thoracic aortic aneurysm (TAA) pathologies: (A) bicuspid aortic valve aortopathy on computed tomography (CT), (B) Marfan syndrome with pectus excavatum on magnetic resonance imaging, (C) mycotic aortic arch aneurysm on CT, (D) Takayasu arteritis on CT, with thickened, inflamed aortic wall.}
\end{figure}
## Table 3

### Indications for prophylactic intervention for thoracic aortic aneurysm

<table>
<thead>
<tr>
<th>Aneurysm location and associated conditions</th>
<th>ACC/AHA 2010&lt;sup&gt;2&lt;/sup&gt;</th>
<th>ESC 2014&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Our recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ascending aorta</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No associated conditions</td>
<td>≥ 5.5 cm (I-C)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≥ 5.5 cm (I-C), lower if small stature, rapid progression, aortic regurgitation (AR), pregnancy, patient preference (IIa-C)</td>
<td>≥ 5.5 cm</td>
</tr>
<tr>
<td></td>
<td>≥ 0.5 cm/year growth (I-C)</td>
<td></td>
<td>π&lt;sup&gt;r&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;/H &gt; 10</td>
</tr>
<tr>
<td>Aortic valve surgery planned</td>
<td>&gt; 4.5 cm (I-C)</td>
<td>&gt; 4.5 cm</td>
<td>&gt; 4.5 cm</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>4.0–5.0 cm (I-C)</td>
<td>≥ 5.0 cm (I-C)</td>
<td>&gt; 4.5 cm</td>
</tr>
<tr>
<td></td>
<td>π&lt;sup&gt;r&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;/H &gt; 10 (Ila-C)</td>
<td>&gt; 4.5 cm with risk factors or family history (Ila-C)</td>
<td>π&lt;sup&gt;r&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;/H &gt; 10</td>
</tr>
<tr>
<td></td>
<td>≥ 5.5 cm without risk factors (I-C)</td>
<td>≥ 0.3 cm/year growth, severe AR, pregnancy desired (Ila-C)</td>
<td>≥ 5.0 cm without risk factors</td>
</tr>
<tr>
<td></td>
<td>≥ 5.0 cm with risk factors, family history, hypertension, aortic coarctation (I-C)</td>
<td>≥ 4.5 cm if AVR planned (I-C)</td>
<td>≥ 4.5 cm with risk factors</td>
</tr>
<tr>
<td></td>
<td>≥ 4.5 cm if AVR planned (I-C)</td>
<td>≥ 0.3 cm/year growth (Ila-C)</td>
<td>π&lt;sup&gt;r&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;/H &gt; 10</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>4.0–5.0 cm (I-C)</td>
<td>Indexed aortic diameter ≥ 27.5 mm/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>≥ 27.5 mm/m&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>π&lt;sup&gt;r&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;/H &gt; 10 (Ila-C)</td>
<td></td>
<td>π&lt;sup&gt;r&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;/H &gt; 10</td>
</tr>
<tr>
<td>Loeys-Dietz syndrome (apply to TGFBR1 or TGFBR2 mutation)</td>
<td>≥ 4.2 cm (TEE) (Ila-C)</td>
<td>≥ 5.0 cm (I-C)</td>
<td>≥ 4.5 cm</td>
</tr>
<tr>
<td></td>
<td>≥ 4.4–4.6 cm (CTA/MRA) (Ila-C)</td>
<td>≥ 4.5 cm with risk factors (Ila-C)</td>
<td>≥ 4.5 cm</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>4.0–5.0 cm (I-C)</td>
<td>No specific threshold recommended</td>
<td>≥ 4.5 cm</td>
</tr>
<tr>
<td></td>
<td>π&lt;sup&gt;r&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;/H &gt; 10 (Ila-C)</td>
<td></td>
<td>π&lt;sup&gt;r&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;/H &gt; 10</td>
</tr>
<tr>
<td>Familial TAA</td>
<td>4.0–5.0 cm (I-C)</td>
<td>No specific threshold recommended</td>
<td>≥ 4.5 cm</td>
</tr>
<tr>
<td></td>
<td>π&lt;sup&gt;r&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;/H &gt; 10 (Ila-C)</td>
<td></td>
<td>π&lt;sup&gt;r&lt;/sup&gt;&lt;sup&gt;2&lt;/sup&gt;/H &gt; 10</td>
</tr>
<tr>
<td><strong>Aortic arch</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>≥ 5.5 cm (Ila-B)</td>
<td>≥ 5.5 cm (Ila-C)</td>
<td>≥ 5.5 cm</td>
</tr>
<tr>
<td></td>
<td>Consider if having ascending or descending TAA surgery (Ila-C)</td>
<td></td>
<td>≥ 5.5 cm</td>
</tr>
<tr>
<td><strong>Descending aorta</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent graft</td>
<td>≥ 5.5 cm (I-B)</td>
<td>≥ 5.5 cm (Ila-C)</td>
<td>≥ 5.5 cm</td>
</tr>
<tr>
<td>Surgery</td>
<td>≥ 6.0 cm (I-C) (include high risk, thoracoabdominal)</td>
<td>≥ 6.0 cm (Ila-C)</td>
<td>≥ 6.0 cm</td>
</tr>
<tr>
<td>Surgery with degenerative, traumatic or saccular TAA, or postoperative pseudo-aneurysm</td>
<td>≥ 5.5 cm (I-B)</td>
<td>No specific threshold recommended</td>
<td>≥ 5.5 cm</td>
</tr>
<tr>
<td>Surgery with connective tissue disorder like Marfan or Loeys-Dietz syndrome</td>
<td>Lower threshold than &gt; 6 cm (I-C)</td>
<td>Lower threshold than &gt; 6 cm</td>
<td>≥ 5.5 cm</td>
</tr>
</tbody>
</table>

<sup>a</sup>Class of recommendation (scale of I to III) and level of evidence (scale of A to C).

ACC = American College of Cardiology; AHA = American Heart Association; AVR = aortic valve surgery; CTA = computed tomographic angiography; ESC = European Society of Cardiology; MRA = magnetic resonance angiography π<sup>r</sup><sup>2</sup>/H = maximal cross-sectional area of TAA divided by height; TAA = thoracic aortic aneurysm
5.3 cm, so a 5.0-cm threshold for intervention rather than a higher one may indeed be preferred in these patients.24

**Marfan syndrome.** The threshold for intervention is 4.5 to 5.0 cm, depending on risk factors.1

**Loeys-Dietz syndrome.** There are mixed views for the threshold of intervention, ie, whether it should be the same as in Marfan syndrome or even lower.1,2,25

**Turner syndrome** is associated with short stature and greater risk of rupture for the same aorta size, so indexed measurements are preferred.26 It is also associated with bicuspid aortic valve and aortic coarctation, so concurrent cardiovascular surgery is often required.27

**Ehlers-Danlos syndrome** is associated with tissue fragility, making surgery challenging. Therefore, surgery remains controversial in this condition, and most patients are conservatively managed.27

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**How Should TAA Be Monitored?**

Patients with TAA should be referred to a cardiologist (and a surgeon, if approaching or exceeding surgical criteria) for optimal decision-making in surveillance and management.

The first thing to consider is the imaging modality to use. Table 4 summarizes the guidelines and our recommendations for TAA surveillance, using TTE, CTA, and MRA.1,3

CTA or MRA is useful at baseline to image the entire aorta and check agreement with TTE measurements. If TTE measurements have close agreement with CTA or MRA, then TTE can be used for regular monitoring, although CTA or MRA should still be performed, though less often, for monitoring segments of the aorta not visible on TTE and checking TTE accuracy over time.

If there is poor agreement between TTE and CTA or MRA measurements, or poor visualization of the aorta with TTE, then CTA or MRA should be used instead for regular monitoring. The latter is preferred to avoid radiation exposure, but the former may be necessary if MRA is contraindicated, eg, because of a cardiac device or claustrophobia.3

Accurate and reproducible measurements are critical in surveillance, especially when nearing the threshold for intervention.

Once the modality is established, timing of surveillance and guideline recommendations depend on aortic dimensions and growth and presence of associated conditions.1,3,9 In the absence of conditions associated with TAA, the recommendation is routine surveillance at the discretion of the clinician, based on
### TABLE 4

**Recommendations for measurement and surveillance of thoracic aortic aneurysms**

<table>
<thead>
<tr>
<th>Associated conditions</th>
<th>ACC/AHA 2010²</th>
<th>ESC 2014¹</th>
<th>ASE/EACVI 2015³</th>
<th>Our recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>None</strong></td>
<td>No specific recommendations except needing surveillance</td>
<td>No specific recommendations except needing surveillance</td>
<td>Every 1–3 years based on risk after diagnosis</td>
<td>TTE and CTA or MRA at baseline and 6 months; If TAA &lt; 5.0 cm and stable, then yearly If TAA &gt; 5.0 cm or growing &gt; 0.5 cm/year, then every 6 months and refer to surgeon</td>
</tr>
<tr>
<td><strong>Marfan syndrome</strong></td>
<td>Measure dimensions and maximum cross-sectional area divided by height TTE at baseline and 6 months, CTA or MRA at baseline to check TTE If stable and &lt; 4.5 cm, then yearly, if not then more frequently</td>
<td>TTE and MRA or CTA If no TAA at baseline, TTE yearly, MRA or CTA every 5 years If any aneurysm is above root, MRA or CTA yearly Refer to 2010 ESC adult congenital disease guidelines¹⁰</td>
<td>Dimensions with normative values based on age, body surface area, and Z scores TTE and CTA or MRA If no TAA at baseline, then every 2–3 years First TAA diagnosis: 6 months then yearly if stable, &lt; 4.5 cm and no dissection history; otherwise every 6 months Postoperatively: 6 months, then yearly if stable CTA or MRA at least every 3 years if using TTE</td>
<td>TTE and CTA or MRA at baseline and 6 months If no TAA, then TTE yearly and CTA or MRA every 2 years First TAA diagnosis: TTE and CTA or MRA yearly if stable (&lt; 0.3 cm/year) and &lt; 4.5 cm, otherwise every 6 months and refer to surgeon</td>
</tr>
<tr>
<td><strong>Bicuspid aortic valve</strong></td>
<td>No specific recommendations after initial imaging TTE and CTA or MRA</td>
<td>TTE and CTA or MRA If no TAA at baseline, repeat TTE yearly If TAA &gt; 4.5 cm or growing at &gt; 3 mm/year, then do CTA or MRA to confirm at same time, then yearly</td>
<td>TTE and CTA or MRA If no at baseline, repeat every 3–5 years First TAA diagnosis: 6 months then yearly if stable, &lt; 4.5 cm and no dissection history; otherwise every 6 months Postoperatively: yearly but individualize</td>
<td>TTE + CTA or MRA at baseline and 6 months No TAA; TTE yearly and CTA or MRA every 2 years First TAA diagnosis: TTE and CTA or MRA yearly if stable (&lt; 0.3 cm/year) and &lt; 4.5 cm, otherwise every 6 months and refer to surgeon</td>
</tr>
<tr>
<td><strong>Turner syndrome</strong></td>
<td>Baseline TTE and CTA or MRA If no TAA or dissection risk factors, repeat every 5–10 years</td>
<td>If no TAA: TTE every 3–5 years for low risk, MRA every 3–5 years for moderate risk, and MRI every 1–2 years for high risk</td>
<td>Index dimensions by body surface area; if indexed diameter &gt; 2 cm/m², repeat yearly</td>
<td>TTE + CTA or MRA at baseline and 6 months Index dimensions by body surface area No TAA: TTE yearly and CTA or MRA every 2 years Indexed diameter &gt; 2 cm/m²: yearly MRA and CTA and refer to surgeon</td>
</tr>
<tr>
<td><strong>Familial TAA</strong></td>
<td>No specific recommendations after initial imaging TTE and CTA or MRA</td>
<td>No specific recommendations after initial imaging TTE and CTA or MRA</td>
<td>Follow plan for Marfan syndrome, but individualize</td>
<td>TTE + CTA or MRA at baseline and 6 months Follow plan for Marfan syndrome but individualize risk</td>
</tr>
<tr>
<td><strong>Loeys-Dietz syndrome</strong></td>
<td>Baseline and 6 months TTE and CTA or MRA, then yearly if stable Whole-body MRA</td>
<td>No specific recommendations after initial imaging TTE and CTA or MRA</td>
<td>Every 1–3 years depending on risk, every 6 months if progression</td>
<td>TTE + CTA or MRA at baseline and 6 months Yearly if low risk, &lt; 4.0 cm and stable (&lt; 0.3 cm/year), otherwise every 6 months and refer to surgeon</td>
</tr>
<tr>
<td><strong>Ehlers-Danlos syndrome</strong></td>
<td>No specific recommendations</td>
<td>No specific recommendations, individualize</td>
<td>No specific recommendations</td>
<td>TTE + CTA or MRA at baseline and 6 months No specific recommendation for surveillance</td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology; AHA = American Heart Association; ASE = American Society of Echocardiography; CTA = computed tomography angiography; EACVI = European Association of Cardiovascular Imaging; ESC = European Society of Cardiology; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; TAA = thoracic aortic aneurysm; TTE = transthoracic echocardiography
individual risk. On the other hand, an early follow-up scan (6 months after initial TAA diagnosis) is recommended to assess for growth of the aneurysm in patients who have genetic conditions, and annually thereafter if measurements have been stable or more frequently if there is accelerated growth.

The measurements recommended may also differ by condition, such as comparing to normalized values by age, sex, and body surface area and using Z scores in those with Marfan syndrome and indexing to body surface area in those with Turner syndrome. No specific recommendations for TAA surveillance and intervention for Ehlers-Danlos syndrome have been made because there is no evidence that intervening is beneficial.

**DO DRUGS SLOW THE RATE OF TAA EXPANSION?**

TAA patients should be referred to a cardiologist to provide guideline-based medical management of the aorta, and to a cardiac surgeon when nearing a threshold for intervention.

Blood pressure control is the cornerstone of medical management of TAA, as it makes pathophysiologic sense to reduce aortic wall shear stress and expansion. However, many recommendations have been extrapolated from studies in patients with Marfan syndrome, with mixed results.

A randomized trial found beta-blockers reduced expansion and even mortality in patients with Marfan syndrome with TAA, though this was not consistently reported in other studies. Nevertheless, beta-blockers are routinely prescribed in TAA, with adequate response represented by reduction in both blood pressure and heart rate, although they should not be used in those with significant aortic regurgitation.

There is also some mixed evidence from randomized trials supporting the use of angiotensin II receptor blockers and angiotensin-converting enzyme inhibitors.

The optimal blood pressure target remains controversial. The European guidelines advocate 140/90 mm Hg, while the American guidelines say 130/80 mm Hg in those with diabetes or chronic renal disease and 140/90 mm Hg in those without.

Statins were seen in one study to reduce events in patients with abdominal aortic aneurysm but not those with TAA, so they are not routinely recommended for TAA. Nevertheless, many patients with TAA have concurrent atherosclerotic disease that would benefit from statin therapy.

**HOW SHOULD TAA BE FIXED?**

Interventions for TAA vary widely in complexity and are classified by location and by modality. Patients should be referred to a high-volume cardiac surgery center with aortic expertise for management to optimize outcomes.

Aneurysm of the ascending aorta mandates surgical repair with median sternotomy, cardiopulmonary bypass, and circulatory arrest. Considerations include the need to operate on the aortic valve (prosthetic valve composite graft or valve-sparing), aortic root (requiring coronary reimplantation), arch (complete or partial, brain protection with hypothermia, and perfusion method), and sometimes the descending aorta.

On the other hand, aneurysm in the descending aorta can be addressed with endovascular repair using percutaneous access in suitable anatomy, with or without arch-vessel transposition (debranching). The potential benefits are lower perioperative mortality risk and faster recovery than with surgery, although late complications such as graft leak, migration, and rupture can occur, and the durability is unknown.

Surgery is the alternative option, with a higher threshold of aortic dimensions for intervention. It is done by thoracotomy and often without cardiopulmonary bypass while protecting the spinal cord. High surgical risk and restricted life expectancy favor endovascular repair, while genetic syndromes, peripheral vascular disease, and unfavorable anatomy favor surgery. A hybrid approach for surgery of the ascending aorta, arch, or both and endovascular repair for the descending aorta is sometimes considered in extensive TAA.

**WHAT ELSE SHOULD BE MANAGED?**

Management of TAA is multidisciplinary, with many aspects beyond medications and interventions. Patient education regarding warning symptoms and signs of TAA complications warranting immediate medical at-
tention is important.\textsuperscript{1,2} Cardiovascular risk reduction is important, with nonpharmacologic measures such as healthy diet and smoking cessation, which have positive effects on blood pressure and lipids.

Exercise is controversial in patients with TAA. Although aerobic activity should probably be encouraged, weight-training activities such as heavy lifting should be avoided, particularly in those with genetic conditions such as Marfan syndrome or Loeys-Dietz syndrome.

There is also a weak association of acute aortic syndromes with fluoroquinolones, so avoidance may be considered.\textsuperscript{34}

Counseling should be considered in patients with genetic conditions associated with TAA, women considering pregnancy or who are pregnant, and patients with indications for aortic interventions but who are being conservatively managed because of medical comorbidities and surgical risk.

In patients with genetic syndromes or bicuspid aortic valves who develop TAA, counseling and family screening starting with first-degree relatives (and beyond if multiple family members are positive) are important.\textsuperscript{1,2} Screening involves TTE, preferably CTA or MRA (used more because of no radiation), and genetic testing. If one or more first-degree relatives of a TAA patient are also found to have TAA, referral to a clinical geneticist for further testing and counseling is recommended. The implicated genes include FBN1 for Marfan syndrome; TGFBR1, TGFBR2, SMAD3, TGFB2, and TGFB3 for Loeys-Dietz syndrome, COL5A1, COL5A2, and COL3A1 for Ehlers-Danlos syndrome, and 45XO for Turner syndrome.\textsuperscript{1,35} Early detection of TAAs with surveillance and intervention have the potential to improve outcomes for patients and family members.

\section*{REFERENCES}


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Managing adult asthma: The 2019 GINA guidelines

ABSTRACT
Asthma is highly prevalent and sometimes deadly, especially in certain groups. The 2019 Global Initiative for Asthma (GINA) guidelines recommend that all asthma patients be treated with inhaled corticosteroids taken daily or as needed; this improves symptoms and outcomes, even in those with mild disease. Further, asthma management requires a stepwise approach, escalating and de-escalating treatment based on symptom control.

KEY POINTS
- Asthma is more common and more severe in women, Black people, and families with low income.
- As asthma progresses in severity, treatment should no longer be taken only as needed but rather daily. Dosages should be increased, and a long-acting muscarinic antagonist should be added.
- Before escalating treatment, clinicians should ensure that the patient is correctly and consistently using the prescribed medications and that asthma triggers have been reduced as much as possible.
- Asthma and chronic obstructive pulmonary disease often occur together in elderly patients and those who smoke, requiring aggressive treatment such as triple therapy with an inhaled corticosteroid, a long-acting beta-agonist, and a long-acting muscarinic antagonist.

The Global Initiative for Asthma (GINA) updated its management guidelines in 2019, recommending for the first time that every patient be treated with an inhaled corticosteroid (ICS), taken as needed or daily. This contrasts with older guidelines that recommended short-acting beta-agonists (SABAs) as rescue medications for mild-intermittent asthma, without any inhaled corticosteroid use.

This article briefly reviews the epidemiology, pathophysiology, clinical presentation, and diagnosis of asthma. Then, using case studies, we outline how to manage patients with mild, moderate, and severe asthma based on the GINA 2019 guidelines, as well as how to manage patients who have combined asthma and chronic obstructive pulmonary disease (COPD).

ASTHMA IS COMMON, ESPECIALLY IN CERTAIN GROUPS
Asthma affects nearly 25 million people in the United States, about 7.7% of the population. But it affects certain subgroups disproportionately, as follows:

- Women (9.8%) more than men (5.5%)
- Non-Hispanic Black people (9.6%) more than non-Hispanic White people (8.2%), and Hispanic people (6.0%)
- People in families with low incomes (< 100% poverty level; 10.8%) more than those with high incomes ( > 450% poverty level; 6.5%).

Death rates reflect and sometimes amplify disparities in prevalence. In 2018, more than 3,400 asthma deaths were reported, with rates of 21.8 per 1 million in Black people, 9.5 per 1 million in White people, and 6.3 per 1 million.

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in Hispanic people. Women died at the rate of 15.3 per 1 million and men at 10.2 per 1 million.1

Healthcare utilization by patients with asthma is high. In 2016, emergency department visits with asthma as the first-listed diagnosis occurred at the rate of 50.3 per 10,000 adults, and hospitalizations occurred at 4.4 per 10,000 adults.1

In 2018, 43% of adults with asthma reported having had at least 1 attack in the previous year.1

**PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS**

The underlying pathophysiology of asthma is chronic airway inflammation, resulting in bronchoconstriction, airway wall thickening, and increased mucus production.2

Asthma can develop at any age, but most often in childhood. It is characterized by recurrent episodic respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough. Manifestations vary over time in duration, frequency, and intensity, so a patient’s physical examination may be normal at the time of presentation. Suggestive findings include expiratory wheezing, pale and swollen nasal mucosa, nasal polyps, and atopic dermatitis.

Typical triggers include respiratory infections, allergens, weather changes, poor air quality, tobacco smoke, exercise, stress, and laughing.2 A family or personal history of allergic disease supports the diagnosis. The diagnosis of asthma requires a compatible history as well as evidence of a variable and significantly reversible expiratory airflow limitation, measured by spirometry or peak flow (Table 1).2

**UPDATED MANAGEMENT GUIDELINES**

When asthma is effectively treated, patients can achieve good symptom control, have productive, physically active lives, and exhibit normal or nearly normal lung function.2 All patients should be assessed and counseled on modifiable risk factors and triggers, such as smoking, medications (eg, nonselective beta-blockers), allergens, rhinosinusitis, obesity, gastroesophageal reflux disease, sleep-disordered breathing, depression, and anxiety.1 Patients should then be managed in a stepwise approach, escalating or de-escalating treatment based on symptom control, and subsequently reviewing treatment response.2

If a particular regimen does not control a patient’s asthma, before stepping up the treatment, one should reassess the patient’s adherence to the prescribed medications (and whether he or she can afford them), inhaler technique, modifiable risk factors, triggers, and comorbidities.2 Indicators of poor symptom control include frequent symptoms or reliever inhaler use, activity limited by asthma, and night-waking due to asthma. Stepped-up therapy can be short-term (1–2 weeks) when a trigger is temporarily present, such as during a respiratory infection, or indefinite if no apparent trigger is identified.2

According to the 2019 GINA guidelines, all patients should be treated with an ICS, taken either daily or driven by symptoms. Multiple randomized controlled trials and observational studies have found that this treatment improves symptoms, reduces decline in lung function, and reduces the risk of serious exacerbations, hospitalizations, and mortality, even in patients with mild asthma.1–4 This recommendation is a change from previous guidelines, which relied on SABAs for rescue for mild-intermittent asthma. ICSs address the underlying inflammatory process, while SABAs do not. Increased use of SABAs, which can signal worsening of asthma, is also associated with higher exacerbation risk.5,6

Management of mild, moderate, and severe asthma is summarized in Figure 1 and detailed in the cases below.
CASE 1. A WOMAN WITH MILD ASTHMA

A 62-year-old woman presents to her doctor’s office for routine asthma follow-up. She was diagnosed with asthma 3 years ago and was initially prescribed a daily medium dose of an ICS plus a long-acting beta-agonist (LABA) inhaler for symptom control. Currently, she has been off maintenance inhaler therapy for more than a year and has not had an exacerbation in 2 years. She is symptom-free and on no medications. She has a short-acting beta-agonist (SABA) rescue inhaler but has not needed to use it in many months. Her comorbidities include obesity and uncontrolled gastroesophageal reflux disease. She received an influenza shot 2 weeks ago.

GINA 2019 recommends the following steps for managing mild asthma.

Step 1. Patients with symptoms occurring less than twice a month and who have no risk factors for exacerbation such as major environmental exposure, socioeconomic problem, or severely decreased lung function should be managed with either of the following regimens (level of evidence B—limited data including small randomized controlled trials and meta-analyses):

- An ICS plus LABA combination (eg, budesonide-formoterol) in low doses as needed
- An ICS and an SABA in low doses, to be used together as needed.

The former is recommended as an alternative to traditional reliever therapy with SABAs, but cost is often a barrier (the list price is $300–$346 for a 30-day supply, depending on dosage). Physicians should consider the cost when determining the treatment plan. Formoterol is the only LABA that is recommended to be used as a reliever, owing to its rapid bronchodilator action.

Step 2. Patients with symptoms occurring twice a month or more should be managed with either of the following regimens (level of evidence A—ample data based on appropriate studies):

- An ICS plus LABA combination in low doses, as needed
- An ICS in low doses daily, plus either one of these for rescue: a low-dose ICS-LABA or an SABA as needed.

Outcomes are similar with either the daily or as-needed strategy for mild disease, so patient preference should be considered, as well as the likelihood of adherence to daily treatment. Compared with patients with mild asthma who were treated with as-needed SABA monotherapy, those treated with daily low-dose ICS had half as many severe exacerbations in a study by Reddel et al, while those receiving as-needed low-dose ICS-LABA treatment had a 64% reduction in a study by O’Byrne et al. Other studies showed as-needed low-dose ICS-LABA therapy to be noninferior to daily ICS use for reducing severe exacerbations and exercise-induced bronchoconstriction. As-needed ICS-LABA treatment was, however, inferior to daily ICS therapy for symptom control.

The clinician can also consider adding a leukotriene receptor antagonist (LTRA).

Case conclusion. The patient has controlled mild intermittent asthma. She is prescribed a low-dose ICS-LABA inhaler to use as needed, driven by symptoms. As obesity and gastroesophageal reflux disease can exacerbate asthma, she is encouraged to lose weight and is prescribed a proton-pump inhibitor. She is given a pneumococcal vaccination.

**TABLE 1**

<table>
<thead>
<tr>
<th>Signs of airflow limitation variability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive bronchodilator reversibility test</strong></td>
</tr>
<tr>
<td>Increase in forced expiratory volume in 1 second (FEV₁) &gt; 12% and &gt; 200 mL from baseline 10–15 minutes after administering 200–400 μg albuterol or equivalent (more likely to be positive if bronchodilator is withheld before test: short-acting beta-agonists for at least 4 hours and long-acting beta-agonists for at least 15 hours before test)</td>
</tr>
<tr>
<td><strong>High variability in peak expiratory flow</strong> (highest of 3 readings), performed twice daily for 2 weeks</td>
</tr>
<tr>
<td>Average daily diurnal variability &gt; 10%</td>
</tr>
<tr>
<td><strong>Significant increase in lung function after 4 weeks of anti-inflammatory treatment</strong></td>
</tr>
<tr>
<td>Increase in FEV₁, by &gt; 12% and &gt; 200 mL</td>
</tr>
<tr>
<td>(or peak expiratory flow by &gt; 20%) from baseline</td>
</tr>
<tr>
<td><strong>Positive exercise challenge test</strong></td>
</tr>
<tr>
<td>Fall in FEV₁, of &gt; 10% and &gt; 200 mL from baseline</td>
</tr>
<tr>
<td><strong>Positive bronchial challenge test</strong></td>
</tr>
<tr>
<td>Fall in FEV₁, from baseline of ≥ 20% with standard doses of methacholine or histamine, or ≥ 15% with standardized hyperventilation, hypertonic saline, or mannitol</td>
</tr>
<tr>
<td><strong>Excessive variation in lung function between visits</strong></td>
</tr>
<tr>
<td>Variation in FEV₁, of &gt; 12% and &gt; 200 mL</td>
</tr>
</tbody>
</table>
A 51-year-old man presents to a physician’s office to establish care. He was diagnosed with asthma and hospitalized at a very young age. His asthma became mild after high school, and he has been off controller therapy for decades. A year ago, he began noticing chest tightness during exercise and recently has had to use his rescue inhaler on a daily basis. His asthma symptoms are triggered by stress, exposure to domestic animals, cold weather, exercise, and chest colds. He also has environmental, mold, and dust allergies. He has not had an exacerbation requiring prednisone since his youth and does not currently have any nighttime symptoms.

A few months ago he was started on low-dose ICS twice daily and LTRA therapy. Besides asthma, he has sleep apnea and uses continuous positive airway pressure most nights.

GINA 2019 recommends the following steps for managing moderate asthma.

**Step 3.** Patients who have symptoms present most days or who are waking up due to asthma at least once a week should be managed with the following regimen (level of evidence A):

- Daily low-dose ICS-LABA combination, plus as-needed combined low-dose ICS-LABA or a SABA.
- The first option uses ICS-LABA as controller and reliever.

For asthma that is uncontrolled on daily low-dose ICS, daily low-dose ICS-LABA leads to a 20% reduction in exacerbations and better lung function.2 For patients with at least 1 exacerbation in the previous year, maintenance and reliever treatment with low-dose ICS-LABA is more effective than maintenance ICS-LABA with as-needed SABA in reducing severe exacerbations, with similar symptom control.2

Another option for patients with uncontrolled symptoms on daily low-dose ICS is to increase it to a medium dose, but this is less effective than adding a daily LABA (level of evidence A).

The clinician may also consider an LTRA for these patients (level of evidence A).

**Step 4.** For patients with persistent symptoms despite adherence to step 3 therapy:

- Manage with daily medium-dose ICS-LABA plus as-needed SABA (level of evidence B)
- Consider daily high-dose ICS, LTRA, and long-acting muscarinic antagonist (LAMA).
If asthma remains uncontrolled, specialty referral should be considered.

**Case conclusion.** The patient has uncontrolled moderate asthma. His maintenance inhaler is switched from low-dose ICS to medium-dose ICS-LABA, and he should continue LTRA therapy. He is encouraged to use continuous positive airway pressure every night rather than most nights, remove animals from the home, use allergen-impermeable bedding covers, wash bedding weekly, clean moldy surfaces with bleach, and fix water leaks in the home as part of a comprehensive asthma treatment plan.

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**TABLE 2**

**Asthma, COPD, and overlap syndrome**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Asthma</th>
<th>COPD</th>
<th>Asthma-COPD overlap syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of onset</strong></td>
<td>Usually childhood</td>
<td>Usually &gt; 40</td>
<td>Usually &gt; 40, but may report symptoms in childhood or early adulthood</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>High variability over time, multiple triggers, worse at night or early morning</td>
<td>Continuous, worse with exertion, chronic cough, and sputum</td>
<td>Persistent exertional dyspnea but prominent variability</td>
</tr>
<tr>
<td><strong>Background</strong></td>
<td>Personal or family history of allergies or asthma</td>
<td>Exposure to noxious substances like tobacco</td>
<td>Personal or family history of allergies or asthma and personal noxious exposure</td>
</tr>
<tr>
<td><strong>Disease course and response to treatment</strong></td>
<td>Symptoms improve spontaneously, respond to bronchodilator and inhaled corticosteroid</td>
<td>Slowly progressive despite treatment, bronchodilator provides only limited relief</td>
<td>Symptoms are partly but significantly reduced by treatment Progression is typical and treatment needs are high</td>
</tr>
<tr>
<td><strong>Chest radiography</strong></td>
<td>Usually normal</td>
<td>Hyperinflated lungs</td>
<td>Hyperinflated lungs</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td>Variable and reversible airflow limitation, may be normal between symptoms or postbronchodilator</td>
<td>Persistent airflow limitation FEV₁ may be improved by therapy but postbronchodilator FEV₁/FVC &lt; 0.7 persists Postbronchodilator FEV₁ ≥ 80% predicted indicates mild limitation and &lt; 80% predicted indicates severe limitation</td>
<td>Airflow limitation is persistent and not fully reversible, but often with current or historic variability FEV₁, may be improved by therapy but postbronchodilator FEV₁/FVC &lt; 0.7 persists Postbronchodilator FEV₁ ≥ 80% predicted indicates mild and &lt; 80% indicates severe limitation</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity

---

**CASE 3. AN ELDERLY WOMAN WITH SEVERE ASTHMA**

A 77-year-old woman presented to her doctor’s office for asthma monitoring. She was diagnosed with asthma in her 30s. Currently, her maintenance regimen is high-dose ICS-LABA and LTRA therapy. She reports adhering to her medications and demonstrates proper inhaler technique in the office. However, she has asthma symptoms daily and awakens because of asthma about twice a week. She was treated for an exacerbation 3 months ago. She reports smoking 4 to 10 cigarettes a day and having severe anxiety and depression.
GINA 2019 recommends the following steps for severe uncontrolled asthma.

**Step 5.** For patients whose asthma remains uncontrolled despite adherence to high-dose ICS-LABA and LTRA treatment, consider adding LAMA maintenance therapy. Specialty referral is strongly recommended. Patients should be evaluated for biologic therapy, ie, a targeted controller therapy that is prescribed by asthma specialists.

**Case conclusion.** The patient has uncontrolled severe asthma. Daily LAMA therapy is added to her regimen, and she is referred to a pulmonologist. As part of her comprehensive asthma management plan, smoking cessation is strongly encouraged, and a selective serotonin reuptake inhibitor is started. She is counseled that symptoms of anxiety and depression are associated with worse asthma symptom control, medication adherence, and asthma-related quality of life.²

# ASTHMA-COPD OVERLAP SYNDROME

Asthma-COPD overlap syndrome is common, particularly in elderly patients and those who smoke.²,⁹ It is characterized by persistent airflow limitation on peak flow or spirometry, and diagnoses or features of both asthma and COPD (Table 2).²,⁹ It is regarded not as a single entity, but as a syndrome that includes several forms of airway disease caused by a range of poorly understood mechanisms.²,⁹

The overlap syndrome poses special challenges. Patients experience frequent exacerbations and tend to have poor quality of life.²,⁹ Their lung function declines more rapidly, their symptoms are more refractory to treatment, their mortality rate is higher, and they use disproportionately more healthcare resources than patients with either asthma or COPD alone.²,⁹,¹⁰

The exact prevalence of asthma-COPD overlap syndrome is difficult to estimate because of its heterogeneous nature, but has been reported to be between 1.1% and 4.5% in general population studies, and up to 27% and 33% in patients with asthma and COPD, respectively.⁹

Data are sparse on how to treat patients with overlap syndrome, as they are often excluded from clinical trials.²,⁹ More research is needed to elucidate underlying mechanisms contributing to the syndrome and to support the development of specific interventions to prevent and manage it.²,⁹

GINA recommends treating asthma-COPD overlap syndrome with low- or medium-dose ICS and adding an LABA or LAMA, or both, as needed to control symptoms.² This recommendation emphasizes the importance of ICS in patients with asthma features. It is reasonable for patients with refractory symptoms to be treated with triple therapy (an ICS plus an LABA plus an LAMA).² In a very small study, Ishiura et al.¹⁰ found improved lung function in patients with asthma-COPD overlap syndrome when an LAMA was added to combined ICS and LABA. Biologics, phosphodiesterase-4 inhibitors, and macrolides may also have a role in treatment, but more research is needed.⁹ Current recommendations are based mostly on expert opinion and not outcome data.⁹

As in patients with asthma alone, risk factors and comorbidities should always be addressed and treated, and medication adherence should be monitored. Patients should be encouraged to exercise regularly, attend pulmonary rehabilitation, use oxygen if indicated, and receive proper vaccinations. Although initial recognition and treatment of asthma-COPD overlap syndrome may occur in primary care, specialty referral for confirmatory investigation is encouraged.²,⁹

## REFERENCES


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