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Myasthenia gravis: An update for internists

Myasthenia gravis (MG) is an uncommon neuromuscular disorder with an estimated prevalence likely under 1 per 10,000. But knowing some of its clinical characteristics and considering it in the differential diagnosis pushes me to probe deeper into the nuances of a patient’s historical narrative when they list fatigue or weakness as a symptom.

MG is an autoimmune disease characterized pathobiologically by the presence of antibodies that recognize components of the muscle side of the neuromuscular junction end plate. The initially recognized and most common target for these antibodies is the acetylcholine receptor (AChR). Unlike common autoimmune conditions with their associated antibodies such as lupus (antinuclear antibodies) and rheumatoid arthritis (rheumatoid factor), the antibodies associated with MG are directly pathogenic. Recognition of the pathophysiologic anti-AChR effect of these antibodies led to the still utilized therapeutic strategy of overcoming the antibody-mediated receptor blockade by increasing the concentration of the receptor’s agonist acetylcholine by slowing its metabolism using inhibitors of acetylcholinesterase. But there is more to the effect of these and other pathogenic antibodies on the progression of MG than simply interfering with the binding of acetylcholine to its cognate receptor.

MG is rare in any internist’s clinic, even for subspecialists who focus on patients with symptoms relating to musculoskeletal and respiratory muscle function. Recognizing the spectrum of MG patients’ verbalized complaints hones our clinical reasoning skills when faced with the commonly expressed symptom of “fatigue.” Clinical and electrodiagnostic fatigability is a hallmark of MG, but that is not how patients are likely to describe their symptoms. As we try to discern between fatigue and sleepiness, fatigue and muscle weakness, fatigue and lack of desire, and weakness and pain, keeping MG in mind as a diagnostic possibility forces us to more deeply explore the symptom domains of muscle fatigue and weakness. Asking the patient if symptoms are dramatically worse at the end of the day or after repetitive but seemingly mild exertion (brushing hair) becomes relevant. Does the patient or those who spend time with the patient notice drooping eyelids or head with prolonged driving or reading, or a more muffled or nasal quality to the voice with prolonged speaking? Has the patient noticed the odd sensation of shortness of breath when lying down? Unlike with some other myopathies, initial static strength testing in the office or measurement of the creatine kinase may not be strikingly abnormal.

Morgen and co-authors in 2 papers in this issue of The Journal1,2 discuss the diagnosis of MG and some of the nuances of treatment.

While the vast majority of patients with MG have detectable antibodies to the AChR, others harbor antibodies against other proteins that affect the function of the neuromuscular junction. Some patients with milder disease may have an adequate response to physiologic therapy that increases the concentration of acetylcholine within the neuromuscular junction using medications such as pyridostigmine. Many, however, will require immunosuppressive therapy directed at reducing the concentration of the pathogenic antibodies. In about 15% of patients, the disease is relatively refractory to available therapies. As with other autoimmune diseases, corticosteroids are a cornerstone of initial therapy with the goal of reducing the pathogenic antibody concentration as well as any inflammatory response triggered by the binding of the antibody to the muscle cell’s

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membrane proteins (including the AChR). Binding of the AChR antibody to the muscle cell triggers internalization of the receptors and also activates complement, resulting in disruption of the specialized junction cellular structure, promoting cell damage and progression of the disease. This observation has been exploited by the successful use of complement-inhibiting drugs to treat patients with MG, even those who may have had a suboptimal response to the commonly used immunosuppressive therapies (eg, mycophenolate, azathioprine, methotrexate). Drugs targeting the fifth component of complement (C5) have been approved by the US Food and Drug Administration for the treatment of generalized MG. A smaller subset of patients with clinical MG have clinically measurable antibodies against a muscle-specific kinase (not the AChR). These antibodies seem to be unique to the immunoglobulin (Ig) G4 subclass. IgG4 antibodies do not activate complement, and patients with this subset of MG, as noted in this issue by Morren and Li, clinically behave somewhat differently. Fortunately, as do patients with the clinically distinct IgG4-related disease, these patients tend to respond robustly to anti-B-cell agents such as rituximab with a decrease in the production of the pathogenic antibody. Thus, serologic characterization has both diagnostic and therapeutic implications.

Two clinical scenarios experienced by patients with MG warrant our awareness. Occasionally, with initiation of corticosteroid therapy, the myasthenic symptoms of weakness markedly and paradoxically worsen. Recognizing this phenomenon should immediately trigger discussion with our neuromuscular colleagues, as “steroid myopathy” is not an acute event occurring at the start of corticosteroid treatment. The second scenario relates to worsening of myasthenic symptoms with use of some medications. The list of potential aggravating medications is long, but relatively few medications warrant true avoidance in the MG patient whose disease is under good control. However, caution should be paid particularly to prescribing antibiotics including aminoglycosides, fluoroquinolones, and some macrolides.

Brian F. Mandell, MD, PhD
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We thank those who reviewed manuscripts submitted to the Cleveland Clinic Journal of Medicine in 2022. Reviewing papers for the Journal—both for specialty content and for relevance to our readership—is an arduous task that involves considerable time and effort. Our publication decisions depend in no small part on the timely efforts of reviewers, and we are indebted to them for contributing their expertise this past year.

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A 56-year-old male was referred by his dentist with noticeable worsening of vitiligo of the tongue, which had been diagnosed as oral leukoplakia 3 years earlier and had been monitored at the dental clinic.

The patient had no significant medical history. He had a continuous smoking habit of more than 36 years but did not consume alcohol. Examination confirmed oral leukoplakia, with an uneven and rough surface, and a white papillary mass was noted within the area of leukoplakia on the right edge of the tongue (Figure 1). No lymph node swelling in the neck was noted. Biopsy of the lesion confirmed it to be squamous cell carcinoma. Computed tomography, magnetic resonance imaging, and ultrasonography showed that the mass was confined to the surface of the tongue.

■ TREATMENT AND FOLLOW-UP

Resection of the mass with at least 10 mm of surrounding tissue was performed under general anesthesia. During surgery, rapid pathological diagnosis was performed to confirm that no tumor cells remained, and the wound was subsequently sutured. Postoperatively, a slight deformation of the tongue and scarring were noted, affecting the patient’s eating, swallowing, and pronunciation, but these functions gradually improved. At 5 years postoperatively, the patient’s clinical course was favorable, without recurrence.

■ PREMALIGNANT ORAL LESIONS

Tongue cancer accounts for 60% of all oral cancers, and usually originates from the tongue border. Nearly 90% of all oral cancers are squamous cell carcinoma, and major risk factors are chronic irritation, smoking, and alcohol consumption.

Most oral cancers have a premalignant lesion stage. Regular monitoring for progression of premalignant lesions is critical for the early detection and treatment of oral cancer. Oral leukoplakia, the most common potentially cancerous oral lesion, progresses to squamous cell carcinoma at a rate ranging from 0.1% to 36.4%. This transformation depends on factors such as sex, age, clinical type, locus, onset mode, and the presence or absence of epithelial atypia, although the mechanism remains unclear to date.

Currently, no clear guidelines exist as to whether aggressive resection or progression monitoring produces better outcomes. Consequently, there is an urgent and unmet need for molecular biological investigation of leukoplakia.

■ IMPORTANCE OF REGULAR FOLLOW-UP

Our report illustrates the importance of regular follow-up of leukoplakia. Before our patient presented, he had been followed regularly by his dentist, and this led to earlier recognition of possible malignant transformation, resulting in earlier resection of the cancer and better prognosis.

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Figure 1. White lesions were observed on the right tongue edge. Papillary cell proliferation was noted in the same area.
TONGUE CANCER

■ DISCLOSURES

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

■ REFERENCES


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Q: What are the treatment options for myasthenia gravis if first-line agents fail?

A: If the patient with myasthenia gravis (MG) has been taking adequate doses of a first-line medication, typically pyridostigmine, for a sufficient duration but without significant efficacy, or has experienced substantial adverse effects, it may be time to consider immunosuppressive therapy. In 5% to 20% of patients, there may be suboptimal efficacy or prohibitive adverse effects with high-dose corticosteroid therapy over a period of a few weeks to 3 months.1–3 For these patients, nonsteroidal immunosuppressive therapy should be considered early instead of continuing high-dose corticosteroids for a longer duration. A targeted examination will help determine if pyridostigmine or other treatment has failed.

MG, the most common disorder of neuromuscular junction transmission, results from an antibody-mediated attack against postsynaptic components of the neuromuscular junction. Clinical manifestations are typically categorized into generalized MG (GMG) or ocular MG subtypes. Acetylcholine receptor (AChR) antibodies are the most common, and the condition is referred to as AChR antibody-positive MG (AChR+MG). Other antibodies have been identified, including those against muscle-specific tyrosine kinase (MuSK) and lipoprotein receptor-related protein 4 (LRP4). Antibody seronegativity occurs in fewer than 10% of GMG patients and fewer than 50% of patients with ocular MG.4 Treatment recommendations are similar for seropositive AChR, seropositive LRP4, and seronegative GMG, while there are important clinical differences and specific treatment considerations with MuSK antibody-positive MG.

This discussion focuses on AChR+MG, which accounts for about 85% of patients with GMG.4

FIRST-LINE THERAPY: PYRIDOSTIGMINE

First-line pharmacologic management of AChR+MG is symptomatic treatment with acetylcholinesterase inhibitors, and pyridostigmine is the only agent used routinely in the clinical setting. Corticosteroids are also used, mainly in patients with marked weakness or poor response to pyridostigmine. When pyridostigmine doses exceed 120 mg every 3 hours, or a total daily dose of 960 mg, adverse effects including risk of cholinergic crisis tend to outweigh benefits. However, if a patient needs more than 240 mg of pyridostigmine per day, it is usually beneficial to move on to immunotherapy. Patients with limited symptoms such as mild ptosis and facial weakness who respond well to pyridostigmine may not need immunosuppressive agents or thymectomy (considered a first-line therapeutic option for certain patients with AChR+MG without thymoma).5

Complete stable remission in MG is typically defined as 1 year with no signs or symptoms of MG without therapy, although some isolated weakness of eyelid closure is generally considered acceptable. Given the difficulty of achieving complete stable remission, an international consensus panel has proposed minimal manifestation status or better with only mild adverse effects as a reasonable therapeutic goal.6 Minimal manifestation status is characterized as no functional limitations but some muscle weakness on examination.
Corticosteroids have been shown in several studies, including 2 controlled trials, to be effective in MG treatment.4 The typical starting daily dose for prednisone is 20 to 60 mg, with the lower-range doses used for patients with mild to moderate symptoms. Depending on the treatment response and tolerance profile, the dose may be increased by 10 mg per day every 1 to 2 weeks, up to about 60 mg daily. An alternative high-dose regimen consists of prednisone 1.0 to 1.5 mg/kg/day, but usually not exceeding 100 mg/day.6 Close monitoring is essential when patients start corticosteroids, especially high-dose regimens.

ASSESSING THERAPEUTIC FAILURE

If the patient has been taking adequate doses of first-line medications (Table 1)5,6 for a sufficient duration but without significant efficacy or has experienced substantial adverse effects, it may be time to consider nonsteroidal immunosuppressive therapy. A targeted examination will help determine if treatment has failed. For example, worsening fatigable weakness in the limbs and the cranial and respiratory muscles despite standard treatment is an indicator that pyridostigmine and corticosteroids are not controlling MG deficits. Fatigable weakness in MG typically has a diurnal pattern, worsening in the evening. In general, weakness predominates in proximal muscles, which may mimic a myopathy, but weakness is typically exacerbated with repetitive or sustained action and improves with rest.

Significant breakthrough symptoms warrant prompt follow-up to look for corroborating signs of uncontrolled MG. In addition to the standard examination, other key components should be included (Table 2) to rule out an impending myasthenic crisis—a life-threatening exacerbation that may necessitate intubation or mechanical ventilation. Components of the examination include the following:

- Neck flexion strength, measured by having the patient push the forehead forward against the
clinician’s hand, while the clinician provides resistance. Scoring is based on the conventional Medical Research Council scale for muscle strength.\(^1\) Neck flexion as well as shoulder external rotation correlate well with respiratory muscle strength.

- **Single-breath counting test**, a measure of respiratory muscle strength. The patient counts aloud at a pace of no more than 1 to 2 counts per second, and the clinician records the highest number reached on a single exhaled breath. A count less than 20 correlates with low forced vital capacity, respiratory muscle weakness, and risk for respiratory failure.\(^1\)

- **Bulbar weakness leading to accumulated salivary and oropharyngeal secretions**, which may interfere with speech and swallowing. The patient may have nasal-sounding or “mushy” speech, especially at the end of long conversations. There may be frequent throat-clearing and chewing weakness.

Notably, pulse oximetry is not a reliable indicator of impending neuromuscular respiratory failure. The problem is not diffusion abnormality across respiratory membranes but rather carbon dioxide retention due to impaired ventilation. Generally, oxygen saturation drops only when neuromuscular respiratory impairment is well advanced.

### ASSESS FOR MYASTHENIC CRISIS

A patient who has features of impending myasthenic crisis such as breathing abnormalities requires prompt admission, possibly to the intensive care unit. Rescue treatments including plasma exchange or intravenous immunoglobulin will likely be needed.

Before appropriate treatment can be started, it is necessary to determine whether breathing abnormalities are due to MG or to another cause such as under-

### TABLE 2

**Clinical features of fatigable weakness in myasthenia gravis by region of involvement**

<table>
<thead>
<tr>
<th>Muscle group/region</th>
<th>Manifestation of fatigable weakness in myasthenia gravis</th>
</tr>
</thead>
</table>
| Ocular              | Fluctuating ptosis (often asymmetrical, worsened by sustained upgaze) with or without variable diplopia  
|                     | Ptotis may improve with application of an ice pack to the eyes, ie, the bedside ice-pack test |
| Bulbar              | Dysarthria with or without dysphonia; worse at the end of long conversations, when especially nasal-sounding, “mushy,” or “wet” speech is significant  
|                     | Painless dysphagia, which may include nasal regurgitation, sialorrhea, and frequent throat-clearing, with or without coughing; may range from weak to frank choking  
|                     | Masticatory or chewing weakness; when severe, the mouth may hang open, and the patient may use a hand to close or manipulate the jaw |
| Facial              | Bilateral weakness with “sagging and expressionless” face and a horizontal smile  
|                     | Inability to close eyes firmly  
|                     | Drooling from poorly sealed lips  
|                     | Inability to whistle, pucker lips, or use a straw |
| Axial               | Weak flexion or extension of the neck, “dropped” head when severe  
|                     | Occasional stooped posture with anteroposterior truncal flexion (camptocormia) or lateral trunk flexion (“Pisa syndrome”) |
| Limb or appendicular| Weakness that affects proximal more than distal upper and lower limb groups  
|                     | Difficulty getting up from low-seated positions, using arms for overhead activities like washing hair; worse with repeated and sustained actions |
| Respiratory         | Orthopnea  
|                     | Dyspnea on exertion or with increased intra-abdominal pressure as when bending forward to tie shoelaces, or when trunk is immersed in a pool  
|                     | Classic features of accessory respiratory muscle use during respiratory distress may be blunted with significant myasthenic weakness of these muscles  
|                     | Decreased counts (< 20) on a single-breath counting test suggest significant respiratory muscle weakness and risk for respiratory failure |
lying heart failure, chronic obstructive pulmonary disease, asthma, or pneumonia. Breathing impairment in MG typically manifests with prominent orthopnea, ie, difficulty breathing when lying flat. Breathing difficulty may be exacerbated when the trunk is immersed, as in a pool, or when the patient bends over as when tying shoelaces, because the weakened diaphragm is unable to counteract upwardly displaced abdominal contents. Dyspnea on exertion that is disproportionate to other symptoms, lower-extremity swelling, venous distention, and adventitious breath sounds like rales, wheezing, and rhonchi on auscultation can point to other non-MG causes.

**WHEN TO CONSIDER NONSTEROIDAL IMMUNOSUPPRESSIVE THERAPY**

Response to corticosteroid therapy in MG is classified as good or poor. A good response is characterized by a smooth response to moderate-dose (about 10–30 mg prednisone daily) or high-dose (about 40–60 mg or more prednisone daily) therapy, with remission maintained after tapering to low-dose prednisone without the need for nonsteroidal immunosuppressive therapy.

For the 5% to 20% of MG patients with a poor response after several weeks to 3 months of high-dose therapy,1–3 rather than continue high-dose corticosteroids, nonsteroidal immunosuppressive therapy should be considered. This therapy is often started before or at the start of steroid weaning. Current agents generally allow for long-term adequate MG control, often minimize the need for pyridostigmine, and spare the patient the adverse effects of high-dose or long-term corticosteroid therapy. For MG patients who are refractory to treatment or who require more complex treatment strategies (beyond first-line agents), early input from a neurologist specializing in neuromuscular medicine and with MG expertise is highly recommended.

**MONITORING TREATMENT**

Immunosuppressive therapy in MG is usually associated with decreased pathologic antibody levels, but there are no evidence-based recommendations for routine measurement of these during treatment. Some data suggest that high antibody levels predict a more severe disease course.12 However, there is significant heterogeneity of clinical features, treatment response, and disease course among patients with comparable antibody levels. Similarly, routine use of electrodiagnostic testing to monitor MG treatment is not well supported. Ultimately, MG disease activity is more reliably assessed clinically, so close follow-up and serial examinations are key.

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84 CLEVELAND CLINIC JOURNAL OF MEDICINE VOLUME 90 • NUMBER 2 FEBRUARY 2023
The constellation of vitamin D, the acute-phase response, and inflammation

In 2016, laboratory tests to detect vitamin D deficiency were ordered more than 10 million times for Medicare patients, up 547% since 2007, at a cost of $365 million.1 In 2017, sales of vitamin D supplements totaled $936 million, a 9-fold increase over the previous decade,1 and expected to rise to $1.3 billion by 2025, for an annual growth rate of 5.8% from 2020 to 2025.2 This astronomic increase in vitamin D testing and supplementation is happening in the absence of any real evidence-based rationale.

See related editorial, page 91

■ UNCERTAINTY OF EVALUATING VITAMIN D STATUS

Evaluation of vitamin D status has long been problematic and plagued with confusion. At first, it was somewhat unclear as to which blood test—1,25-dihydroxyvitamin D or 25-hydroxyvitamin D (25(OH)D)—is the most informative. After 25(OH)D was settled on,3 debate ensued over which blood levels are the most informative in assessing vitamin D status and what the cutoff points should be. It was concluded that the terms insufficiency and deficiency could be distinguished from one another, although they seem much the same to many clinicians. Even experts in the field of bone health cannot agree on which levels are acceptable (Table 1).3,4

■ IS VITAMIN D DEFICIENCY OR INSUFFICIENCY TRULY A PANDEMIC?

The prevalence of vitamin D deficiency is considered to be remarkably high: 41.6% of American adults had serum 25(OH)D levels below 20 ng/mL (50 nmol/L) in 2011,5 levels considered to be consistent with vitamin D deficiency. The prevalence is high enough to be dubbed pandemic by some authors.6 Worldwide, it has been estimated that 1 billion people have vitamin D deficiency or insufficiency,7 which many find difficult to believe.7 Much of this confusion is caused by the presumption that serum levels of 25(OH)D reflect nothing but vitamin D status. But is it possible that the levels are influenced by something else?

■ THE CASE FOR VITAMIN D AS A NEGATIVE ACUTE-PHASE REACTANT

The short answer is yes, there is compelling evidence that 25(OH)D is a negative acute-phase reactant—its serum levels decrease in the presence of inflammatory states.8–11 Several lines of evidence support this conclusion:

- Serum C-reactive protein and 25(OH)D levels are inversely associated, as would be expected if 25(OH)D were a negative acute-phase reactant.12–16 In quantitative terms, the inverse relation between 25(OH)D below its median and C-reactive protein levels was found to be significant: a geometric mean change in C-reactive protein of 0.11 mg/dL for each 10-ng/mL change in 25(OH)D (95% confidence interval 0.16 to −0.04) on multivariate linear regression analysis.12
- Low blood levels of 25(OH)D have repeatedly been found to be associated with a variety of inflammatory states.17–26
- Most tellingly, 25(OH)D levels fall after a variety of inflammatory insults, a classic test for acute-phase reactant behavior.9,10,27 A surgical procedure, an induced inflammatory insult, may be associated with a 40% reduction in circulating 25(OH)D levels when compared with preoperative values.28

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Low levels of 25(OH)D found in patients with obesity persist despite various aggressive vitamin D supplementation regimens, as would be expected of a negative acute-phase reactant.\textsuperscript{29}

**THE ACUTE-PHASE RESPONSE**

The acute-phase response refers to a large number of behavioral, physiologic, biochemical, and nutritional changes that occur during inflammatory states. Figure 1 shows examples of positive and negative acute-phase reactants.\textsuperscript{30} A 1999 review reported that C-reactive protein and fibrinogen are prototypical positive acute-phase proteins whose plasma concentrations increase during inflammatory states, whereas albumin and transferrin are negative acute-phase proteins whose concentrations decrease.\textsuperscript{30} Although the review largely focused on acute-phase proteins, the other components of the systemic response to inflammation should not be forgotten. Cations may also display acute-phase behavior. Examples include a decrease in concentrations of zinc and iron and an increase in copper concentration. Most significant for our purposes is research documenting the negative acute-phase behavior of a variety of vitamins.\textsuperscript{31} This has been problematic for investigators and clinicians because the acute-phase behavior of these molecules tends to be overlooked. It has been noted that misclassification of vitamin A status can occur because serum retinol levels decrease during the acute-phase response.\textsuperscript{32}

Similar problems are raised by other acute-phase reactants. Low serum albumin levels are often taken as evidence of malnutrition, although the low levels frequently reflect albumin's behavior as a negative acute-phase reactant. A similar tale can be told about iron. While low serum iron levels may indicate iron deficiency, they may instead reflect an underlying inflammatory process. Clinicians are aided by the fact that transferrin, usually estimated by total iron binding capacity, is a negative acute-phase reactant. When low transferrin levels are found, it suggests the presence of an inflammatory process, whereas elevated transferrin values are usually seen in iron deficiency.

**WHAT IS MEANT BY INFLAMMATION?**

It is common for patients to ask us, “What can I do to lower my inflammation?” We should not be surprised by this. Patients are inundated with media reports that inform them that they can “fight inflammation” based on the premise that inflammation constitutes a single malicious process in the body. In fact, inflammation, a widely abused term, is not at all a simple process. It is a complex biological cascade that may involve, to varying degrees, a number of different cell types as well as multiple cytokines, histamines, bradykinin, prostaglandins, leukotrienes, platelet-activating factor, complement components, inflammasomes, and a family of molecules that promote cell adhesion. It is important that clinicians be aware of the complexity of these processes and impart that information to their patients.

Inflammation has classically been defined as a defense mechanism against infection and tissue injury, employing the innate immune response to localize and eliminate injurious factors and remove damaged tissue components. Its ultimate purpose is to return tissues to their normal state. A large number of medical conditions (eg, cardiovascular disease, obesity, type 2 diabetes), however, have been found to be associated with components of the inflammatory response, in the absence of infection or tissue injury. While it is generally presumed that inflammation participates in the pathogenesis of these conditions, it is equally likely that metabolic perturbations induce inflammation. Indeed, it has become apparent in the last decades that low-grade inflammation can be induced by tissue stress and malfunction (“metaflammation”), by changes from the optimal internal environment and the absence of infection or overt tissue injury.\textsuperscript{33,34}

**LOW-GRADE INFLAMMATION**

Low-grade inflammation (metaflammation) differs from the inflammation resulting from infection or tissue injury. It is not accompanied by the 4 classic signs of inflammation—rubor (redness), tumor (swelling), calor (warmth), and dolor (pain)—and manifests...
only minor degrees of C-reactive protein elevation, commonly regarded as an indicator of the presence of inflammation. While the purposes of classic inflammation are defense, healing, and tissue repair, the purpose of low-grade inflammation is the restoration of normal homeostasis. Acute inflammation is largely triggered by the pattern-recognition molecules PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns), while low-grade inflammation is triggered by sentinel cells that monitor for deviations from the optimal homeostatic state.35,36

Low-grade inflammation is not rare. Modest C-reactive protein elevation, defined as concentrations between 3 and 10 mg/L, has been documented in approximately 30% of the US population.37 Low-grade inflammation, manifested by modest C-reactive protein elevation, is associated with an astounding number of conditions and lifestyles, most of which are associated with poor health. These conditions represent or reflect minor metabolic perturbations, capable of inducing metaflammation. A partial list includes obesity, diabetes, atrial fibrillation, obstructive sleep apnea, hypertension, prehypertension, sleep deprivation, low levels of physical activity, lumbar disc herniation, polycystic ovary syndrome, various unhealthy diets, hypoxia, social isolation, and aging, as well as smoking and exposure to environmental irritants such as second-hand smoke.38

■ WHY SO MUCH INTEREST IN VITAMIN D?

It is well established that vitamin D is essential for skeletal health, but in recent years, evidence has been presented purporting to show that it plays a critical role in host defense39 and in modulating both innate and adaptive immune responses.40 It has been proposed that vitamin D administration inhibits inflammation and lowers the incidence of cancer and cardiovascular events.41 Attempts have been made to link inadequate vitamin D levels to high susceptibility to chronic infections and to autoimmune diseases. Observational studies have found associations between low vitamin D levels and the risk of fractures, falls, mortality, diabetes, hypertension, and a variety of other disorders,32,42 and a 2022 systematic review that found that patients with severe COVID-19 infection had lower levels of 25(OH)D than patients with milder infection.44

Figure 1. Examples of positive and negative acute-phase reactants.

Based on information in reference 30.

progress, to determine whether vitamin D supplementation can reduce the likelihood that these conditions will occur or can avert severe disease associated with COVID-19. However, a nationwide, randomized, placebo-controlled trial found that supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo,45 a conclusion supported by other investigators who have similarly reported that vitamin D supplementation did not lead to significant reduction in all-cause mortality or mortality from cancer and cardiovascular disease.46,47 And no significant difference has been found in major health-related outcomes in COVID-19 with vitamin-D supplementation.48,49

Are such clinical trials justified? One might argue that it is appropriate research, as there is much interest in the topic, and we do not have definitive answers. True. But the scientific rationale for carrying out such studies is undermined somewhat by the fact that vitamin D is a negative acute-phase reactant and that low levels of 25(OH)D may merely reflect metabolic perturbations.

■ THE SOCIETAL COST OF TOO MUCH CURIOSITY ABOUT VITAMIN D

As noted earlier, the increase in vitamin D testing and supplementation in the absence of a strong evidence base leads to an accelerating rise in economic costs. The Choosing Wisely Canada program40 recommends checking serum 25(OH)D levels in patients with only a few select medical conditions (osteoporosis, inflammatory bowel disease, celiac disease, kidney and liver
VITAMIN D

disease, and pancreatitis) and recommends against testing in the general population. The Choosing Wisely campaign of the American Society for Clinical Pathology also recommends against population-based vitamin D testing and recommends testing only in similar select populations. However, it states that laboratory testing is appropriate in higher-risk patients when results will be used to institute more aggressive therapy (eg, osteoporosis, chronic kidney disease, malabsorption, some infections, obesity).51

■ WHEN SHOULD WE RECOMMEND VITAMIN D SUPPLEMENTATION?

The high prevalence of low-grade inflammation in the general population argues against reflexively concluding that some degree of insufficiency or deficiency of vitamin D is present when a decreased concentration of serum 25(OH)D is found. Thus, finding a low vitamin D level in a patient whose C-reactive protein level is not elevated supports the possibility of vitamin D deficiency. However, finding an elevated C-reactive protein concentration or low albumin level is consistent with the possibility that systemic inflammation underlies the depressed 25(OH)D level, as well as the possibility that both vitamin D deficiency and systemic inflammation are present. In addition, the recent finding that the analytical performance of immunoassays for 25(OH)D is highly variable further complicates the interpretation of laboratory test results.52 All of this argues, of course, against routinely prescribing vitamin D supplements, even when low 25(OH)D levels are found.

■ THE NEXUS OF INFLAMMATION AND VITAMIN D: WHAT A MESS!

Much uncertainty lies in when to evaluate vitamin D, in the reliability of assays, in the significance of various 25(OH)D levels, and in the level of true deficiency. Often overlooked is the recognition that 25(OH)D levels may be low in the presence of both acute and low-grade inflammation and may represent a true nutritional deficiency. Despite expert guidance on when to determine vitamin D levels, many practicing clinicians are pressured into inappropriate ordering of this test and repleting “low” levels. We encourage conversations between clinicians and their patients regarding vitamin D testing and supplementation.

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■ DISCLOSURES

Dr. Epstein has reported consulting for Bayer Healthcare. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Vitamin D: A metabolic bone disease perspective

In this issue of the Journal, Antonelli and colleagues\(^1\) present an important reminder that vitamin D levels are lowered during inflammation, behaving as a negative acute-phase reactant. They acknowledge the high prevalence of low serum levels of 25-hydroxyvitamin D (25(OH)D) and seem to argue that because inflammation is ubiquitous, the widespread findings of reportedly low vitamin D levels are due in large part to inflammation. They assert that lack of appreciation that inflammation is the culprit has led to unnecessary testing and overestimation of the prevalence of hypovitaminosis D, and has contributed to uncertainty about the “cutoff point” for an adequate level of vitamin D.

However, there are many factors that influence 25(OH)D levels. It should not be surprising that low levels of vitamin D are common. Sun exposure, which initiates vitamin D synthesis, may be limited by working indoors, geography, seasonal variation of sun intensity, and use of solar protective agents. The ability to make vitamin D precursors is also affected by skin type, age, and genetics. Vitamin D is rare in food, except for fatty fish and fatty fish oils and some foods that are artificially and not always reliably fortified. Obesity, which has increased in the United States, results in a volumetric dilution of 25(OH)D, as this fat-soluble vitamin is distributed into the increased fat, muscle, and liver compartments that are associated with obesity, even though total body stores of vitamin D may be adequate. Many drugs—antiepileptics, glucocorticoids, antiestrogens, antiretrovirals, antineoplastics, and herbs such as kava and St. John’s wort—lower vitamin D levels by upregulating degradative enzymes. All these mechanisms are independent of inflammatory reactions that are the focus of the commentary by Antonelli et al.\(^1\)

**EFFECTS ON BONE**

Circulating 25(OH)D is the substrate for physiologically active vitamin D, critical in maintenance of calcium homeostasis and bone integrity. Low vitamin D stimulates an increased parathyroid hormone response, with levels often within the normal range, but it can also cause an elevation above normal.\(^2,3\) An increase in parathyroid hormone will maintain the serum calcium level within the normal range, but at the expense of phosphate excretion and removal of calcium from bone, thus adversely affecting bone strength. Initially this is clinically silent, but a chronically reduced active 25(OH)D substrate level from any cause, whether from poor diet, inadequate sun exposure, or low grade inflammation, will still result in reduced vitamin D compounds and a bone-adverse physiologic effect. A 25(OH)D level of approximately 50 nmol/L (approximately 20 ng/mL) is sufficient to maintain calcium and phosphate homeostasis and prevent osteomalacia and rickets but insufficient to lower fracture risk.\(^4,5\) Higher serum levels of around 75 nmol (30 ng/mL) are needed for bone health\(^4,6\) and are required to reduce risk of nonvertebral and hip fracture.\(^4,5\)

It is tempting to add vitamin D supplements if the vitamin D level is below 75 nmol/L (30 ng/mL), but that alone may not reduce fracture risk. In a large, well-designed, double-blind, placebo-controlled study, vitamin D, supplementation of 2,000 IU daily without coadministered calcium did not lower risk of fractures, regardless of the baseline 25(OH)D level, even in participants with levels below 12 ng/mL.\(^6\) The complexity of bone healthcare requires attention to multiple factors and a deeper understanding of the role of vitamin D.
Antonelli and colleagues point out that checking vitamin D levels is recommended in select populations such as patients with osteoporosis, inflammatory bowel disease, kidney and liver disease, and pancreatitis. I would also suggest routinely monitoring patients on medications known to adversely affect vitamin D concentrations and prior to initiating therapy with denosumab, a potent inhibitor of osteoclast activity helpful in treating osteoporosis.

Hypocalcemia is listed as a serious adverse reaction in patients receiving the Prolia brand of denosumab, and the product’s package insert specifically advises to “adequately supplement all patients with calcium and vitamin D” and “instruct patients to take calcium 1,000 mg daily and at least 400 IU vitamin D daily,” thus recognizing the important biologic significance of vitamin D in maintaining serum calcium levels.

There are no national published guidelines specifying a minimal vitamin D level, although some National Health Service hospitals in the United Kingdom require that 25(OH)D levels be above 50 nmol/L before administering denosumab. Future research may provide evidence-based rationale for maintaining specific quantities of vitamin D in other conditions.

When checking levels, clinicians should keep in mind that vitamin D levels fluctuate by season of the year and time of day, and that different laboratories may use different assays that yield different results. Without supplements or dietary adjustments, a person’s vitamin D serum concentration varies with different amounts of sun exposure. Serum 25(OH)D levels tend to be highest at the end of summer and lowest at the end of winter. There is also a diurnal rhythm, with levels higher during the day and lower at night. Though perhaps not clinically crucial, comparing subsequent vitamin D levels taken at the same season, same time of day, and using the same trusted laboratory will help to assess true changes. For a patient who is acutely ill, as Antonelli et al point out, it is best to delay testing until the patient recovers.

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A 50-year-old man presents with shortness of breath

A 50-YEAR-OLD MAN with a history of bilateral carpal tunnel syndrome presented with progressive shortness of breath on exertion for the previous 3 months. Cardiovascular physical examination showed jugular venous distention to the middle neck at 30 degrees, a palpable maximal impulse displaced inferiorly and laterally with a prominent S4 heart sound, and bilateral bronchovesicular lung sounds. Tinel sign was present, as noted by a tingling sensation following percussion over the median nerve on both wrists. Further investigation revealed a serum creatinine level of 1.4 mg/dL (reference range 0.74–1.35) with undetectable troponin T enzyme, elevated N-terminal-pro-brain natriuretic peptide (NT-proBNP) of 2,145 pg/mL (reference range < 125 pg/mL), and electrocardiogram (ECG) with low voltage, normal sinus rhythm, and Q waves in the anterior leads.

Which of the following diagnostic studies is the most appropriate to obtain next?

□ Echocardiography
□ Chest radiography
□ Exercise stress testing
□ Coronary angiography

DIFFERENTIAL DIAGNOSIS

The initial differential diagnosis for a patient who presents with dyspnea on exertion, abnormal ECG findings, and negative cardiac enzymes includes heart failure, myocardial ischemia, pericardial effusion, and noncardiac etiologies.1

Chest radiography would be beneficial to determine lung involvement and evaluate cardiac silhouette to screen for any abnormalities. However, cardiovascular abnormalities seen on chest radiography such as altered shape or widened mediastinum would be nonspecific in this patient, and there are better imaging studies for heart function and anatomy. Additionally, in the context of abnormal physical examination findings, including abnormal heart sounds, elevated jugular venous pressure, and NT-proBNP elevation, a cardiac manifestation is more likely.

The cardiac stress test is a common diagnostic modality for patients with chest pain who are at risk for obstructive coronary artery disease. The patient’s lack of cardiovascular risk factors and younger age make ischemia less likely, particularly if the chest discomfort is not thought to be an angina-equivalent. Similar reasoning can be used as to why a coronary angiogram would not be the ideal initial study to obtain. The patient has Q waves on the ECG, yet although an ischemic etiology is imperative to remain within the differential, in the context of no other findings suggestive of angina-equivalent symptoms, coronary angiography would not be the next step in management.

The best diagnostic study for this patient would be an echocardiogram to accurately assess the structure and function of the patient’s heart. This will allow the clinician to narrow the potential reasons for the patient’s presentation. According to the American College of Cardiology/American Heart Association appropriate use criteria, there are numerous indications for an echocardiographic evaluation, including suspicion of heart failure, as in our clinical presentation.2

CASE CONTINUED: IMAGING RESULTS

Echocardiography showed a left-ventricular ejection fraction of 55% and concentric left-ventricular wall hypertrophy with a wall thickness of 15 mm (Figure 1). Echocardiography with strain imaging
to evaluate function of the myocardium revealed longitudinal impairment with apical sparing, ie, the “cherry-on-top” appearance. There was no pericardial effusion.

■ RED FLAGS FOR CARDIAC AMYLOIDOSIS

At this time, infiltrative and hypertrophic pathologies should be considered (Table 1) such as Fabry disease, Danon disease, mucopolysaccharidosis, and hypertrophic cardiomyopathy. However, in the context of this patient’s presentation it is important to consider cardiac amyloidosis, a type of infiltrative cardiomyopathy.

In this patient, red flags for cardiac amyloidosis include the ECG findings accompanied by a history of carpal tunnel syndrome and evidence of renal dysfunction. ECG findings generally include a discordance in ECG voltage, which may be reduced or normal, and the degree of hypertrophy on imaging. Cardiac amyloidosis typically demonstrates abnormal global longitudinal strain with apical sparing, which helps differentiate this disease process from other etiologies of hypertrophy. A history of carpal tunnel syndrome is common in patients with systemic amyloidosis as protein deposition can occur in both cardiac and noncardiac organ systems. Amyloidosis is an infiltrative disease due to the accumulation of misfolded precursor proteins that make up amyloid. Two major types of amyloidosis include light chain amyloidosis (AL) and transthyre-
yet the sensitivity for ATTR is approximately 50%, leading to unnecessary pain for the patient and potential false-negative results.5,12 Endomyocardial biopsy would be warranted after conflicting or equivocal findings of another less-invasive test.5,12

PATHOGENESIS OF CARDIAC AMYLOIDOsis

Two of the primary types of systemic amyloidosis include ATTR amyloidosis, in which the liver produces an excess amount of protein that ultimately misfolds and deposits in various tissues, and AL amyloidosis, which is primarily a bone marrow dyscrasia in which monoclonal proteins are overproduced and deposit in the various tissues.1,5 These two conditions can have similar presentations but their treatment pathways are completely different, so it is of the utmost importance to rule out AL early in disease stage.5,11–13 With a 6-month median survival of patients from time of diagnosis with AL, an urgent hematology-oncology evaluation is warranted.13 Sensitivity of over 99% for AL is achieved when combining serum immunofixation electrophoresis, urine immunofixation electrophoresis, and serum light chain concentration.12 Serum plasma electrophoresis has an inferior sensitivity of approximately 70% and should be avoided.12 These three tests should be ordered before or simultaneously with diagnostic imaging to avoid delay of targeted treatment.

Amyloidosis involves the misfolding and subsequent deposition of precursor proteins, infiltrating numerous organ systems within the body.5,11–13 Transthyretin is a tetramer that acts as a tertiary carrier protein for thyroxine and holo-retinol binding protein and is mostly secreted from the liver into the blood.12 In hATTR, a single amino acid mutation occurs on chromosome 18 where the transthyretin gene is found, causing aggregation to be more efficient.5,11,12 In ATTRwt, the wild-type protein becomes unstable without any evidence of damage to the genetic sequence.5,11

What is the next step in confirming suspicion of ATTR?

☐ Cardiac magnetic resonance imaging (MRI)
☐ Fluorodeoxyglucose-positron emission tomography (FDG-PET)
☐ Technetium-99m pyrophosphate scintigraphy
☐ Endomyocardial heart biopsy

Cardiac MRI would be beneficial in this patient if echocardiography was inconclusive and further investigation was warranted. Cardiac MRI would not give a definitive diagnosis for ATTR but may be useful when excluding other pathologies such as hypertrophic cardiomyopathy or a different infiltrative process. It can be suggestive of amyloidosis but not diagnostic. FDG-PET is used to detect sarcoidosis or malignancy but would not be useful in the diagnosis of cardiac amyloidosis.

Although endomyocardial biopsy still has a role in certain clinical conditions, it would be an invasive and more aggressive modality to help make the diagnosis compared with more conventional imaging modalities.

### TABLE 1

<table>
<thead>
<tr>
<th>Extracardiac manifestations</th>
<th>Cardiac manifestations</th>
<th>Imaging findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral carpal tunnel syndrome</td>
<td>Persistent mildly elevated troponin levels</td>
<td>Echocardiography: increased thickness of left ventricle, right ventricular free wall, atrioventricular valves, interatrial septum</td>
</tr>
<tr>
<td>Unprovoked biceps tendon rupture</td>
<td>Symptomatic hypotension or orthostasis in response to hypertensive medication</td>
<td>Electrocardiography: discrepancy in QRS voltage and left ventricular thickness</td>
</tr>
<tr>
<td>Lumbar stenosis</td>
<td>Unexplained atrioventricular block, heart block, or bundle branch block</td>
<td>Strain echocardiography: longitudinal impairment with apical sparing</td>
</tr>
<tr>
<td>Sensorimotor polyneuropathy</td>
<td>Elevated N-terminal-pro-brain natriuretic peptide not proportionate to severity of heart failure</td>
<td>Cardiac magnetic resonance imaging: increased extracellular volume or late enhancement</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
<td>Family history of cardiomyopathy</td>
<td>Chest radiography: cardiomegaly</td>
</tr>
</tbody>
</table>
Technetium-99m pyrophosphate scintigraphy is the recommended diagnostic tool for ATTR-CM. It is cost-effective, noninvasive, and relatively widely available. The radiotracer used in this scan is generally absorbed by bone structures and amyloid deposition in the myocardium, and therefore the degree of uptake in the myocardium is generally compared with that of the contralateral ribs. In normal myocardium, no uptake would be present, but in patients with ATTR-CM, radiotracer uptake is usually comparable to or exceeds that of the contralateral ribs based on the severity of the disease process. Due to the diffuse deposition of amyloid throughout the myocardial tissue, the sensitivity of endomyocardial biopsy for the diagnosis of cardiac amyloidosis is nearly 100%. Nonetheless, the risks of the procedure and limited access make it the less favorable option. When observing 103 patients undergoing diagnostic endomyocardial biopsy for ATTR-CM, a radiotracer uptake of grade 2 to 3 had sensitivity of 94% and specificity of 89%, with 100% specificity for grade 3.

While false-positive results may occur with this test, further investigations are recommended to diminish the likelihood of this. To distinguish blood-pooling from myocardial uptake, single-photon emission computed tomography is necessary after technetium-99m pyrophosphate scintigraphy has shown evidence of ATTR-CM. Once blood-pooling and AL amyloidosis have been ruled out, ATTR-CM will meet diagnostic criteria if scintigraphy shows grade 2 to 3 cardiac uptake 3 hours after injection, as seen in our patient (Figure 2). ATTR should only be established after AL has been ruled out with serum immunofixation electrophoresis, urine immunofixation electrophoresis, and serum light chain concentration.

What is the best disease-modifying medical treatment for cardiac amyloidosis?

- Doxycycline
- Tafamidis
- Inotropes
- Nonsteroidal anti-inflammatory drugs (NSAIDs)

Although doxycycline and NSAIDs have been used historically in the treatment of cardiac amyloidosis, there are no data to support their ability to alter the disease process or to show a survival benefit. These treatments were used on the premise of having efficacy in other inflammatory and infectious cardiac etiologies. Inotropes and diuretics may improve the quality of life for patients with specific types of cardiomyopathies but will not change the progression of the disease. The pathogenesis of ATTR-CM involves...
the deposition of proteins. Therefore these methods would not alter the disease course.

The goal of drugs that target ATTR is to slow the progression of the disease. However, cardiac and extracardiac manifestations of ATTR must also be managed. Due to the low stroke volume of the heart in ATTR-CM, beta-blockers should be avoided, though they may be necessary for rate control of arrhythmias that commonly occur owing to atrial involvement of the disease. Referral to a neurologist may be necessary as the patient may experience polyneuropathy and autonomic instability evidenced by orthostatic hypotension.

Disease-modifying therapies for ATTR-CM target transthyretin through silencing, stabilization, and disruption. Tafamidis is the first treatment approved by the US Food and Drug Administration for ATTR-CM and is used in both the wild-type and hereditary subtypes. The mechanism of this medication is to stabilize the transthyretin protein in its tetrameric configuration, ultimately preventing breakdown into unstable monomers that infiltrate various organ systems. In the ATTR Tafamidis in Transthyretin Cardiomyopathy Clinical Trial, patients randomized to tafamidis therapy not only had a decrease in cardiovascular-related hospitalizations but also showed less decline in functional capacity and reduced all-cause mortality. Over a 30-month span of treatment with tafamidis, therapy was tolerated well with safety profiles similar to those with placebo. Furthermore, patients randomized to tafamidis experienced less worsening of their general health, reduced or no worsening in heart failure symptoms, and improved quality of life. Other transthyretin-stabilizing drugs such as diflunisal have been shown to improve survival in patients with cardiac ATTR. Further research targeting ATTR through silencing and disruption shows promising results: medications like patisiran and inotersen have reduced the production of transthyretin by up to 80%, ultimately stabilizing or partially relieving peripheral neuropathy in patients included in the trial.

The goal of drugs that target ATTR is to slow the progression of the disease, but cardiac and extracardiac manifestations must also be managed.

This patient was initiated on tafamidis therapy, but 2 years later he was noted to have a reduced left ventricular ejection fraction of 35%, small left ventricle cavity size, worsening symptoms of heart failure, and a negative coronary angiogram. What treatment option should be considered at this juncture?

- Left ventricular assist device
- Heart transplantation
- Addition of diuretics to tafamidis treatment
- Hospice or palliative care

**FURTHER MANAGEMENT IN AMYLOIDOSIS PATIENT**

Left ventricular assist devices (LVADs) are used for patients with end-stage heart failure with reduced ejection fraction. LVADs have demonstrated survival and quality-of-life benefits among select patient populations. Patients with cardiac amyloidosis tend to have small ventricle sizes as a result of hypertrophy, which will likely preclude successful LVAD implantation.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Effect on transthyretin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tafamidis</td>
<td>Wild-type or hereditary ATTR cardiomyopathy</td>
<td>Stabilizer</td>
</tr>
<tr>
<td>Vutrisiran</td>
<td>Hereditary ATTR with neuropathy</td>
<td>Silencer</td>
</tr>
<tr>
<td>Patisiran</td>
<td>Hereditary ATTR with neuropathy</td>
<td>Silencer</td>
</tr>
<tr>
<td>Inotersen</td>
<td>Hereditary ATTR with neuropathy</td>
<td>Silencer</td>
</tr>
</tbody>
</table>

**TABLE 2**

Disease-modifying therapies for transthyretin amyloidosis (ATTR) approved by the US Food and Drug Administration
tation, and no study has demonstrated improvement in morbidity or mortality in this patient population.\textsuperscript{21} Therefore, LVAD therapy would not be an ideal option for our patient.

Diuretics are an adjunct to traditional guideline-directed therapies in patients with reduced ejection fraction. Although diuretics improve symptoms by way of decongestion, they do not increase survival and will not modify disease progression in heart failure with reduced ejection fraction. Hospice or palliative care may be an option for a patient with ATTR-CM who elects not to proceed with more invasive treatments or would not be able to tolerate them.

The age of the patient and lack of other significant comorbidities should warrant consideration for heart transplantation as the next step in management.

**CASE CONCLUSION**

The patient was ultimately considered for and underwent successful orthotopic heart transplant without complications.

**REFERENCES**


**TAKE-HOME POINTS**

- Amyloidosis involves the misfolding of precursor proteins, resulting in an infiltrative pathology of protein deposition involving numerous organ systems, including the heart.
- Amyloidosis is a multisystem disease; therefore, clinicians should be aware of extracardiac involvement that may raise suspicion for the diagnosis.
- Once a high suspicion of cardiac amyloidosis has been established, prioritization of differentiation between AL-CM and ATTR-CM is of utmost importance, as treatment differs drastically, and disease course may progress rapidly without intervention.
- Although cardiac amyloidosis is considered rare, data demonstrate a much higher prevalence than previously thought, giving emphasis to the need to screen patients with clinical features consistent with ATTR.

**DISCLOSURES**

Dr. Wolinsky reports consulting with Alnylam Pharmaceuticals and Pfizer, and consulting, teaching, and speaking with Akcea Therapeutics and Astellas Pharma US. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

Dr. Wolinsky reports consulting with Alnylam Pharmaceuticals and Pfizer, a potential conflict of interest.


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Myasthenia gravis: Frequently asked questions

ABSTRACT
Myasthenia gravis is a disorder of neuromuscular junction transmission, the result of antibodies against the postsynaptic aspect of the neuromuscular junction. Its clinical hallmark is fatigable weakness of skeletal muscles, which tends to vary in location and severity among patients. It is treated with pyridostigmine, immunotherapy, and thymectomy. Treatment is often individualized according to disease severity, antibody status, comorbidities, and other factors. This review uses a question-and-answer format to provide up-to-date, high-yield, clinically relevant information on myasthenia gravis.

KEY POINTS
Diagnosis often starts with antibody testing, while electrodiagnostic tests are useful in selected patients.

Pyridostigmine is often given to patients with mild symptoms, or as an ancillary therapy for patients with more severe illness.

Corticosteroids and corticosteroid-sparing agents are given based on a variety of patient characteristics.

Thymectomy is mostly reserved for younger patients with acetylcholine receptor antibody-positive generalized myasthenia gravis.

Newer selective immunotherapies for myasthenia gravis are emerging.

THE NAME “MYASTHENIA GRAVIS” COMES FROM THE GREEK FOR MUSCLE WEAKNESS AND THE LATIN WORD FOR GRAVE OR SERIOUS. A CHRONIC AUTOIMMUNE NEUROMUSCULAR DISORDER CAUSING SKELETAL MUSCLE WEAKNESS, ITS PRIMARY PATHOPHYSIOLOGY INVOLVES DYSFUNCTION OF THE POSTSYNAPTIC ASPECT AT THE NEUROMUSCULAR JUNCTION, MAINLY A LOSS OF ACETYLCHOLINE RECEPTOR (AChR) FUNCTION ON THE MUSCLE MEMBRANE.

CERTAIN SKELETAL MUSCLE GROUPS ARE MORE LIKELY TO BE INVOLVED THAN OTHERS, BUT THE PATTERN VARIES WIDELY AMONG PATIENTS AND DEPENDS ON THE CLINICAL COURSE IN THE INDIVIDUAL PATIENT. ACCORDINGLY, MYASTHENIA GRAVIS IS TYPICALLY CATEGORIZED AS EITHER OCULAR (IN WHICH WEAKNESS IS LIMITED TO THE EXTRINSIC OCULAR MUSCLES AND LEVATOR PALPEBRAE SUPERIORIS), OR GENERALIZED (IN WHICH MUSCLES BEYOND THOSE IN THE OCULAR FORM ARE INVOLVED, INCLUDING THOSE OF THE LIMBS, THE BULBAR AND OROPHARYNGEAL REGION, AND MUSCLES OF RESPIRATION).

The following 12 frequently asked questions and answers aim to provide up-to-date, high-yield, clinically relevant information about myasthenia gravis.

WHICH POPULATIONS ARE AT RISK?
Family members, particularly first-degree relatives of those with myasthenia gravis, have a higher risk not only for myasthenia gravis but also for other autoimmune diseases.1 In addition, the disease has interesting patterns of age, sex, and phenotype.

Myasthenia gravis can strike at any age, but the age of onset has a bimodal distribution, with the first peak in patients in their teens and 20s, in which girls and women outnum-
### TABLE 1
**Key features distinguishing myasthenia gravis from other common diagnoses**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Similarities to myasthenia gravis</th>
<th>Differences from myasthenia gravis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lambert-Eaton myasthenic syndrome</strong></td>
<td>Weakness and fatigue</td>
<td>Less prominent ocular or oculobulbar features, Areflexia or hyporeflexia, Autonomic features (dry mouth, erectile dysfunction), Positive antibody against P/Q voltage-gated calcium channel, High-frequency repetitive nerve stimulation testing shows an incremental response (ie, a progressive increase in motor amplitude)</td>
</tr>
<tr>
<td><strong>Botulism</strong></td>
<td>Ocular findings (diplopia and ptosis, bulbar dysfunction, generalized weakness)</td>
<td>Acute attack, possible history of food poisoning, Descending paralysis, Dilation of the pupil (mydriasis), Prominent autonomic dysfunction, Monophasic course, High-frequency repetitive nerve stimulation testing shows an incremental response</td>
</tr>
<tr>
<td><strong>Amyotrophic lateral sclerosis</strong></td>
<td>Bulbar dysfunction and weakness</td>
<td>Slow progressive course, No ocular findings, Symptoms do not fluctuate, Findings of upper motor neuron dysfunction (eg, hyperreflexia, spasticity), Electromyography showing prominent active and chronic denervation or reinnervation, or both</td>
</tr>
<tr>
<td><strong>Myopathy</strong></td>
<td>Proximal limb weakness</td>
<td>Relative absence of ocular findings, Symptoms do not fluctuate, Creatine kinase elevation and presence of myositis-specific antibodies in cases of autoimmune or inflammatory myositis, Repetitive nerve stimulation testing is normal, while needle electromyography shows short-duration, low-amplitude, polyphasic motor-unit potentials, with or without abnormal spontaneous activity</td>
</tr>
<tr>
<td><strong>Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy</strong></td>
<td>Generalized weakness</td>
<td>Sensory symptoms such as pain and paresthesia, Symptoms do not fluctuate, Hyporeflexia or areflexia, Cerebrospinal fluid has protein elevation, no significant pleocytosis, Nerve conduction studies reveal findings consistent with demyelination</td>
</tr>
<tr>
<td><strong>Thyroid eye disease</strong></td>
<td>Diplopia</td>
<td>Ptosis is infrequent, Symptoms do not fluctuate, Other ocular findings such as edema, redness, conjunctival injection and exophthalmos, Magnetic resonance imaging showing extraocular tissue enlargement</td>
</tr>
<tr>
<td><strong>Oculopharyngeal muscular dystrophy</strong></td>
<td>Ptosis, diplopia, dysphagia</td>
<td>Slowly progressive course, Absence of symptomatic fluctuation, Relative absence of prominent limb weakness, Elevation of creatine kinase, Mutations in the PABPN1 gene; mostly autosomal dominant pattern of inheritance</td>
</tr>
</tbody>
</table>
ber boys and men, and the second peak in patients in their 50s and 60s, in which men outnumber women.\(^2,3\)

In the past, female patients outnumbered male patients overall. However, the age at onset has progressively increased, together with the proportion of men, so that the preponderance of women is becoming less.\(^4,5\) There is a male predominance in ocular myasthenia gravis as well.\(^6\) Boys and girls are equally affected before puberty, but more girls than boys get the disease afterward.\(^7\)

The myasthenia gravis subtype possessing antibodies to muscle-specific tyrosine kinase (MuSK) has a marked female predominance (more than 70% in all studies reviewed), and its mean age of onset is 36 to 38 years.\(^2,8\)

African Americans may have slightly higher rates of myasthenia gravis incidence and prevalence, and more severe disease.\(^9,10\) In the United States, 28% to 47% of patients with MuSK antibodies are African American.\(^8\) In addition, MuSK antibody-positive myasthenia gravis occurs in a higher proportion of those of Asian ancestry than in those of European or African ancestry.\(^11\)

About 13% of patients with myasthenia gravis have a comorbid autoimmune disorder.\(^12\) Thyroid disease (Hashimoto thyroiditis, Graves disease) is the most common, followed by rheumatoid arthritis.\(^12,13\) Up to about 10% of patients with myasthenia gravis may have associated thymoma.

Fortunately, myasthenia gravis is uncommon. In a systematic review of 55 studies, Carr et al\(^14\) calculated that the pooled incidence was 5.3 per million person-years, and the prevalence was 77.7 per million persons—both considerably lower, for example, than those of hypothyroidism or Guillain-Barré syndrome, which are in the differential diagnosis.

Although the incidence of myasthenia gravis has changed little over time, its estimated prevalence has significantly increased since the 1950s, mostly owing to improvements in diagnosis and treatment that have reduced the mortality rate, so that more people are living with the disease.

**WHEN SHOULD A CLINICIAN THINK ABOUT THIS DIAGNOSIS?**

Think about myasthenia gravis when a patient has fatigable weakness, especially weakness of ocular muscles producing variable diplopia, ptosis, and weak eye-closure. These are the core clinical features. At initial presentation, which is typically subacute, up to 85% of patients have ocular symptoms.\(^15\)

Fatigable is key. The muscle weakness fluctuates, classically worsening with sustained or repetitive physical activity, worsening by evening or nighttime, and improving with rest. In the arms and legs, the weakness generally tends to affect proximal muscles more than distal ones. In the mouth and neck, prominent bulbar weakness, including dysarthria, nasal speech, dysphagia, poor saliva control, difficulty chewing, and neck weakness including a drooped-head phenotype may be seen in about 15% of patients at presentation.\(^15\) Myasthenia gravis-related weakness may progress in severity over weeks or months, often with exacerbations and remissions during its course.

**Think about myasthenia gravis when a patient has fatigable weakness, especially weakness of ocular muscles producing variable diplopia, ptosis, and weak eye-closure**

Of importance, patients with myasthenia gravis typically have no sensory or pain symptoms, bowel or bladder dysfunction, or changes in mental status or cognition. In addition, deep tendon reflexes are usually intact, even if the patient has marked weakness.

Table 1 lists common disorders in the differential diagnosis of myasthenia gravis and their distinguishing features.

**WHAT TESTS SHOULD BE ORDERED?**

Antibody tests are ordered first, followed in some patients by electrodiagnostic and other tests (Figure 1).

**Antibody tests**

First-line diagnostic tests are typically serologic.

**Anti-AChR antibody** (particularly the binding subtype) is highly specific (> 90%) and very sensitive (up to about 85%) in those with generalized myasthenia gravis.\(^2\)

**Anti-MuSK antibodies.** In patients with myasthenia gravis who are seronegative for anti-AChR antibodies, up to 37% possess anti-MuSK antibodies.\(^8\) However, the sensitivity of anti-AChR antibody is lower, about 50%, in those who have purely ocular myasthenia gravis. Anti-MuSK antibodies rarely occur in the group of patients with purely ocular myasthenia gravis.\(^15\)

**Antilipoprotein-related protein 4 (LRP4) antibody** is found in 3% to 50% of the remaining patients with generalized myasthenia gravis who are seronegative to both anti-AChR and anti-MuSK antibodies.
Antistriated muscle antibodies. On immunofluorescent staining, antistriated muscle antibodies bind in a cross-striational pattern to a number of muscle proteins including titin, ryanodine receptor, actin, myosin, tropomyosin, and filamin. They are much less specific for myasthenia gravis and are seen in about 30% of patients, and they are more useful as a marker for thymoma, especially in the nonelderly. Thus, myasthenia gravis cannot be reliably diagnosed on the basis of positive antistriated muscle antibody alone.

Electrodiagnostic tests
Two electrodiagnostic tests—repetitive nerve stimulation and single-fiber electromyography—provide objective evidence of impairment of neuromuscular junction transmission and are helpful in diagnosing myasthenia gravis. They need not be performed in

Figure 1. Diagnostic algorithm for myasthenia gravis. If the anti-AChR binding and modulating antibody tests are negative, two options are reasonable, as indicated.

AChR = acetylcholine receptor; LRP4 = lipoprotein-related protein 4; MuSK = muscle-specific tyrosine kinase
all patients, but they provide supportive diagnostic evidence, especially in seronegative patients and when prompt confirmation of the diagnosis is needed.

**Repetitive nerve stimulation** uses repeated “trains” of nerve stimulations to generate electrical muscle responses. The amplitudes of these responses can be measured to gauge the fatigability of neuromuscular junction transmission. The sensitivity and specificity of repetitive nerve stimulation depends on the nerve-muscle combinations examined, the severity of myasthenia gravis, and the cutoff values used for a decremental response. Its overall diagnostic sensitivity ranges from about 30% to 80% for generalized myasthenia gravis, with lower sensitivity in milder disease or when distal muscles are tested. In ocular myasthenia gravis, its sensitivity is only 10% to 30%.16

**Single-fiber electromyography** uses small needle electrodes to measure the variability of single muscle fiber potentials, a reflection of neuromuscular junction transmission. This test is often considered only when other diagnostic tests are unrevealing. It is more sensitive than repetitive nerve stimulation (62% to 99% for ocular myasthenia gravis, and 75% to 98% for generalized myasthenia gravis). Thus, a normal result in a clinically weak muscle essentially rules out myasthenia gravis. Its reported specificity varies from 66% to 98% for ocular myasthenia gravis and up to 98% for generalized myasthenia gravis, and abnormal results can be seen in other neuromuscular disorders such as motor neuron disease, congenital myasthenia gravis, or myopathy.17

**Other tests**

Also useful in patients suspected of having myasthenia gravis are tests for common comorbid conditions, eg, chest computed tomography or magnetic resonance imaging for thymic abnormalities. One should be alert for clinical features that may suggest comorbid autoimmune conditions that would call for additional serologic tests such as thyroid-stimulating immunoglobulin, antithyroid peroxidase, antithyroglobulin, or rheumatoid factor.

### HOW DOES THE NATURAL COURSE AFFECT THE TREATMENT STRATEGY?

Myasthenia gravis tends to progress, especially in the first several years, so we recommend treating it aggressively with immunosuppressants at the outset and then gradually easing back.

Not until the late 1960s was myasthenia gravis recognized as an immune-mediated disorder, and immunotherapies such as corticosteroids, azathioprine, and methotrexate started to be used as treatments for it.18 As a result, studies of its outcome done before the late 1960s generally reflected its natural course. In several such early studies, the mortality and morbidity rates were highest within the first 3 years of the disease and lower thereafter.19-21

In particular, ocular myasthenia gravis reaches its maximal severity within the first 3 years in most patients.21 In older studies, approximately two-thirds of cases of ocular myasthenia gravis subsequently progressed into the generalized subtype, and of these, approximately 80% did so within the first year and 90% within the first 3 years.21,22 In more recent series, the percentage of generalization from the ocular subtype was less, as low as 20%23 to 50%.24

More immunotherapies for myasthenia gravis are now available. However, the aforementioned studies of the natural course help guide the assessment of risks and benefits of immunosuppressive treatment. While the early goal should focus on aggressive treatment to improve the patient’s functional status, care must be taken to avoid serious adverse effects from intense immunotherapy. Patients who endure the first 3 years with relatively good symptom control tend to have a higher chance of gradual improvement or a steady state and, less often, worsening of the disease.21,25,26 An exception is in refractory myasthenia gravis, which accounts for approximately 10% of patients with generalized myasthenia gravis and can be associated with relapses and exacerbations late in the course.

In the long term, it is preferable to steadily minimize immunosuppression if the patient’s condition remains stable, while watching for relapse or exacerbation. Approximately half of patients can achieve remission or minimal symptoms with low-dose immunotherapy.26 However, clinicians should be cautious about discontinuing immunotherapy completely, as only about 10% of patients may achieve complete stable remission off immunotherapy.27
WHAT INSTRUCTIONS SHOULD PATIENTS RECEIVE?

After myasthenia gravis is diagnosed, patients should be educated about its typical course and largely benign prognosis. Points to discuss include:

- Specific symptoms of the disease, including red flags
- The importance of the progressive trend of symptom severity and frequency, rather than their transient worsening
- Common triggers of exacerbation, such as heat, infection, surgery, pregnancy, emotional disturbance, and certain medications (see discussion below)
- The intended medication regimen, particularly immunotherapy, and potential side effects, to ensure compliance.

If a patient needs more than 240 mg of pyridostigmine per day, it is time to move on to immunotherapy.

Many patients with myasthenia gravis are cautious about physical exertion, fearing that exercise might worsen their symptoms. However, most can tolerate and benefit from some form of exercise. Patients with mild disease can participate in resistance and aerobic training. For those with severe symptoms, stretching exercises such as tai chi, yoga, and balance training are usually most appropriate. Simply being more active and reducing overall sedentary time are important.

Fatigue is common, reported in approximately 80% of patients at some stage of their disease. It is important to recognize differences between fatigue and fatigable weakness, as fatigue does not call for escalating myasthenia gravis treatment. The cause of fatigue in myasthenia gravis is multifactorial and includes deconditioning, cognitive blunting, sleep disturbance, and weight gain. Management of fatigue may include regular exercise, sleep evaluation, psychotherapy, and cognitive behavioral therapy.

WHICH MEDICATIONS ARE BEST AVOIDED?

Because some medications can trigger or worsen myasthenic symptoms, all patients with myasthenia gravis, especially those with significant weakness, should be observed for increased weakness whenever a new medication is started. In principle, if a patient’s condition deteriorates when given a new drug, the drug should be withdrawn. Drugs that are most clearly contraindicated in myasthenia gravis include telithromycin, intravenous magnesium, botulinum toxin, penicillamine, and immune checkpoint inhibitors (see discussion below).

Other medications that can worsen the disease include fluoroquinolones, macrolide antibiotics, aminoglycoside, beta-blockers, chloroquine, statins, and iodinated contrast (mostly associated with a low overall risk of aggravating myasthenia gravis). Most patients with mild to moderate disease or in stable remission tolerate these drugs without ill effect. Some medications (eg, aminoglycosides) are probably best avoided, as many alternatives are available. More robust data are needed to ascertain and quantify the risk of myasthenia gravis worsening with the other medications mentioned above.

Immune checkpoint inhibitors, used to treat malignancies, have become the most common iatrogenic cause of myasthenia gravis. They include blockers of programmed cell death receptor 1 (nivolumab, pembrolizumab), programmed cell death ligand 1 (atezolizumab, durvalumab, and avelumab), and cytotoxic T cell lymphocyte-associated antigen 4 (ipilimumab).

Immune checkpoint inhibitors can exacerbate symptoms in patients with myasthenia gravis or cause de novo disease. Many patients who develop myasthenia gravis as a result of these drugs have elevations of creatine kinase and troponin due to coexisting necrotizing myositis and myocarditis. The range of these autoimmune complications is wide—mild and monophasic in some patients, fulminant and even fatal in others. Prompt recognition is critical, as the immune checkpoint inhibitor needs to be stopped promptly and immunotherapy added.

HOW SHOULD PYRIDOSTIGMINE BE USED?

Pyridostigmine, the most commonly used acetylcholinesterase inhibitor for symptomatic treatment of myasthenia gravis, is typically used alone in mild cases or in combination with immunosuppressants in more severe ones. However, its efficacy may be minimal in patients with long-standing or severe myasthenia gravis.

Pyridostigmine’s onset of effect is 30 to 60 minutes after each dose, and its duration is 3 to 6 hours. It should be taken 30 minutes before meals if dysphagia is present. A typical starting dose is 60 mg every 6 hours during daytime.

Patients who awaken with morning weakness can take a 180-mg extended-release formulation before sleep. However, the response to this formulation varies due to erratic absorption.
The dosage of pyridostigmine can be titrated up to 240 to 360 mg daily, but side effects are more common at higher doses, and overdose may result in increased weakness. In practice, if a patient needs more than 240 mg per day, it is time to move on to immunotherapy. Once myasthenia gravis is controlled with immunotherapy, most patients do not need pyridostigmine. In a 1973 study in animals, long-term acetylcholinesterase inhibitor treatment at high doses led to degeneration and dysfunction of the neuromuscular junction, but clinical experience suggests that pyridostigmine is generally safe without significant long-term complications.

The most common side effects are gastrointestinal, eg, abdominal cramping, loose stool, and flatulence. Bradycardia, bronchospasm, increased sweating, excessive lacrimation, muscle twitching, and cramping are other effects.

To manage side effects, oral glycopyrrolate or hyoscymamine can be taken concurrently with pyridostigmine doses. Dosage adjustment may be required in patients with renal impairment. One should be vigilant for the development of bronchospasm in patients with asthma.

Patients with MuSK antibody-positive myasthenia gravis may not respond well to pyridostigmine or may develop profuse cramps and fasciculations, even with low doses, possibly owing to reduction of cholinesterase levels at the neuromuscular junction.

### WHEN SHOULD CORTICOSTEROIDS BE USED?

According to consensus guidelines, corticosteroids or nonsteroidal immunosuppressive drugs should be used in all patients with myasthenia gravis who have not met their treatment goals after an adequate trial of pyridostigmine.

Only 2 controlled trials have evaluated the efficacy of corticosteroids in generalized myasthenia gravis. However, retrospective studies of oral steroids (prednisone or prednisolone) as the main myasthenia gravis treatment also provide evidence that these drugs are effective. Corticosteroids help nearly all patients with all subtypes of myasthenia gravis, resulting in marked improvement in more than 80%. Their onset of action is relatively rapid, 2 weeks on average.

Outpatients with mild to moderate symptoms can start prednisone at 20 mg daily and gradually increase the daily dose by 10 mg every 1 to 2 weeks up to approximately 60 mg daily, titrating to clinical response. Other corticosteroids with proven efficacy in myasthenia gravis include methylprednisolone, given intramuscularly or intravenously, and oral dexamethasone.

Some patients respond better than others to corticosteroids. Good responders have a smooth and consistent response to moderate or high corticosteroid doses and can be kept in remission with low doses (eg, 5 to 7.5 mg of prednisone daily) without the need for nonsteroidal immunosuppressive agents. The long-term risk of such low-dose prednisone therapy is considered minimal. Data suggest that patients over age 40, and especially those over age 60, are more likely to be good responders compared with younger patients.

### WHEN SHOULD OTHER IMMunosUPPRESSIVES BE USED?

Nonsteroidal immunosuppressive therapies should be considered in the following situations:

- Lack of significant response to prednisone
- More than 1 relapse upon prednisone tapering
- Inability to wean prednisone to an acceptable minimal dosage
- Contraindications to prednisone such as morbid obesity, brittle diabetes mellitus, peptic ulcer disease, high risk for osteoporosis, or significant side effects from prednisone.

Nonsteroidal immunosuppressive drugs such as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, tacrolimus, and rituximab have
been extensively used in myasthenia gravis to spare the use of corticosteroids in some patients. Newer agents recently approved such as eculizumab, ravulizumab, and efgartigimod could also serve this purpose in selected patients.41–43

Other factors such as antibody status, comorbidities, desired time course of action, and physician or patient preference may modify the choice of nonsteroidal immunosuppressive therapy. Rituximab is particularly effective for MuSK antibody-positive myasthenia gravis. Azathioprine, methotrexate, and mycophenolate mofetil may take 6 to 12 months to work, while the onset action of cyclosporine, tacrolimus, and rituximab is generally quicker. Several of these drugs can damage the bone marrow, liver, kidneys, and lungs, and the functional status of these organs may influence their usage.44

At times, nonsteroidal immunosuppressive therapy may also be given as the initial immunosuppressant for patients with mild disease who are content with a slow course of improvement. In patients with significant weakness who have contraindications to corticosteroids, intravenous immunoglobulin, efgartigimod, or plasmapheresis can be used in the beginning to expedite clinical improvement while allowing time for an alternative nonsteroidal immunosuppressive therapy to produce its therapeutic effect.45

Because of the delayed action of some nonsteroidal immunosuppressive therapies, prednisone should be started concurrently. However, in general, one should avoid combining more than 2 immunosuppressants (eg, prednisone and a nonsteroidal immunosuppressive drug) in view of increased risks of infection and other side effects. An exception is in refractory myasthenia gravis, which often requires intense immunotherapy with multiple agents.46

For patients who gain good control by taking the combination of prednisone and a nonsteroidal immunosuppressive drug, prednisone is usually tapered first. After prednisone is tapered off or reduced to an acceptable minimal dose, the nonsteroidal drug can be tapered next, but much more slowly, usually over years. In some patients, both prednisone and the nonsteroidal drug can be kept at low dosages for optimal disease control and to minimize the side effects of each while taking advantage of their different mechanisms of action.

WHAT IS THE ROLE OF THE THYMUS?
WHO SHOULD UNDERGO THYMECTOMY?

The thymus gland is essential in the development of central tolerance and T-cell differentiation, and thus likely plays an important role in the immunopathogenesis of myasthenia gravis.

In approximately 10% of patients, myasthenia gravis is a paraneoplastic manifestation of an underlying thymic neoplasm (usually thymoma, rarely thymic carcinoma). However, thymic lymphoid hyperplasia is seen in up to 65% of patients with myasthenia gravis. Lymphoid hyperplasia consists of numerous lymphocytes, macrophages, and plasma cells, reflecting the autoimmunity underlying myasthenia gravis that often begins in the thymus gland.

There is also evidence to suggest that autoimmunity against acetylcholine receptor may be due to intrathymic “myoid” cells and medullary thymic epithelial cells that elaborate acetylcholine receptor or subunits of it on their cell surface.48

Indicated in patients with thymic neoplasms, and those similar to patients in the MGTX trial

The decision to remove the thymus is often influenced by whether patients have thymomatous or nonthymomatous myasthenia gravis. Thymectomy is indicated in all patients with thymic neoplasms. Otherwise, candidacy for thymectomy depends on several factors including AChR antibody status, myasthenia gravis type, disease duration, and patient age.

Supportive evidence comes from the landmark Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone Therapy (MGTX).49 To enter that trial, patients had to meet the following criteria:

- Have generalized myasthenia gravis
- Be AChR antibody-positive
- Be within 5 years of symptom onset.

Thymectomy in similar adult patients age 50 or younger is likely to improve clinical outcomes and permit minimal pharmacotherapy, including immunosuppressant use and dosage.

The benefit of thymectomy in patients ages 51 to 65 is more equivocal, and thymectomy is generally avoided in patients over age 65, since the risk-to-benefit ratio is less favorable.

There is no significant evidence to support thymectomy in those with MuSK antibody-positive myasthenia gravis. However, most experts would also consider thymectomy for patients with generalized myasthenia gravis who are “triple seronegative” (without antibodies to AChR, MuSK, or LRP4). This appears to be supported by evidence of similar benefits in both AChR antibody-positive and AChR antibody-negative myasthenia gravis subgroups.50
Thymectomy for patients with strictly ocular myasthenia gravis is controversial. Although the surgery employed in the MGTX trial was traditional extended transsternal thymectomy via a median sternotomy, this has largely been replaced by less invasive procedures including video-assisted and robotic-assisted thymectomy via a transsternal approach, and extended transcervical thymectomy through a low horizontal neck incision. Retrospective studies have shown similar clinical outcomes from the different surgical techniques. The major advantages of less invasive surgical approaches relate to their lower postoperative complication rates and shorter length of stay in the hospital.

### HOW CAN MYASTHENIC CRISIS BE PREVENTED, RECOGNIZED, AND TREATED?

A myasthenic crisis is a life-threatening worsening of myasthenia gravis-related respiratory or bulbar muscle weakness that is severe enough to necessitate intubation or mechanical ventilation, or both. If a patient has marked dysphagia, managing saliva and other oropharyngeal secretions can become difficult and the risk of aspiration is high.

Key measures in preventing myasthenic crisis are consistent disease control (including adherence to the medication regimen and careful weaning from immunosuppressants) and avoiding triggers or precipitants.

#### Recognizing myasthenic crisis

Most patients with myasthenic crisis do not present with respiratory insufficiency alone. Rather, neuromuscular respiratory weakness usually occurs in the context of already worsening generalized or bulbar weakness, or both. Therefore, clinical features indicating significant worsening deficits in these areas may provide warning signs.

Of note, classic features of respiratory distress such as use of accessory muscles of respiration may be blunted during a myasthenic crisis, so these should not be overly relied upon. Orthopnea is a more specific feature than dyspnea, indicating significant neuromuscular respiratory weakness (especially of the diaphragm). Significant weakness in neck flexors and shoulder external rotators also typically correlates with respiratory muscle weakness.

A screening test that can be done at the bedside or over the telephone is the single-breath counting test. The patient is asked to take a deep inspiration and on subsequent expiration count from 1 onwards at a routine speaking pace (about 2 counts per second) until they need to take another breath. Inability to count to 20 with a single breath indicates significant respiratory weakness.

However, more formal spirometric measures are ideal, and the “20-30-40 rule” should be kept in mind. This means that patients should be admitted or transferred to the intensive care unit for airway and respiratory management if vital capacity falls below 20 mL/kg, if the maximal inspiratory pressure (also known as negative inspiratory force) becomes less negative than −30 cm H₂O, or if the maximal expiratory pressure falls below 40 cm H₂O. Intensive care may also be warranted if the values are falling quickly (> 30% over 24 hours). It is very important that spirometry be done with a well-fitting face mask instead of a mouthpiece when there is significant weakness of facial muscles (particularly orbicularis oris), causing poor seal.

Measures of oxygenation, including pulse oximetry and arterial partial pressure of oxygen, are less helpful than those for carbon dioxide retention because of the prevailing mechanism of ventilatory compromise.
**WHAT NEW TREATMENTS ARE ON THE HORIZON?**

The complement inhibitors eculizumab and ravulizumab and the neonatal Fc-receptor blocker efgartigimod have been recently approved by the US Food and Drug Administration for treating AChR antibody-positive myasthenia gravis, and many newer treatments with various mechanisms of actions are being studied (Table 2). Several of them (including rozanoliximab and zilucoplan) have had positive results in phase 3 trials.56

The newer immunotherapies are generally more selective in their immunologic targets than the older ones. Accordingly, they have the advantage of causing fewer adverse effects, including life-threatening infections. However, they are very expensive, and a major drawback is their “financial toxicity.” For many patients, the older broad-spectrum immunotherapies will remain a key component of treatment due to lower cost, ease of use, and potential of inducing remission. Nonetheless, the pace of major therapeutic innovations in the field is unprecedented, and the future of myasthenia gravis treatment is promising.

**DISCLOSURES**

Dr. Li reports consulting for ArgenX, Catalyst, Immunovant, and UCB; research as principal investigator for Alexion, ArgenX, Catalyst, Immunovant, and UCB; receiving grant support from ArgenX; serving as advisor or review panel participant for Immunovant; and membership on the Clinical Practice Scientific Advisory Board for Alexion. Dr. Morren reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

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Resistant hypertension: A stepwise approach

ABSTRACT
Resistant hypertension can be challenging to manage, but a stepwise approach to diagnosis, evaluation, and treatment can lead to better blood pressure control. In this article, we review the definition and prevalence of resistant hypertension and its diagnostic workup and management, including lifestyle modifications, drugs, and experimental interventional therapies.

KEY POINTS
Owing to stricter definitions and targets in the 2017 guidelines than in earlier guidelines, the prevalence of hypertension and resistant hypertension has increased.

Patients with resistant hypertension are at higher risk of complications including cardiovascular disease, stroke, kidney failure, and death.

It is important to identify common factors that contribute to resistant hypertension to mitigate their effects. Hypertensive patients who have resistant hypertension should undergo evaluation for secondary causes.

Along with lifestyle modification, a stepwise approach to management using antihypertensive medications with differing mechanisms of action is critical to achieving blood pressure control. Patients may require more antihypertensive medications.

MOVING THE GOALPOST: HYPERTENSION IS NOW 130/80 MM HG OR HIGHER

The 2017 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines define hypertension as systolic blood pressure 130 mm Hg or higher or diastolic blood pressure 80 mm Hg or higher, based on at least 2 readings obtained on at least 2 occasions. This is stricter than the 2003 guidelines from the Seventh Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, which defined hypertension as blood pressure 140/90 mm Hg or higher. As a result of the new definition, the prevalence of hypertension in the United States increased from roughly 32% to 47%.

Hypertension is a leading cause of cardiovascular disease and death. Its management costs the US healthcare system approximately $131 billion annually.

GOAL IS INDIVIDUALIZED, BUT LESS THAN 130/80 FOR MOST

Blood pressure targets should be individualized based on patient characteristics, medication side effects, patient tolerance, and preferences.
Office blood pressure above goal on at least 3 antihypertensive medications (typically ACEi or ARB, diuretic, and calcium channel blocker)

Confirm with out-of-office monitoring (ABPM or SMBP)

Review and assess medication adherence

Reinforce lifestyle modifications such as low-sodium DASH diet, weight management, physical activity, and limiting alcohol use

Stop medications that may potentially interfere with blood pressure control, including NSAIDs, OCPs, nasal decongestants, herbal supplements containing licorice, and illicit substances

Consider evaluation for obstructive sleep apnea

Exclude secondary causes of hypertension

Optimize medications including dosing at maximal or maximally tolerated doses

Chlorthalidone or indapamide are preferred thiazide-like diuretics

Short-acting loop diuretics should be dosed at least twice daily

Avoid dual ACEi/ARB therapy

Add MRA (spironolactone preferred, eplerenone if not tolerated)

Additional agents:

Vasodilatory beta-blockers are first-line therapy if compelling indications are present

Central alpha-receptor agonists such as clonidine patch or guanfacine, a longer-acting agent

Alpha-receptor antagonists such as prazosin, doxazosin, or terazosin

Vasodilators hydralazine or minoxidil

Figure 1. Management of resistant hypertension, recommendations adapted from the American Heart Association scientific statement on resistant hypertension, reference 2.

Refers to guideline recommendations with evidentiary support

Refers to therapy to be individualized to the patient

ABPM = ambulatory blood pressure monitoring; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; DASH = Dietary Approaches to Stop Hypertension; MRA = mineralocorticoid receptor antagonist; NSAIDs = nonsteroidal anti-inflammatory drugs; OCPs = oral contraceptive pills; SMBP = self-measured blood pressure
In patients with cardiovascular disease or with a risk of an atherosclerotic cardiovascular disease event of 10% or higher in the next 10 years, the 2017 ACC-AHA guidelines say that a goal of less than 130/80 mm Hg “is recommended.”

In patients at lower risk, the ACC-AHA guidelines say the same goal “may be reasonable.”

In patients with chronic kidney disease, the 2021 Kidney Disease Improving Global Outcomes guidelines recommended keeping the systolic blood pressure lower than 120 mm Hg contingent on proper blood pressure measurement. This recommendation is based largely on the cardiovascular benefits of this lower goal demonstrated in the Systolic Blood Pressure Intervention Trial, in which patients at risk of cardiovascular disease but without diabetes were randomized to goal blood pressures of either less than 120 mm Hg or less than 140 mm Hg. In a chronic kidney disease subgroup analysis, the intensive group had a slightly higher rate of change in estimated glomerular filtration rate (−0.47 vs −0.32 mL/min/1.73 m² per year; P < .03) after 6 months. The decline in kidney function may be hemodynamically mediated as a result of more intensive blood pressure control.

In patients with diabetes, the American Diabetes Association recommends a target blood pressure lower than 130/80 mm Hg.

Most people are not meeting these goals. According to an estimate from the US Centers for Disease Control and Prevention, of the 116 million Americans with hypertension, only 23.9 million (20.6%) have their blood pressure controlled using the 2017 ACC-AHA definitions. Resistant hypertension is associated with worse outcomes, particularly adverse kidney outcomes and cardiovascular morbidity and death. In a study of 10,001 patients, apparent treatment-resistant hypertension was associated with a 64% higher incidence of the composite cardiovascular outcome of fatal coronary heart disease, nonfatal myocardial infarction, cardiac arrest, and stroke. Apparent treatment-resistant hypertension was shown to increase the risk of kidney failure in an analysis of participants from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (hazard ratio 1.95; 95% confidence interval 1.11–3.41).

■ RESISTANCE, PSEUDORESISTANCE, OR APPARENT RESISTANCE?

Resistant hypertension is defined by the ACC-AHA as blood pressure that is above goal despite the patient receiving at least 3 medications with different mechanisms of action. All medications must be prescribed at maximally tolerated doses and should preferably include a long-acting dihydropyridine calcium channel blocker, either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB), and a diuretic. Resistant hypertension is also defined as controlled blood pressure on at least 4 antihypertensive medications.

Pseudoresistance is suboptimal blood pressure control secondary to medication nonadherence, white-coat effect, or poor measurement technique.

Apparent treatment-resistant hypertension is the term used in epidemiologic studies to refer to cases in which patients meet the criteria for resistant hypertension but have unverified adherence or medication dosing or have not undergone out-of-office blood pressure monitoring to rule out the white-coat effect.

■ PREVALENCE AND PROGNOSIS

The prevalence of resistant hypertension is difficult to ascertain precisely, given the need to rule out pseudoresistance. However, an estimate from the National Health and Nutrition Examination Survey (NHANES) put the prevalence of apparent treatment-resistant hypertension (using the cutoff of ≥ 140/90 mm Hg) in the general public at 12.8%. In hypertensive patients in the Chronic Renal Insufficiency Cohort, the prevalence of apparent treatment-resistant hypertension using the same definition was 40.4%. Other comorbidities associated with resistant hypertension include older age, obesity, diabetes mellitus, and obstructive sleep apnea.

Of the 116 million Americans with hypertension, only 23.9 million (20.6%) have their blood pressure controlled using the 2017 ACC-AHA definitions.

Resistant hypertension is associated with worse outcomes, particularly adverse kidney outcomes and cardiovascular morbidity and death. In a study of 10,001 patients, apparent treatment-resistant hypertension was associated with a 64% higher incidence of the composite cardiovascular outcome of fatal coronary heart disease, nonfatal myocardial infarction, cardiac arrest, and stroke. Apparent treatment-resistant hypertension was shown to increase the risk of kidney failure in an analysis of participants from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (hazard ratio 1.95; 95% confidence interval 1.11–3.41).

■ DIAGNOSIS OF RESISTANT HYPERTENSION

The diagnosis of resistant hypertension requires ruling out pseudoresistance due to medication nonadherence, improper blood pressure measurement, and the white-coat effect.
Is the patient taking the medication?
Medication nonadherence is a discrepancy between how a medication is prescribed and how the patient is actually taking it. Its prevalence in patients with apparent treatment-resistant hypertension is difficult to determine. Studies have shown it ranging from 3% to 86%, with a pooled estimate of 31% in a meta-analysis.

Medication adherence can also be difficult to address, but several techniques have been studied. Some laboratories offer serum and urine assays to detect metabolites of antihypertensive drugs, and pharmacy-based assessments include pharmacy fill history and pill counting. Directly observed therapy has been shown to reduce resistant hypertension by 29%. Each of these methods has limitations such as inaccuracies in patient reporting and physician interviewing, as well as the impracticality and cost of directly observing therapy or measuring drug metabolites.

Ensuring that patients understand their medication instructions and involving them in shared decision-making are important to improve adherence.

Are the measurements accurate?
Measuring blood pressure accurately requires proper technique, proper cuff size, and use of validated devices.

Automated office blood pressure monitoring devices are favored over conventional manual auscultatory devices for office use. These devices are designed to take multiple blood pressure readings in one sitting.

In one study, the mean systolic blood pressure taken by automated office blood pressure devices was 11 mm Hg lower than those obtained with manual in-office devices, and the results from in-office automated devices were more consistent with those of ambulatory blood pressure monitoring.

Sources of inaccuracy with auscultatory blood pressure measurement include inadequate operator skill, inability to hear Korotkoff sounds, and terminal digit bias. If you measure blood pressure using the auscultatory technique, you should pay careful attention to operator training, proper cuff size, and technique. Aneroid sphygmomanometers require more frequent calibration than oscillatory machines.

What is the patient’s blood pressure out of the office?
Current guidelines recommend measuring blood pressure out of the office to complement in-office measurement to control hypertension, but not as the sole measurement. It can improve diagnostic accuracy and help detect other forms of hypertension such as white-coat or masked hypertension (see discussion below). Two monitoring methods are used: ambulatory and self-measured.

Self-measurement means the patient takes their blood pressure at regular times during the day. While there is no consensus on the optimal schedule for checking blood pressure at home, 2 to 3 consecutive measurements can be performed twice daily in the morning and evening, for a minimum of 3 and ideally 5 to 7 consecutive days every month. We recommend measuring blood pressure before taking antihypertensive medications to better assess control.

Ambulatory monitoring records blood pressure over a 24-hour period. An advantage is its ability to measure nocturnal blood pressure. Blood pressure normally dips by 10% to 20% during sleep, and patients who are “nondippers” are at higher risk of cardiovascular events.

White-coat hypertension is elevated in-office blood pressure readings with normal out-of-office blood pressure in a person not being treated with antihypertensive medication (Table 2). In contrast, the white-coat effect is the same pattern in a person who...
is receiving treatment for hypertension. The white-coat effect may be seen in 28% to 39% of those with resistant hypertension.

Untreated white-coat hypertension is associated with a higher risk of cardiovascular events compared with sustained normotension. In contrast, in a recent meta-analysis, patients with the white-coat effect (ie, on treatment, with normal blood pressures at home but high blood pressure in the office) showed no increase in cardiovascular risk compared with those with controlled hypertension.

Masked hypertension is normal office blood pressure readings but elevated out-of-office readings. Patients with masked hypertension are at higher risk of cardiovascular events than normotensive patients or those with white-coat hypertension.

**Table 2**

**Patterns of in-office and out-of-office blood pressure in treated hypertension**

<table>
<thead>
<tr>
<th>Out-of-office blood pressure (by daytime ambulatory or home blood pressure monitoring)</th>
<th>Normal</th>
<th>High*</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-office blood pressure</td>
<td>High*</td>
<td>Uncontrolled hypertension</td>
</tr>
<tr>
<td>Normal</td>
<td>Controlled hypertension</td>
<td>Masked uncontrolled hypertension</td>
</tr>
</tbody>
</table>

*Blood pressure 130/80 mm Hg or higher.

Adapted from information in reference 7.

**Does the patient have lifestyle factors that raise blood pressure?**

**Obesity**

The relationship between increased adiposity and elevated blood pressure has been well established. NHANES participants who had a body mass index of 30 kg/m² or higher were twice as likely to have resistant or apparent treatment-resistant hypertension.

Pathogenic mechanisms of obesity-related hypertension include increased salt sensitivity, increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone system, and aldosterone secretion by adipose tissue. Of these mechanisms, aldosterone secretion by adipose tissue is the only one that is obesity-specific, as the others can also occur in diseases such as chronic kidney disease and heart failure.

In hypertensive adults in NHANES, ACE inhibitors and ARBs had a more pronounced antihypertensive effect in women with obesity than in women without obesity. This effect was not seen in men. However, there are currently no blood pressure guidelines that have specific medication recommendations for patients with obesity vs nonobesity.

**The amount of sodium in the diet**

Dietary sodium increases blood pressure. This effect may not occur in all people, but certain groups are more salt-sensitive, including older adults, Black people, and patients with chronic kidney disease.

In a randomized crossover trial in 12 patients with resistant hypertension, reducing dietary sodium from 250 mmol/day (5,750 mg) per day for 1 week to 50 mmol (1,150 mg) per day for 1 week lowered office systolic blood pressure by 22.7 mm Hg (95% confidence interval −33.5 to −11.8; P = .008). Patients with resistant hypertension had more significant blood pressure reductions than other patients with hypertension or the general population, suggesting salt sensitivity may play a bigger role in the pathogenesis of resistant hypertension and reinforcing the importance of including a diuretic in the treatment plan.

Patients should be counseled to adhere to a diet with less than 2 g of sodium per day (5 g of table salt) in addition to the DASH (Dietary Approaches to Stop Hypertension) diet, which is low in sodium and rich in fruit, vegetables, and low-fat dairy products, as the combination of these 2 was shown to be more effective than either alone.

**Recommended exercise**

Aerobic exercise has been shown to reduce blood pressure in patients with hypertension and resistant hypertension. Patients with resistant hypertension who enrolled in a treadmill exercise program of 8 to 12 weeks lowered their daytime systolic ambulatory blood pressure by 5.9 mm Hg (± 11.6 mm Hg; P = .03). In another study, those who exercised for 60
minutes in a heated pool 3 times per week for 2 weeks experienced a reduction of 12 mm Hg in 24-hour ambulatory systolic blood pressure and a reduction of 9 mm Hg in diastolic blood pressure.31

Patients should engage in at least 150 minutes per week of moderate-intensity aerobic exercise or 75 minutes per week of vigorous aerobic activity.2 Both isometric and dynamic-resistance exercise have been shown to lower blood pressure, presenting other options for patients with limited mobility who cannot do aerobic exercise.1

Alcohol consumption
Regular alcohol consumption has been shown to increase blood pressure by 1 mm Hg for every 10 g of alcohol consumed (approximately 1 standard drink), an effect that is reversible within a few weeks of cessation.32

Smoking, chewing, vaping
Nicotine, most commonly contained in cigarettes, vaping fluid, and smokeless tobacco, causes an acute rise in blood pressure.33 Cessation should be recommended to all patients in general, and especially to those with resistant hypertension to ameliorate their already increased risk of cardiovascular events.

Nonsteroidal anti-inflammatory drugs can raise blood pressure by 2 to 5 mm Hg at any dose high enough to relieve pain

IS THE PATIENT TAKING MEDICATIONS THAT RAISE BLOOD PRESSURE?

Medications that can raise blood pressure include the following:2
- Nonsteroidal anti-inflammatory drugs, including cyclo-oxygenase 2 inhibitors. These drugs are ubiquitous and can raise blood pressure at any dose high enough to relieve pain, by 2 to 5 mm Hg34,35; importantly, low-dose aspirin is not associated with blood pressure elevation36
- Glucocorticoids
- Serotonin-norepinephrine reuptake inhibitors
- Estrogen-containing contraceptives and other estrogen-containing medications; the blood pressure effects of these medications are typically reversible when the medication is stopped
- Sympathomimetics (pseudoephedrine, ephedrine, cocaine, amphetamine)
- Vascular endothelial growth factor inhibitors
- Erythropoietin-stimulating agents
- Calcineurin inhibitors (cyclosporine, tacrolimus);

blood pressure elevation with calcineurin inhibitors is typically treated with calcium channel blockers
- Tyrosine kinase inhibitors
- Dietary supplements, including ginseng and licorice.

The degree of blood pressure effect from these medications may vary widely from person to person.

EVALUATE FOR SECONDARY HYPERTENSION

Patients with resistant hypertension should be evaluated for secondary hypertension, since recognition and directed therapy may improve blood pressure control. In this section, we discuss common causes of secondary hypertension, the clinical context in which they should be suspected, and the basic screening for each.

Kidney parenchymal disease
Hypertension is both a cause and a consequence of chronic kidney disease and is common in this patient population.37 Of 3,612 patients participating in the Chronic Renal Insufficiency Cohort study,38 85.7% had a diagnosis of hypertension at their baseline visit. Fewer than half (46.1%) had their blood pressure lower than 130/80 mm Hg.38

Proposed mechanisms of hypertension in kidney disease include an upregulated renin-angiotensin-aldosterone system, increased salt and fluid retention, endothelial dysfunction, and increased sympathetic nervous system activity.39

Kidney disease should be assessed and considered as a risk factor for resistant hypertension in patients with an elevated serum creatinine or abnormal urinalysis.

Primary aldosteronism
Primary aldosteronism (ie, hyperaldosteronism) is due to autonomous hypersecretion of aldosterone. Excess circulating aldosterone leads to salt and water retention and renal potassium wasting, which results in hypertension and cardiovascular disease.40

Primary aldosteronism is more common than previously thought and often goes undiagnosed, with a prevalence ranging from 8% to 30% in various hypertensive populations.41 Hypokalemia as a result of renal potassium wasting is present in only 9% to 37% of patients who have primary aldosteronism, so this disease can be underrecognized.42

Measuring the plasma aldosterone-to-renin ratio is the test most often used to screen for primary aldosteronism. However, this test has the potential for false-positive and false-negative results, depending on whether patients are taking medications that interfere
Obstructive sleep apnea with CPAP is recommended to reduce the risk of other cardiovascular complications, a meta-analysis found only a modest reduction of 2.46 mm Hg in systolic blood pressure. Obesity and obstructive sleep apnea are both risk factors for resistant hypertension, but a study that looked at the effect of CPAP therapy on blood pressure in patients with obesity vs those without obesity found no significant difference between the groups.

Given the high prevalence of obstructive sleep apnea in those with resistant hypertension, screening for it should be common in this population. Screening tools such as the STOP-BANG score can help risk-stratify patients who have suggestive symptoms and who should be tested with polysomnography, the gold standard for diagnosis. (STOP-BANG consists of 8 factors, which spell the acronym: snoring, tired or sleepy during the day, observed stopping breathing while sleeping, high blood pressure, body mass index higher than 35 kg/m², age older than 50, neck circumference ≥ 17 inches if a man or ≥ 16 inches if a woman, and male gender. If 3 or more factors are present, the patient has a high risk of obstructive sleep apnea.)

Renovascular hypertension
Renovascular hypertension is a syndrome of elevated blood pressure due to diminished renal arterial blood flow resulting in kidney ischemia. It is most commonly caused by atherosclerosis of the renal arteries, but other pathologic processes include fibromuscular dysplasia, renal artery infarct or dissection, and vasculitis.

The diagnosis of renal artery stenosis includes imaging with duplex ultrasonography, computed tomography angiography, or magnetic resonance angiography. At least 70% of the renal artery must be stenosed before the lesion can be considered to be causing the hypertension.

Atherosclerotic renovascular disease is considered a coronary artery disease equivalent, and its treatment consists of medical management focused on blood pressure, lipid and glucose control, and antiplatelet therapy. Percutaneous revascularization should generally be considered in patients with the following high-risk features:
- Recurrent heart failure or unexplained flash pulmonary edema
- Resistant hypertension with failure of optimal medical management
- Unexplained rapid decline in glomerular filtration rate
- Bilateral renal artery stenosis or a single functioning kidney with stenosis associated with any of the above.
Other endocrinopathies

Catecholamine-secreting tumors such as pheochromocytomas and paragangliomas are rare causes of hypertension, accounting for 0.2% to 0.6% of cases, but are associated with significant mortality risk. Symptoms that should prompt screening include paroxysmal headaches, diaphoresis, and tachycardia.52

The 2014 Endocrine Society guidelines recommend screening by measuring either plasma free metanephrines or 24-hour urine fractionated metanephrines. Patients who have plasma metanephrines measured should lie supine for at least 30 minutes before sampling. Normetanephrine and metanephrine levels 3 or more times higher than the upper limit of normal are highly suggestive of a catecholamine-producing tumor.

Medications that can lead to elevated levels of metanephrines and catecholamines include tricyclic antidepressants, amphetamines, monoamine oxidase inhibitors, and levodopa, and withdrawal from clonidine can have the same effect.

Cushing disease or syndrome (hypercortisolism from glucocorticoid excess) is a relatively uncommon cause of resistant hypertension. Cushing syndrome is a constellation of symptoms that classically include glucose intolerance, acne, osteoporosis, obesity, menstrual changes, hirsutism, muscle wasting, and moon facies. Interestingly, in one study, 26.5% of patients with resistant hypertension but no overt signs and symptoms of Cushing syndrome had biochemical evidence of hypercortisolism,53 suggesting that clinicians should consider testing for it in patients without the classic syndrome. Patients should be screened by measuring the 24-hour urine cortisol level or late-night salivary cortisol level, or by a low-dose dexamethasone suppression test.

Less common endocrine disorders that can contribute to resistant hypertension include disorders of the thyroid and parathyroid glands. Thyroid-stimulating hormone should be checked in those with difficult-to-control hypertension. Testing for primary hyperparathyroidism should be considered in any patient presenting with hypercalcemia.

Management of Resistant Hypertension

All patients diagnosed with resistant hypertension should be screened for causes of secondary hypertension based on history, physical findings, and individual risk factors. A multifactorial approach to treat resistant hypertension includes a combination of lifestyle modification, pharmacotherapy, and addressing underlying contributing diseases.

Patients with resistant hypertension should be screened for end-organ damage—eg, with serum creatinine and urinalysis to look for kidney disease, electrocardiography or echocardiography to assess for left ventricular hypertrophy, and an ophthalmologic examination to look for hypertensive retinopathy.

Pharmacologic therapy

Prescribing antihypertensive therapy begins with identifying comorbidities that require first-line agents that have a compelling indication, such as beta-blockers for heart failure, history of myocardial infarction, or aortic dissection, or drugs that block the renin-angiotensin-aldosterone system for proteinuria.

The initial pharmacologic approach to resistant hypertension consists of 3 medications, each mechanistically different, at maximally tolerated doses, as follows:

- An ACE inhibitor or ARB (ARBs may better tolerated than ACE inhibitors, as they do not carry the same risk of angioedema or cough, and some experts recommend them as initial therapy over ACE inhibitors54)
- A long-acting dihydropyridine calcium channel blocker
- A diuretic.

In patients with preserved glomerular filtration rate, the preferred first-line diuretic is either chlorothalidone or indapamide because of their longer half-life and more potent antihypertensive effect compared with hydrochlorothiazide.55,56 Loop diuretics are preferred in patients with an estimated glomerular filtration rate less than 30 mL/min/1.73 m². Torsemide can be used once a day, but shorter-acting loop diuretics such as furosemide or bumetanide must be dosed at least twice a day.1 A recent randomized controlled trial showed that chlorthalidone was effective in those with an estimated glomerular filtration rate of 15 to 30 mL/min/1.73 m², thus representing another available agent in this population.57

If blood pressure is still not controlled on maximally tolerated therapy with these 3 agents, a mineralocorticoid receptor antagonist (spironolactone or eplerenone) should be the fourth-line agent. The PATHWAY-2 trial7 demonstrated that spironolactone was superior in reducing blood pressure compared with bisoprolol (a beta-blocker), doxazosin (an alpha-blocker), or placebo as add-on therapy in patients with resistant hypertension on 3 blood pressure medications.57

Side effects of spironolactone include hyperkalemia and gynecomastia, and the drug should be used with caution in chronic kidney disease. If gynecomastia becomes intolerable, spironolactone can be switched to eplerenone, a selective aldosterone recep-
tor antagonist that has minimal interaction with sex hormone steroid receptors. However, spironolactone is preferred since it has been extensively studied, costs less, and requires only daily dosing because of its longer half-life compared with eplerenone.58

The addition of other agents should be based on individual factors. Vasodilating beta-blockers (labetalol, carvedilol, nebivolol, bisoprolol) may be the preferred fifth-line agent. Other choices include clonidine, a centrally acting alpha-2 agonist. Clonidine can be given as a transdermal patch to improve adherence, minimize frequent oral dosing, and lower the risk of rebound hypertension.

According to the AHA guidelines, if blood pressure is still not at goal, hydralazine may be initiated at a starting dose of 25 mg 3 times a day, with the addition of a nitrate in the presence of heart failure if adherence is still not at goal, hydralazine may be initiated at a starting dose of 25 mg 3 times a day, with the addition of a nitrate in the presence of heart failure.

Recent studies have shown that aldosterone synthase inhibitors and dual endothelin antagonists may be effective in resistant hypertension. While neither are approved at this time by the US Food and Drug Administration (FDA) for this indication, these agents may represent additional treatment options upon further study.59,60

Patients should be referred to a hypertension specialist if blood pressure remains uncontrolled despite the above therapies.

Devices and next steps
Experimental devices and other therapies are currently being explored in patients with resistant hypertension. Renal denervation to blunt sympathetic tone showed no benefit in the Renal Denervation in Patients With Uncontrolled Hypertension (SYMPLECTITY HTN-3) study.61 The Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN TRIO),62 utilizing a newer catheter design and a stricter medication protocol, demonstrated a decrease of 5.8 mm Hg compared with controls, a modest benefit.62

Other experimental therapies aimed at sympathetic tone modulation include carotid baroreceptor activation therapy and carotid baroreceptor amplification therapy. None of these device therapies are currently FDA-approved, and more studies are needed to determine their long-term efficacy and safety.

DISCLOSURES
Dr. Calle has disclosed being an advisor or review panel participant for Precision Biosciences, and teaching and speaking for Travere Therapeutics. Dr. Taliercio has disclosed being an advisor or review panel participant for Otsuka Pharmaceuticals. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES
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