VOLUME 90 • NUMBER 2 • FEBRUARY 2023 • www.ccjm.org

CME MOC

Cleveland Clinic Journal of Medicine

Myasthenia gravis: An update for internists

Oral leukoplakia and oral cancer

Treatment options for myasthenia gravis if first-line agents fail

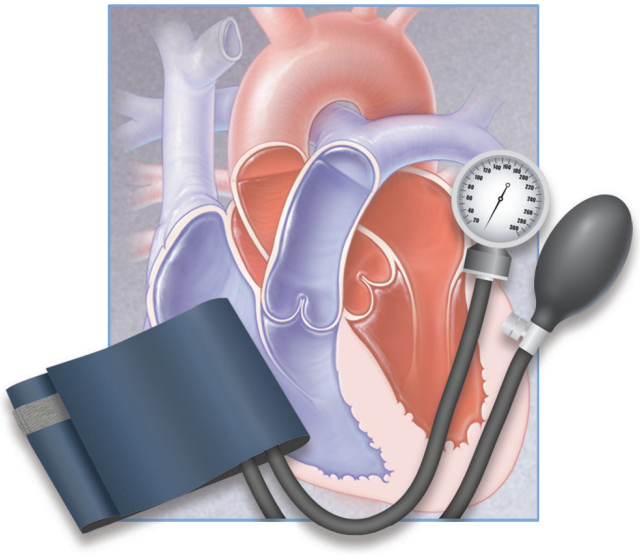
The constellation of vitamin D, the acute-phase response, and infl ammation

A metabolic bone disease perspective on vitamin D

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

Myasthenia gravis: Frequently asked questions

Resistant hypertension: A stepwise approach



CLEVELAND CLINIC JOURNAL OF MEDICINE

ADVERTISING
Sima Sherman, Director of Sales and Marketing
SHERMAN MEDICAL MARKETING GROUP
1628 John F. Kennedy Blvd., #2200, Philadelphia, PA 19103
(610) 529-0322 • sima@shermanmmg.com

SUBSCRIPTIONS
U.S. and possessions: Personal $160; institutional $188; single copy/back issue $20

Foreign: $205; single copy/back issue $20

Institutional (multiple-reader rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

Please make check payable to *Cleveland Clinic Journal of Medicine* and mail to: Cleveland Clinic Education Foundation, P.O. Box 373291, Cleveland, OH 44193-3291. To purchase a subscription with a credit card, please visit www.ccjm.org.

REPRINTS
(610) 529-0322 • sima@shermanmmg.com

PHOTOCOPYING
Authorization to photocopy items for internal or personal use is granted by *Cleveland Clinic Journal of Medicine* (ISSN 0891-1150 [print], ISSN 1939-2869 [online]), published by Cleveland Clinic, provided that the appropriate fee is paid directly to Copyright Clearance Center, 222 Rosewood Drive, Danvers, MA 01923 USA (978) 750-8400. Prior to photocopying items for educational classroom use, please contact Copyright Clearance Center, Inc., at the address above. For permission to reprint material, please fax your request with complete information to the Republication department at CCC, fax (978) 750-4470. For further information visit CCC online at www.copyright.com. To order bulk reprints, see above.

CHANGE OF ADDRESS
To report a change of address, send a recent mailing label along with new information to:

AMA, Data Verification Unit, 330 N. Wabash Ave., Suite 39300, Chicago, IL 60611-5885 • Phone (800) 621-8335 • Fax (312) 464-4880 • dpprodjira@ama-assn.org

Cleveland Clinic Journal of Medicine uses the AMA database of physician names and addresses. The database includes all US physicians and not just AMA members. Only the AMA can update changes of address and other data.

SUBSCRIPTIONS, EDITORIAL, BILLING, AND PRODUCTION
9500 Euclid Avenue, JJ44, Cleveland, OH 44195 • Phone (216) 444-2661 • Fax (216) 444-9385 • ccjm@ccf.org • www.ccjm.org

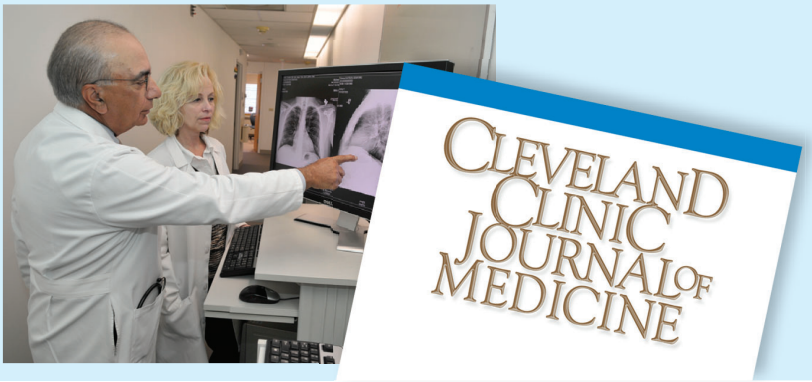
Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic at 9500 Euclid Avenue, JJ44, Cleveland, OH 44195.

Table of Contents

CONTINUED ON PAGE 70

Upcoming Features

- Variola virus: Looking back, looking ahead
- Contraception options: A case-based discussion



CONTINUED FROM PAGE 68

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.

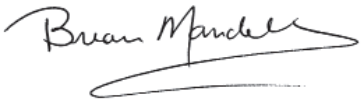
Morren and co-authors in 2 papers in this issue of *The Journal*[1,2] discuss the diagnosis of MG and some of the nuances of treatment.

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

doi:10.3949/ccjm.90b.02023

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.[3] 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,[1] 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.[1] However, caution should be paid particularly to prescribing antibiotics including aminoglycosides, fluoroquinolones, and some macrolides.



Brian F. Mandell, MD, PhD
Editor in Chief

1. **Morren JA, Li Y.** Myasthenia gravis: frequently asked questions. Cleve Clin J Med 2023; 90:103–113. doi:10.3949/ccjm.90a.22017
2. **Zust C, Morren JA.** What are the treatment options for myasthenia gravis if first-line agents fail? Cleve Clin J Med 2023; 90:81–84. doi:10.3949/ccjm.90a.22022
3. **Dalakas MC.** Role of complement, anti-complement therapeutics, and other targeted immunotherapies in myasthenia gravis. Expert Rev Clin Immunol 2022; 18(7):691–701. doi:10.1080/1744666X.2022.2082946

Cleveland Clinic | Comprehensive COVID Care

Participate in an interdisciplinary educational resource for the care of COVID-19 patients

Learn best practices in current therapy and rapidly evolving management strategies for COVID-19 patients

Review new safety protocols and procedures that ensure the safety of caregivers and patients in a COVID-19 environment

Attain key concepts pertinent to inpatient management of COVID and Non-COVID medical care for physicians preparing for redeployment

Access Just-in-Time care management guides for quick and easy referencesvon diagnosis and strategies for patient care treatment.

Participate Today! **healthcareedu.ccf.org**

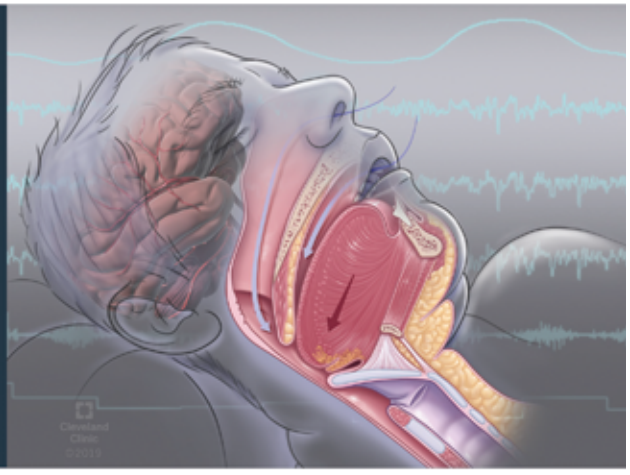
These activities have been approved for *AMA PRA Category 1 Credit™*

Cleveland Clinic

Obstructive Sleep Apnea:

A Cleveland Clinic State-of-the-Art Review

CME-Certified Online Series



Participate in the complimentary Obstructive Sleep Apnea: A Cleveland Clinic State-of-the-Art Review online series for an in-depth review of OSA, including screening, diagnosis, and therapy. Via on-demand webcasts and text-based articles, learn how Cleveland Clinic faculty quickly and effectively identify OSA and treat patients.

Watch the webcasts and read the Cleveland Clinic Journal of Medicine Online Journal Supplement

Obstructive Sleep Apnea Basics

Want to know the symptoms, risk factors and prevalence of OSA? **Jessica Vensel Rundo, MD, MS,** discusses screening tools that can be used to assess for OSA risk.

Sleep Apnea and the Heart

Are you able to identify the physiology of sleep-heart interactions? **Reena Mehra, MD, MS**, describes the association of OSA and cardiovascular health.

Beyond Heart Health: Consequences of Obstructive Sleep Apnea

Ever wondered about the relationship between OSA and metabolic disease, and OSA and cognitive impairment? **Harneet K. Walia, MD**, presents OSA's impact on one's quality of life.

Positive Airway Pressure: Making an Impact on Sleep Apnea

Do you know the newest clinical trials and large observational studies related to PAP therapy for OSA? **Colleen G. Lance, MD**, discusses advanced PAP therapies, as well as the problem achieving PAP adherence.

Treatment of Obstructive Sleep Apnea: Alternatives to PAP Therapy

Want to know alternatives to PAP therapy? **Tina Waters, MD**, highlights conservative option, surgical interventions, oral appliance therapy, and nasal expiratory positive airway pressure therapy.

View Today!

ccfcme.org/sleepapnea

These activities have been approved for *AMA PRA Category 1 Credit™*.

19-EDU-1751626

Cleveland Clinic

Improve Your Virtual Patient Visit Skills

Many patients are eager to visit their physicians virtually, but not all physicians are comfortable conducting virtual visits.

You can take advantage of a free series of self-directed online modules to help you build your virtual patient visit skills.

The free course offers:

- brief introduction to virtual visits
- guidance for demonstrating communication and empathy
- best practices for taking a patient history
- instructions for conducting a physical examination, based on organ system

To help you master the content, the free course includes many video demonstrations and knowledge checks throughout.

Visit clevelandclinic.org/virtual-training

With the exception of the physical examination module, these activities have been approved for *AMA PRA Category 1 Credit™.*

2023

FEBRUARY

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: COACHING AND MENTORING ESSENTIALS FOR HEALTHCARE PROFESSIONALS
February 1–2
Live stream

VALVE DISEASE, STRUCTURAL INTERVENTIONS, AND DIASTOLOGY/IMAGING SUMMIT
February 2–5
Miami Beach, FL

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: HEALTHCARE PROFESSIONALS COACH TRAINING
February 8–9
Live stream

MANAGEMENT OF CHECKPOINT INHIBITOR-RELATED TOXICITY
February 9–10
Cleveland, OH

BREAST CANCER UPDATE: REVIEW OF BREAST CANCER SYMPOSIA
February 15
Independence, OH

ADVANCES IN CONGENITAL HEART DISEASE SUMMIT
February 16–18
Orlando, FL

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) SPECIALIST COURSE
February 20–22
Cleveland, OH

BASIC AND CLINICAL IMMUNOLOGY FOR THE BUSY CLINICIAN
February 25–26
Scottsdale, AZ

MARCH

INTERNATIONAL PTEN SYMPOSIUM: FROM PATIENT-CENTERED RESEARCH TO CLINICAL CARE
March 27
Cleveland, OH

COMPREHENSIVE CARE FOR THE LIFETIME TREATMENT OF ADULT CONGENITAL HEART DISEASE
March 31– April 1
Chicago, IL

APRIL

IBD MASTER CLASS: THE CLEVELAND CLINIC MEDICAL AND SURGICAL TEAM APPROACH TO COMPLEX IBD
April 3–4
Live stream

SOUTHWESTERN CONFERENCE ON MEDICINE
April 13–16
Tucson, AZ

EASE YOUR WAY INTO THE ESOPHAGUS
April 14
Cleveland, OH

LEARN TO DIAGNOSE MALNUTRITION: CLEVELAND CLINIC MALNUTRITION WORKSHOPS 2023
April 26
Cleveland, OH

MAY

BIOLOGIC THERAPIES SUMMIT X AND VASCULITIS 2023
May 11–13
Cleveland, OH

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: COACH APPROACH TO THE ANNUAL PROFESSIONAL REVIEW
May 17–18
Live stream

DIABETES DAY
May 18
Cleveland, OH, and live stream

JUNE

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 12–16
Live stream

JULY

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

AUGUST

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

PEDIATRIC BOARD REVIEW
August 27–September 1
Cleveland, OH

SEPTEMBER

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

INNOVATIONS IN NEUROSCIENCE
September 8
Cleveland, OH

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

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

GLOBAL EP
September 29–30
Cleveland, OH

MIDWEST GLAUCOMA SYMPOSIUM
September 30
Cleveland, OH

OCTOBER

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

NOVEMBER

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

FOR SCHEDULE UPDATES AND TO REGISTER, VISIT: WWW.CCFCME.ORG/LIVE

OUR PEER-REVIEWERS FOR 2022

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.

—Brian F. Mandell, MD, PhD, Editor in Chief

Ahmed, Zubair
Alfes, John
Allareddy, Raghavendra R.
Altman, Andrew
Alvarez, Paulino
Anand, Akhil
Anthony, John Scott
Arbesman, Joshua
Arobelidze, Salome
Aronica, Mark A.
Aronowitz, Paul
Auron, Moises
Azok, Joseph Thomas
Bagga, Shiv
Baggott, Brian
Bakaeen, Faisal
Baker, Mark E.
Banda, Kanakalingeswara
Barbastefano, Juan
Bartnicki, Rebecca
Bartolomeo, Korey
Batur, Pelin
Bautista, Jan
Beck, Avi
Bedsole, Russell
Beer Furlan, Andre
Benedetto, Paul X.
Bernstein, Eden
Bhat, Pavan
Bindra, Akhil
Bishop, G. Jay
Borghei-Razavi, Hamid
Brant, Ashley
Brateanu, Andrei
Bravo, Lulette Tricia
Brotman, Daniel J.
Butsch, W. Scott
Cable, Christian
Cain, Robert A.
Callahan, Thomas
Carey, William D.
Castro, Fernando
Cetin, Derrick C.
Chaisson, Neal
Chandra Prakash, Aparna
Claeys, Kimberly
Clauw, Daniel
Clemons, Anne
Cohn, Steven L.
Cordova, Christine
Correa Marquez, Ricardo
Cove, Matthew
Crone, Timothy
Curtis, Gregory
Dean, Robert M.
Delgado, Glenda
Demirjian, Sevag
Dober, Gregory
Dugar, Siddarth
Duran Crane, Alejandro
Dutton, Wesley Paul
Eidelman, Frank J.
El Hage, Lea
Estela Cubells, José Ramón
Factora, Ronan M.
Fares, Maan
Farrar, Jennifer
Faulx, Michael D.
Feldman, Myra
Fendrikova Mahlay, Natalia
Feng, Jenny
Feyda, George
Finet, J. Emanuel
Fiocchi, Claudio
Freiberg, Marina
Fu, Kathy
Fuchs, Margaret
Funchain, Pauline
Gall, Nicholas Peter
Gambir, Harvir Singh
Ganesh, Santosh Yatam
Gans, William
Garber, Ari
Gilligan, Timothy
Gnanapandithan, Karthik
Goldfarb, Johanna
Graham, Ruffin J.
Grossman, Shamai
Gyawali, C. Prakash
Habib, Ali A.
Hajji, Raouf
Hanks, Justin G.
Hanna, Mazen
Harano, Yoshihiro
Hoogwerf, Byron J.
Jacob, Ceena Neena
Jneid, Hani
Johnson, Danielle
Kapoor, Aanchal
Keller, David L.
Kent, Brian D.
Kerns, Michelle
Khawam, Elias
Khorana, Alok
Koncilja, Kenneth
Kransdorf, Lisa N.
Laffin, Luke J.
Lashner, Bret
Le, Phuc
Lee, Byron
Licata, Angelo
Lindenmeyer, Christina C.
Lipman, Jeremy
Litwinowicz, Kamil
Lyden, Sean P.
Mankaney, Gautam
Manne, Mahesh B.
Massoud, Omar
Mauer, Yael
Mayock, Robert T.
McCoy, Dalia
McGannon, Peter
McLafferty, Scott
McWilliams, Carla
Mehta, Atul C.
Mendlovic, Daniel
Mikhli, Paul
Miller, Ryan
Modha, Kunjam
Morey Vargas, Oscar
Morgan, Daniel J.
Murthy, Neil
Nasr, Christian
Ng, Henry H.
Nielsen, Craig D.
Nissen, Steven E.
Nussenblatt, Veronique
Olansky, Leann
Paladugu, Srikanth
Peereboom, David M.
Perez, Rolando
Piliang, Melissa P.
Podolsky, Seth
Post, Stephen G.
Pozuelo, Leopoldo
Prabhakaran, Anbazhagan
Punia, Vineet
Reaves, Cristina B.
Reddy, Aswanth
Remer, Erick M.
Richardville, Kyle
Rincon-Choles, Hernan
Rogers, Nick
Rosen, Harold Noah
Rosenquist, Richard Wayne
Ruggieri, Paul M.
Rutecki, Gregory
Ruzhansky, Katherine
Schils, Jean P.
Schimmel, Jennifer Jaye
Schmitt, Steven K.
Sekar, Arjun
Shoemaker, Laura Kay
Shrestha, Nabin K.
Siegel, Allison
Silver, Bernard J.
Singh, Katherine
Snyder, Sandra M.
So, Richard
Solomon, Glen D.
Soni, Payal
Sossai, Paolo
Sroubek, Jakub
Steiger, Ezra
Stevens, Tyler
Stillman, Alexandra Marion
Streem, David
Stubbe, Hermann
Sumego, Marianne J.
Sutton, Jazmine
Taege, Alan J.
Tchang, Beverly G.
Thacker, Holly
Thomas, George
Thomas, Holly
Thornhill, Martin
Thota, Prashanthi
Timen, Micah
Tough DeSapri, Kristi
Tovoli, Francesco
Traboulsi, Elias I.
Tuck, Matthew
Umeda, Naoki
Unwala, Rashmi
Walsh, R. Matthew
Weitz, Howard H.
Wilson, Robert
Wilson, Stephen
Wojtkowski, Andrew
Woodson, Erika A.
Yadav, Manajyoti
Young, Bessie

Takeshi Onda, DDS, PhD
Department of Oral and Maxillofacial Surgery, Tokyo Dental College, Tokyo, Japan

Kamichika Hayashi, DDS, PhD
Department of Oral and Maxillofacial Surgery, Tokyo Dental College, Tokyo, Japan

Akira Katakura, DDS, PhD
Department of Oral Pathological Science and Surgery, Tokyo Dental College, Tokyo, Japan

Masayuki Takano, DDS, PhD
Department of Oral and Maxillofacial Surgery, Tokyo Dental College, Tokyo, Japan

Oral leukoplakia and oral cancer

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.

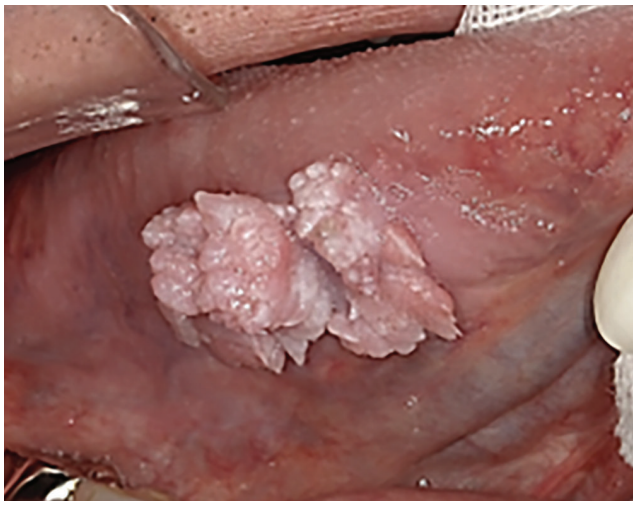


Figure 1. White lesions were observed on the right tongue edge. Papillary cell proliferation was noted in the same area.

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.[1] Nearly 90% of all oral cancers are squamous cell carcinoma, and major risk factors are chronic irritation, smoking, and alcohol consumption.[2]

Most oral cancers have a premalignant lesion stage.[3] 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%.[4] This transformation depends on factors such as sex, age, clinical type, locus, onset mode, and the presence or absence of epithelial atypia,[5] 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. ■

doi:10.3949/ccjm.90a.22044

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

1. **Omura K.** Current status of oral cancer treatment strategies: surgical treatments for oral squamous cell carcinoma. Int J Clin Oncol 2014; 19(3):423–430. doi:10.1007/s10147-014-0689-z
2. **Abati S, Bramati C, Bondi S, Lissoni A, Trimarchi M.** Oral cancer and precancer: a narrative review on the relevance of early diagnosis. Int J Environ Res Public Health 2020; 17(24):9160. doi:10.3390/ijerph17249160
3. **Yang SW, Lee YS, Chang LC, Yang CH, Luo CM, Wu PW.** Oral tongue leukoplakia: analysis of clinicopathological characteristics, treatment outcomes, and factors related to recurrence and malignant transformation. Clin Oral Investig 2021; 25(6):4045–4058. doi:10.1007/s00784-020-03735-1
4. **Evren I, Brouns ER, Poell JB, et al.** Associations between clinical and histopathological characteristics in oral leukoplakia. Oral Dis 2021; 10.1111/odi.14038. doi:10.1111/odi.14038
5. **Speight PM, Khurram SA, Kujan O.** Oral potentially malignant disorders: risk of progression to malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol 2018; 125(6):612–627. doi:10.1016/j.oooo.2017.12.011

Address: *Takeshi Onda, DDS, PhD, Department of Oral and Maxillofacial Surgery, Tokyo Dental College, 2-9-18, Kanda-Misakicho, Chiyoda-ku, Tokyo 101-0061, Japan; ondatake@tdc.ac.jp*

Christopher Zust, MD
Staff Neurologist, McLeod Neurological Associates, Florence, SC

John A. Morren, MD
Staff, Neuromuscular Center, and Program Director, Neuromuscular Medicine Fellowship, Neurological Institute, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

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.

doi:10.3949/ccjm.90a.22022

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[4] (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.[5] Minimal manifestation status is characterized as no functional limitations but some muscle weakness on examination.

TABLE 1
Ranking of therapies for acetylcholine receptor antibody-positive generalized myasthenia gravis

First-line	Pyridostigmine, prednisone, thymectomy[a]
Second-line	Azathioprine, mycophenolate mofetil, intravenous immunoglobulin
Third-line	Methotrexate, tacrolimus,[b] eculizumab,[c] ravulizumab,[c] efgartigimod,[c] plasmapheresis
Fourth-line	Rituximab, cyclosporine[b]
Fifth-line	Cyclophosphamide

[a]For certain patients with acetylcholine receptor antibody-positive generalized myasthenia gravis without thymoma (see reference 5).
[b]May be considered as an early treatment option, depending on clinical context.
[c]Newer agents with emerging data; may be considered as early treatment option for refractory acetylcholine receptor antibody-positive generalized myasthenia gravis, but cost may be prohibitive.

Based on information in references 5 and 6.

MANAGING CORTICOSTEROID THERAPY

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

Given the many potential adverse effects of long-term corticosteroid therapy, prednisone is carefully tapered to the lowest effective dose that maintains therapeutic benefit. Weaning should be started when MG symptoms have significantly improved but need not wait until maximal efficacy is reached. In most patients, improvement is achieved after several weeks of higher-dose corticosteroids. Weaning starts with a slow taper, ie, a dose reduction of 5 to 10 mg per month, until a daily dose of less than 5 mg is reached. At that point, a very slow taper of 1 mg per month may help to avoid relapse.[7]

The preferred goal of minimal but effective prednisone dosing is less than 7.5 mg daily, as this avoids most adverse effects of long-term corticosteroid use.[8,9] When a patient needs maintenance prednisone dosing greater than 7.5 mg daily, other nonsteroidal immunosuppressive therapies should be considered. Steroid "dipping" is a well-described phenomenon of paradoxical worsening of symptoms in some MG patients, with manifestations that range from mild symptoms to, less commonly, respiratory failure. Accordingly, 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 craniobulbar 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

TABLE 2
Clinical features of fatigable weakness in myasthenia gravis by region of involvement

Muscle group/region	Manifestation of fatigable weakness in myasthenia gravis
Ocular	Fluctuating ptosis (often asymmetrical, worsened by sustained upgaze) with or without variable diplopia Ptosis 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

clinician's hand, while the clinician provides resistance. Scoring is based on the conventional Medical Research Council scale for muscle strength.[10] 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.[11]
- **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-

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.

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

1. **Pascuzzi RM, Coslett HB, Johns TR.** Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. Ann Neurol 1984; 15(3):291–298. doi:10.1002/ana.410150316
2. **Sghirlanzoni A, Peluchetti D, Mantegazza R, Fiacchino F, Cornelio F.** Myasthenia gravis: prolonged treatment with steroids. Neurology 1984; 34(2):170–174. doi:10.1212/wnl.34.2.170
3. **Cosi V, Citterio A, Lombardi M, Piccolo G, Romani A, Erbetta A.** Effectiveness of steroid treatment in myasthenia gravis: a retrospective study. Acta Neurol Scand 1991; 84(1):33–39. doi:10.1111/j.1600-0404.1991.tb04899.x
4. **Morren J, Li Y.** Maintenance immunosuppression in myasthenia gravis, an update. J Neurol Sci 2020; 410:116648. doi:10.1016/j.jns.2019.116648
5. **Narayanaswami P, Sanders DB, Wolfe G, et al.** International consensus guidance for management of myasthenia gravis: 2020 update. Neurology 2021; 96(3):114–122. doi:10.1212/WNL.0000000000011124
6. **Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ.** Treatment of myasthenia gravis. Neurol Clin 2018; 36(2):311–337. doi:10.1016/j.ncl.2018.01.011
7. **Keesey JC.** Clinical evaluation and management of myasthenia gravis. Muscle Nerve 2004; 29(4):484–505. doi:10.1002/mus.20030
8. **Curtis JR, Westfall AO, Allison J, et al.** Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum 2006; 55(3):420–426. doi:10.1002/art.21984
9. **Huscher D, Thiele K, Gromnica-Ihle E, et al.** Dose-related patterns of glucocorticoid-induced side effects. Ann Rheum Dis 2009; 68(7):1119–1124. doi:10.1136/ard.2008.092163
10. **UK Research and Innovation.** Medical Research Council: aids to the examination of the peripheral nervous system. Updated January 15, 2016. https://www.ukri.org/publications/aids-to-the-examination-of-the-peripheral-nervous-system/ Accessed January 11, 2023.
11. **Juel VC.** Myasthenia gravis: management of myasthenic crisis and perioperative care. Semin Neurol 2004; 24(1):75–81. doi:10.1055/s-2004-829595
12. **Heldal AT, Eide GE, Romi F, Owe JF, Gilhus NE.** Repeated acetylcholine receptor antibody-concentrations and association to clinical myasthenia gravis development. PLoS One 2014; 9(12):e114060. Published 2014 Dec 2. doi:10.1371/journal.pone.0114060

Address: *John Morren, MD, Program Director, Neuromuscular Medicine Fellowship, Neurological Institute, S90, Cleveland Clinic 9500 Euclid Avenue, Cleveland, OH 44195; morrenj@ccf.org*

COMMENTARY

Maria J. Antonelli, MD
Assistant Professor of Medicine, Department of Medicine, Division of Rheumatology, Case Western Reserve University, MetroHealth Medical Center, Cleveland, OH

Irving Kushner, MD
Emeritus Professor of Medicine, Department of Medicine, Division of Rheumatology, Case Western Reserve University, MetroHealth Medical Center, Cleveland, OH

Murray Epstein, MD, FASN, FACP
Emeritus Professor of Medicine, Division of Nephrology and Hypertension, University of Miami Miller School of Medicine, Miami, FL

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?

doi:10.3949/ccjm.90a.22048

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]

TABLE 1
Recommendations for deficiency and inadequacy of 25-hydroxyvitamin D

Endocrine Society[3]	
Deficiency	< 20 ng/mL (< 50 nmol/L)
Insufficiency	21–29 ng/mL (52.5–72.5 nmol/L)
Sufficiency	30–100 ng/mL (75–250 nmol/L)
Institute of Medicine[4]	
At risk for deficiency	< 12 ng/mL (< 30 nmol/L)
At risk of inadequacy	12–19 ng/mL (30–49 nmol/L)
Sufficiency	20–50 ng/mL (50–125 nmol/L)
Concentration of possible concern	> 50 ng/mL (> 125 nmol/L)

- 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.[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.[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.[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.[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.[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.[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 defense[39] 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,[42,43] 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]

Based on the assumption that low 25(OH)D levels reflect nothing but less-than-optimal vitamin D status, clinical trials have been conducted, and more are in 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]

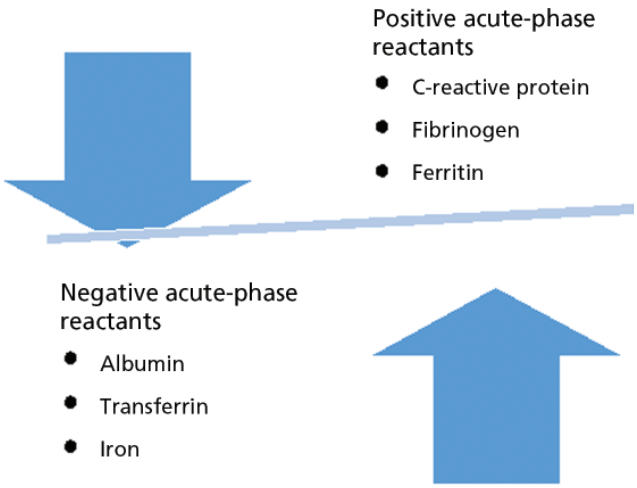


Figure 1. Examples of positive and negative acute-phase reactants.

Based on information in reference 30.

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 program[50] 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

disease, and pancreatitis) and recommends against testing in the general population. The Choosing Wisely campaign of the American Society for Clinical Pathology[51] 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 uncertainly 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.

***Acknowledgment**: We are grateful to Nathan Berger, MD, for his helpful comments.*

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.

REFERENCES

1. **Szabo L.** Vitamin D, the sunshine supplement, has shadowy money behind it. The New York Times. August 18, 2018. https://www.nytimes.com/2018/08/18/business/vitamin-d-michael-holick.html. Accessed January 6, 2023.
2. **Mordor Intelligence.** United States vitamin D supplements market—growth, trends, Covid-19 impact, and forecasts (2022–2027). https://www.mordorintelligence.com/industry-reports/united-states-vitamin-d-supplement-market-growth-trends-and-forecast. Accessed January 6, 2023.
3. **Holick MF, Binkley NC, Bischoff-Ferrari HA, et al.** Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline [published correction appears in J Clin Endocrinol Metab 2011; 96(12):3908]. J Clin Endocrinol Metab 2011; 96(7):1911–1930. doi:10.1210/jc.2011-0385
4. **Ross AC, Manson JE, Abrams SA, et al.** The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011; 96(1):53–58. doi:10.1210/jc.2010-2704
5. **Forrest KY, Stuhldreher WL.** Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res 2011; 31(1):48–54. doi:10.1016/j.nutres.2010.12.001
6. **Holick MF.** The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017; 18(2):153–165. doi:10.1007/s11154-017-9424-1
7. **Palacios C, Gonzalez L.** Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol 2014; 144 Pt A: 138–145. doi:10.1016/j.jsbmb.2013.11.003
8. **Antonelli M, Kushner I.** Low serum levels of 25-hydroxyvitamin D accompany severe COVID-19 because it is a negative acute phase reactant. Am J Med Sci 2021; 362(3):333–335. doi:10.1016/j.amjms.2021.06.005
9. **Waldron JL, Ashby HL, Cornes MP, et al.** Vitamin D: a negative acute phase reactant. J Clin Pathol 2013; 66(7):620–622. doi:10.1136/jclinpath-2012-201301
10. **Silva MC, Furlanetto TW.** Does serum 25-hydroxyvitamin D decrease during acute-phase response? A systematic review. Nutr Res 2015; 35(2):91–96. doi:10.1016/j.nutres.2014.12.008
11. **Ghashut RA, Talwar D, Kinsella J, Duncan A, McMillan DC.** The effect of the systemic inflammatory response on plasma vitamin 25(OH)D concentrations adjusted for albumin. PLoS One 2014; 9(3):e92614. doi:10.1371/journal.pone.0092614
12. **Amer M, Qayyum R.** Relation between serum 25-hydroxyvitamin D and C-reactive protein in asymptomatic adults (from the continuous National Health and Nutrition Examination Survey 2001 to 2006). Am J Cardiol 2012; 109(2):226–230. doi:10.1016/j.amjcard.2011.08.032
13. **Bellia A, Garcovich C, D'Adamo M, et al.** Serum 25-hydroxyvitamin D levels are inversely associated with systemic inflammation in severe obese subjects. Intern Emerg Med 2013; 8(1):33–40. doi:10.1007/s11739-011-0559-x
14. **Yang F, Sun M, Sun C, et al.** Associations of C-reactive protein with 25-hydroxyvitamin D in 24 specific diseases: a cross-sectional study from NHANES. Sci Rep 2020; 10(1):5883. doi:10.1038/s41598-020-62754-w
15. **Xu S, Song J, Zhang ZH, et al.** The vitamin D status is associated with serum C-reactive protein and adhesion molecules in patients with renal cell carcinoma. Sci Rep 2019; 9(1):16719. doi:10.1038/s41598-019-53395-9
16. **Jin D, Zhu DM, Hu HL, et al.** Vitamin D status affects the relation-

ship between lipid profile and high-sensitivity C-reactive protein. Nutr Metab (Lond) 2020; 17:57. doi:10.1186/s12986-020-00455-x
17. **Holick MF.** The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017; 18(2):153–165. doi:10.1007/s11154-017-9424-1
18. **Ginde AA, Mansbach JM, Camargo CA Jr.** Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 2009; 169(4):384–390. doi:10.1001/archinternmed.2008.560
19. **Agmon-Levin N, Theodor E, Segal RM, Shoenfeld Y.** Vitamin D in systemic and organ-specific autoimmune diseases. Clin Rev Allergy Immunol 2013; 45(2):256–266. doi:10.1007/s12016-012-8342-y
20. **Chandrakar AK, Alexander A, R M, Rajendiran K, Ramasamy K.** 25-hydroxyl vitamin D deficiency in nasal polyposis. Int Arch Otorhinolaryngol 2020; 24(3):e308–e312. doi:10.1055/s-0039-3399541
21. **Cheng S, Massaro JM, Fox CS, et al.** Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. Diabetes 2010; 59(1):242–248. doi:10.2337/db09-1011
22. **Savastano S, Barrea L, Savanelli MC, et al.** Low vitamin D status and obesity: role of nutritionist. Rev Endocr Metab Disord 2017; 18(2):215–225. doi:10.1007/s11154-017-9410-7
23. **Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB.** Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev 2015; 16(4):341–349. doi:10.1111/obr.12239
24. **Bang UC, Novovic S, Andersen AM, Fenger M, Hansen MB, Jensen JE.** Variations in serum 25-hydroxyvitamin D during acute pancreatitis: an exploratory longitudinal study. Endocr Res 2011; 36(4): 135–141. doi:10.3109/07435800.2011.554937
25. **Esnafoglu E, Subaşı B.** Association of low 25-OH-vitamin D levels and peripheral inflammatory markers in patients with autism spectrum disorder: vitamin D and inflammation in autism. Psychiatry Res 2022; 316:114735. doi:10.1016/j.psychres.2022.114735
26. **Vieira NFL, do Nascimento CQ, da Silva Nascimento J, Vasconcelos SML, Barros-Neto JA, Dos Santos ACO.** 25-hydroxyvitamin D insufficiency and inflammation increase cardiovascular risk in older people. Exp Gerontol 2022; 165:111864. doi:10.1016/j.exger.2022.111864
27. **Krishnan A, Ochola J, Mundy J, et al.** Acute fluid shifts influence the assessment of serum vitamin D status in critically ill patients. Crit Care 2010; 14(6):R216. doi:10.1186/cc9341
28. **Reid D, Toole BJ, Knox S, et al.** The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. Am J Clin Nutr 2011; 93(5):1006–1011. doi:10.3945/ajcn.110.008490
29. **Chakhtoura MT, Nakhoul NN, Shawwa K, Mantzoros C, El Hajj Fuleihan GA.** Hypovitaminosis D in bariatric surgery: a systematic review of observational studies. Metabolism 2016; 65(4):574–585. doi:10.1016/j.metabol.2015.12.004
30. **Gabay C, Kushner I.** Acute-phase proteins and other systemic responses to inflammation [published correction appears in N Engl J Med 1999; 340(17):1376]. N Engl J Med 1999; 340(6):448–454. doi:10.1056/NEJM199902113400607
31. **Louw JA, Werbeck A, Louw ME, Kotze TJ, Cooper R, Labadarios D.** Blood vitamin concentrations during the acute-phase response. Crit Care Med 1992; 20(7):934–941. doi:10.1097/00003246-199207000-00007
32. **Stephensen CB, Gildengorin G.** Serum retinol, the acute phase response, and the apparent misclassification of vitamin A status in the third National Health and Nutrition Examination Survey. Am J Clin Nutr 2000; 72(5):1170–1178. doi:10.1093/ajcn/72.5.1170
33. **Antonelli M, Kushner I.** It's time to redefine inflammation [published correction appears in FASEB J 2017; 31(7):3206]. FASEB J 2017; 31(5):1787–1791. doi:10.1096/fj.201601326R
34. **Hotamisligil GS.** Inflammation, metaflammation and immunometabolic disorders. Nature 2017; 542(7640):177–185. doi:10.1038/nature21363
35. **Bianchi ME.** DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol 2007; 81(1):1–5. doi:10.1189/jlb.0306164
36. **Zindel J, Kubes P.** DAMPs, PAMPs, and LAMPs in Immunity and Sterile Inflammation. Annu Rev Pathol 2020; 15:493–518. doi:10.1146/annurev-pathmechdis-012419-032847
37. **Woloshin S, Schwartz LM.** Distribution of C-reactive protein values in the United States. N Engl J Med 2005; 352(15):1611–1613. doi:10.1056/NEJM200504143521525
38. **Kushner I, Rzewnicki D, Samols D.** What does minor elevation of C-reactive protein signify? Am J Med 2006; 119(2):166.e17–166.e1.66E28. doi:10.1016/j.amjmed.2005.06.057
39. **Weiss ST, Litonjua AA.** Vitamin D in host defense: implications for future research. Am J Respir Cell Mol Biol 2017; 56(6):692–693. doi:10.1165/rcmb.2017-0064ED
40. **Yin K, Agrawal DK.** Vitamin D and inflammatory diseases. J Inflamm Res 2014; 7:69–87. doi:10.2147/JIR.S63898
41. **Zhang Y, Leung DY, Richers BN, et al.** Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. J Immunol 2012; 188(5):2127–2135. doi:10.4049/jimmunol.1102412
42. **Annweiler C, Montero-Odasso M, Schott AM, Berrut G, Fantino B, Beauchet O.** Fall prevention and vitamin D in the elderly: an overview of the key role of the non-bone effects. J Neuroeng Rehabil 2010; 7:50. doi:10.1186/1743-0003-7-50
43. **Heath AK, Kim IY, Hodge AM, English DR, Muller DC.** Vitamin D status and mortality: a systematic review of observational studies. Int J Environ Res Public Health 2019; 16(3):383. doi:10.3390/ijerph16030383
44. **Pereira M, Dantas Damascena A, Galvão Azevedo LM, de Almeida Oliveira T, da Mota Santana J.** Vitamin D deficiency aggravates COVID-19: systematic review and meta-analysis. Crit Rev Food Sci Nutr 2022; 62(5):1308–1316. doi:10.1080/10408398.2020.1841090
45. **Manson JE, Cook NR, Lee IM, et al.** Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med 2019; 380(1):33–44. doi:10.1056/NEJMoa1809944
46. **Zhang Y, Fang F, Tang J, et al.** Association between vitamin D supplementation and mortality: systematic review and meta-analysis [published correction appears in BMJ 2020; 370:m2329]. BMJ 2019; 366:l4673. doi:10.1136/bmj.l4673
47. **Schoenmakers I.** Vitamin D supplementation and mortality. Lancet Diabetes Endocrinol 2022; 10(2):88–90. doi:10.1016/S2213-8587(22)00002-X
48. **Rawat D, Roy A, Maitra S, Shankar V, Khanna P, Baidya DK.** Vitamin D supplementation and COVID-19 treatment: a systematic review and meta-analysis. Diabetes Metab Syndr 2021; 15(4):102189. doi:10.1016/j.dsx.2021.102189
49. **Murai IH, Fernandes AL, Sales LP, et al.** Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. JAMA 2021; 325(11):1053–1060. doi:10.1001/jama.2020.26848
50. **Choosing Wisely Canada.** Vitamin D tests. https://choosingwisely-canada.org/vitamin-d-tests/. Accessed January 6, 2023.
51. **Choosing Wisely.** American Society for Clinical Pathology. Don't perform population based screening for 25-OH-vitamin D deficiency. Released February 21, 2013. https://www.choosingwisely.org/clinician-lists/american-society-clinical-pathology-population-based-screening-for-vitamin-d-deficiency/. Accessed January 6, 2023.
52. **Altieri B, Cavalier E, Bhattoa HP, et al.** Vitamin D testing: advantages and limits of the current assays. Eur J Clin Nutr 2020; 74(2): 231–247. doi:10.1038/s41430-019-0553-3

***Address**: Maria Antonelli, MD, Department of Medicine, Division of Rheumatology, MetroHealth Medical Center, 2500 MetroHealth Drive, H586, Cleveland, OH 44109; mantonelli@metrohealth.org*

EDITORIAL

Bruce Long, MD, FACR, BS Pharm
Retired Staff, Center for Osteoporosis and Metabolic Bone Disease, Department of Rheumatologic and Immunologic Disease, Cleveland Clinic, Cleveland, OH

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.

See related article, page 85

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]

doi:10.3949/ccjm.90a.22086

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_3 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[7] 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,"[7] 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.[8,9] 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,[1] perhaps it is best to delay testing until the patient recovers.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Antonelli MJ, Kushner I, Epstein M.** The constellation of vitamin D, the acute-phase response, and inflammation. Cleve Clin J Med 2023; 90(2):85–89. doi:10.3949/ccjm.90a.22048
2. **Chapuy MC, Preziosi P, Maamer M, et al.** Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 1997; 7(5):439–443. doi:10.1007/s001980050030
3. **Holick MF, Siris ES, Binkley N, et al.** Prevalence of vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab 2005; 90(6):3215–3224. doi:10.1210/jc.2004-2364
4. **Dawson-Hughes B.** What is the optimal dietary intake of vitamin D for reducing fracture risk? Calcif Tissue Int 2013; 92(2):184–190. doi:10.1007/s00223-012-9606-5
5. **Bischoff-Ferrari HA, Willett WC, Wong JB, et al.** Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Arch Intern Med 2009; 169(6):551–561. doi:10.1001/archinternmed.2008.600
6. **LeBoff MS, Chou SH, Ratliff KA, et al.** Supplemental vitamin D and incident fractures in midlife and older adults. N Engl J Med 2022; 387(4):299–309. doi:10.1056/NEJMoa2202106
7. **Amgen Inc.** Prolia (denosumab) package insert. https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/Prolia/prolia_pi.pdf. Accessed January 11, 2023.
8. **Hull and East Yorkshire Hospitals.** Prescribing framework for denosumab (Prolia) in osteoporosis. https://www.hey.nhs.uk/wp/wp-content/uploads/2016/03/denosumab.pdf. Accessed January 11, 2023.
9. **Oxford University Hospitals.** https://www.ouh.nhs.uk/osteoporosis/useful-info/documents/InitiatingDenosumabinprimarycareJan2015.pdf. Accessed January 11, 2023.

***Address**: Bruce Long, MD, FACR, BS Pharm, Department of Rheumatologic and Immunologic Disease, A50, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; longbmd@gmail.com*

Join Our Team

Growth. Advancement. Opportunity.

These are just a few reasons to join our team of physicians and advance practice providers at Cleveland Clinic in Ohio, Florida, Nevada, Abu Dhabi and London. As a physician-led organization, we base our culture on collaboration and Patients First. Because we push the boundaries of performance, we offer competitive compensation and benefits that equal or surpass our peer organizations.

To learn more and view our physician staff and advanced practice listings, please visit jobs.clevelandclinic.org.

Cleveland Clinic is pleased to be an equal employment/ affirmative action employer: Women/Minorities/Veterans/ Individuals with Disabilities. Smoke/drug free environment.

Cleveland Clinic

Every life deserves world class care.

GREGORY W. RUTECKI, MD, Section Editor

Kaylee Watson, MD
Fellow Researcher, Department of Cardiology and Cardiothoracic Surgery, Cleveland Clinic Florida, Weston, FL

David Wolinsky, MD
Section Head, Nuclear Cardiology, Medical Director, Cardiac Amyloid Center, Department of Cardiology and Cardiothoracic Surgery, Cleveland Clinic Florida, Weston, FL

Mauricio Velez, MD
Section of Heart Failure and Cardiac Transplant Medicine, Department of Cardiology and Cardiothoracic Surgery, Cleveland Clinic Florida, Weston, FL

David Snipelisky, MD, FACC
Section of Heart Failure and Cardiac Transplant Medicine, Department of Cardiology and Cardiothoracic Surgery, Cleveland Clinic Florida, Weston, FL

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.

1 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

doi:10.3949/ccjm.90a.22021

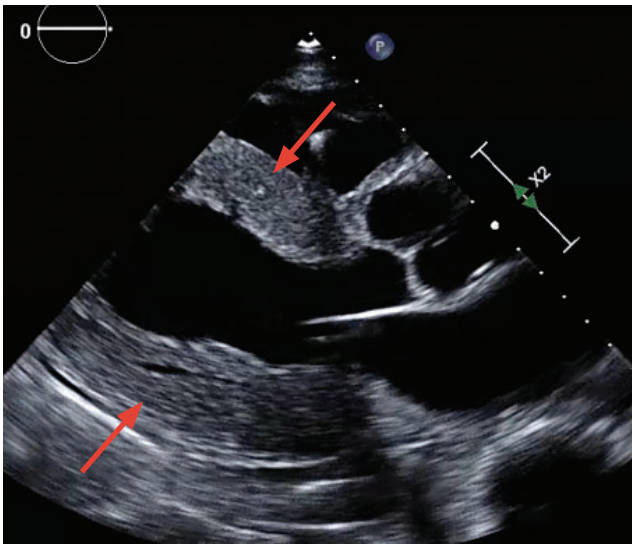


Figure 1. Parasternal long-axis view on echocardiography demonstrates diffuse concentric left ventricular hypertrophy (arrows).

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.[1] 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.[1] 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.[3] 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.[1]

Amyloidosis is an infiltrative disease due to the accumulation of misfolded precursor proteins that make up amyloid.[1,4,5] Two major types of amyloidosis include light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR), which is further subdivided into hereditary (hATTR) and wild-type (ATTRwt). While cardiac amyloidosis has been historically thought to be a rare disease, emerging imaging and other advancements in medicine have revealed a greater prevalence of ATTR than what was previously believed. This may be due to the phenotypic heterogeneity in the presentation of the disease.[1,4,5] A survey of patients with ATTR and their caregivers showed that 57% of patients with hATTR and 39% of patients with ATTRwt received a misdiagnosis, 17% sought care from 5 different physicians before proper diagnosis, and those who were misdiagnosed received treatment for the wrong disease 75% of the time.[4]

Patients typically do not receive appropriate care owing to similarities of clinical presentation of cardiac amyloidosis with other etiologies of heart failure, the relatively advanced age of the patient population, misconceptions pertaining to the disease process, and common misdiagnosis.[1,4,5] Arrhythmias and bilateral carpal tunnel syndrome commonly precede heart failure symptoms in patients with transthyretin amyloid cardiomyopathy (ATTR-CM) by many years.[1,6,7] It is also important to identify the myriad noncardiac manifestations that can be affected by the disease. For instance, patients tend to have a degree of renal dysfunction, neuropathies, and tendinopathies, including unprovoked tendon rupture, autonomic dysfunction,[8] lumbar spinal stenosis,[9] need for early joint replacements, issues with bowel motility,[10] and even retinal deposition of the misfolded protein.[1,5] A thorough history from the patient and care team along with a high suspicion for ATTR-CM is essential for a clinician to piece together the diagnosis.

2 What diagnostic studies should be performed early in the suspicion of cardiac amyloidosis?

- ☐ Fat pad biopsy
- ☐ Monoclonal protein testing with free light chain analysis
- ☐ Genetic testing
- ☐ Endomyocardial heart biopsy

In a patient with high suspicion for cardiac amyloidosis, the clinical priority is differentiating between an etiology of AL or ATTR, and genetic testing would not provide a definitive diagnosis.[5,11] Genetic testing is warranted once ATTR is discovered to determine the form of disease being hATTR or ATTRwt[5]; hATTR indicates that first-degree relatives are at higher risk for the development of this pathology.[5] Fat-pad biopsies can be used to evaluate for amyloid deposition,

TABLE 1
Findings that may warrant cardiac amyloidosis workup

Extracardiac manifestations	Cardiac manifestations	Imaging findings
Bilateral carpal tunnel syndrome	Persistent mildly elevated troponin levels	Echocardiography: increased thickness of left ventricle, right ventricular free wall, atrioventricular valves, interatrial septum
Unprovoked biceps tendon rupture	Symptomatic hypotension or orthostasis in response to hypertensive medication	Electrocardiography: discrepancy in QRS voltage and left ventricular thickness
Lumbar stenosis	Unexplained atrioventricular block, heart block, or bundle branch block	Strain echocardiography: longitudinal impairment with apical sparing
Sensorimotor polyneuropathy	Elevated N-terminal-pro-brain natriuretic peptide not proportionate to severity of heart failure	Cardiac magnetic resonance imaging: increased extracellular volume or late enhancement
Autonomic dysfunction	Family history of cardiomyopathy	Chest radiography: cardiomegaly

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]

3 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.

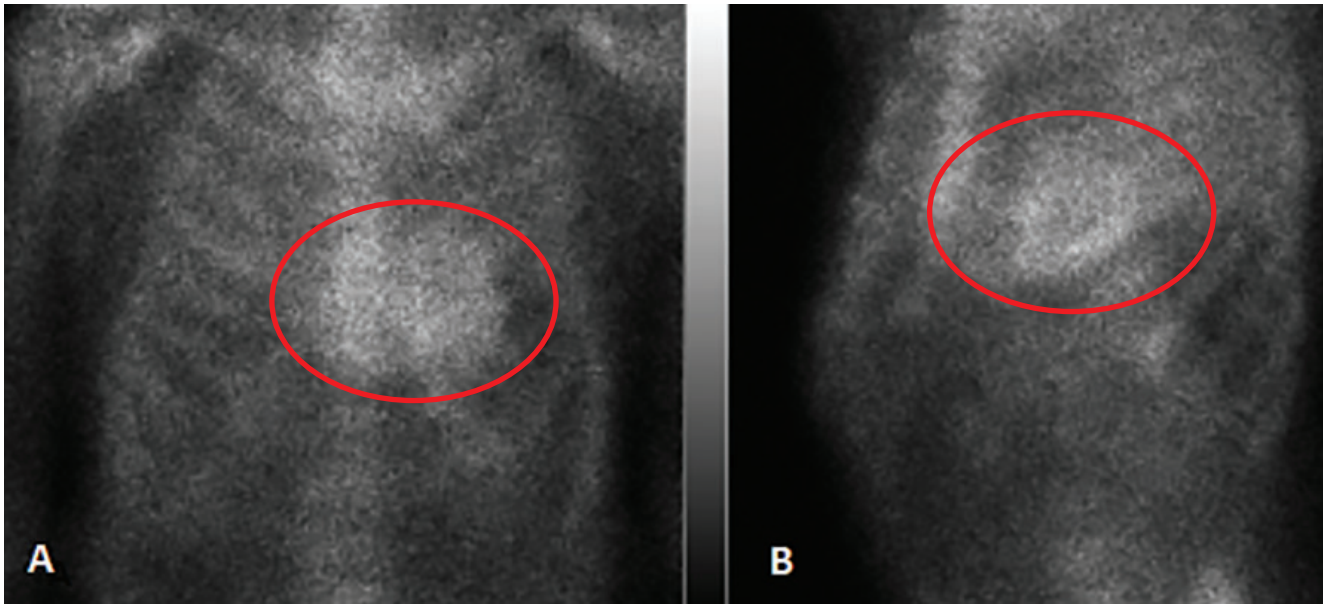


Figure 2. Technetium-99m pyrophosphate scintigraphy. (A) Anterior and (B) left anterior oblique views in our patient demonstrated grade 2 to 3 myocardial uptake of the radiotracer (circles) 3 hours after injection, thus meeting diagnostic criteria for transthyretin amyloid cardiomyopathy.

DIAGNOSIS OF AMYLOIDOSIS

Technetium-99m pyrophosphate scintigraphy is the recommended diagnostic tool for ATTR-CM. It is cost-effective, noninvasive, and relatively widely available.[14,15] 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.[14,15] 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%.[14] 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.[15]

While false-positive results may occur with this test, further investigations are recommended to diminish the likelihood of this.[14,15] 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.[12,15] 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**).[14] ATTR should only be established after AL has been ruled out with serum immunofixation electrophoresis, urine immunofixation electrophoresis, and serum light chain concentration.[12,15]

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

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

MANAGEMENT OF CARDIAC AMYLOIDOSIS

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.[5,12] These treatments were used on the premise of having efficacy in other inflammatory and infectious cardiac etiologies.[5] 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.[16] The pathogenesis of ATTR-CM involves

TABLE 2
Disease-modifying therapies for transthyretin amyloidosis (ATTR) approved by the US Food and Drug Administration

Drug	Indication	Effect on transthyretin
Tafamidis	Wild-type or hereditary ATTR cardiomyopathy	Stabilizer
Vutrisiran	Hereditary ATTR with neuropathy	Silencer
Patisiran	Hereditary ATTR with neuropathy	Silencer
Inotersen	Hereditary ATTR with neuropathy	Silencer

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.[16] Referral to a neurologist may be necessary as the patient may experience polyneuropathy and autonomic instability evidenced by orthostatic hypotension.[16]

Disease-modifying therapies for ATTR-CM target transthyretin through silencing, stabilization, and disruption (**Table 2**).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.[17,18] 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,[17] 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.[17] 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.[18] Other transthyretin-stabilizing drugs such as diflunisal have been shown to improve survival in patients with cardiac ATTR.[19] 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.[20]

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

5 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 implan-

tation, and no study has demonstrated improvement in morbidity or mortality in this patient population.[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.

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.

REFERENCES

1. **Witteles RM, Bokhari S, Damy T, et al.** Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC Heart Fail 2019; 7(8):709–716. doi:10.1016/j.jchf.2019.04.010
2. **Cheitlin MD, Armstrong WF, Aurigemma GP, et al.** ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to update the 1997 guidelines for the clinical application of echocardiography). J Am Soc Echocardiogr 2003; 16(10):1091–1110. doi:10.1016/S0894-7317(03)00685-0
3. **Nardozza M, Chiodi E, Mele D.** Left ventricle relative apical sparing in cardiac amyloidosis. J Cardiovasc Echogr 2017; 27(4):141–142. doi:10.4103/jcecho.jcecho_22_17
4. **Lousada I, Maurer M, Warner M, Guthrie S, Hsu K, Grogan M.** Amyloidosis research consortium cardiac amyloidosis survey: results from patients with ATTR amyloidosis and their caregivers. Orphanet J Rare Dis 2017; 12(suppl 1):165. doi:10.1186/s13023-017-0710-5
5. **Donnelly JP, Hanna M.** Cardiac amyloidosis: an update on diagnosis and treatment. Cleve Clin J Med 2017; 84(12suppl3):12–26. doi:10.3949/ccjm.84.s3.02
6. **González-López E, López-Sainz Á, Garcia-Pavia P.** Diagnosis and treatment of transthyretin cardiac amyloidosis. Progress and hope. Rev Esp Cardiol (Engl Ed) 2017; 70(11):991–1004. doi:10.1016/j.rec.2017.05.036
7. **Gillmore JD, Maurer MS, Falk RH, et al.** Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016 ; 133(24):2404–2412. doi:10.1161/CIRCULATIONAHA.116.021612
8. **Siddiqi OK, Ruberg FL.** Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. Trends Cardiovasc Med 2018; 28(1):10–21. doi:10.1016/j.tcm.2017.07.004
9. **Yanagisawa A, Ueda M, Sueyoshi T, et al.** Amyloid deposits derived from transthyretin in the ligamentum flavum as related to lumbar spinal canal stenosis. Mod Pathol 2015; 28(2):201–207. doi:10.1038/modpathol.2014.102
10. **Dubrey SW, Cha K, Anderson J, et al.** The clinical features of immunoglobulin light-chain (AL) amyloidosis with heart involvement. QJM 1998; 91(2):141–157. doi:10.1093/qjmed/91.2.141
11. **Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS.** Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. J Am Coll Cardiol 2019; 73(22):2872–2891. doi:10.1016/j.jacc.2019.04.003
12. **Kittleson MM, Maurer MS, Ambardekar AV, et al.** Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. Circulation 2020; 142(1):e7–e22. doi:10.1161/CIR.0000000000000792
13. **Sperry BW, Ikram A, Hachamovitch R, et al.** Efficacy of chemotherapy for light-chain amyloidosis in patients presenting with symptomatic heart failure. J Am Coll Cardiol 2016; 67(25):2941–2948. doi:10.1016/j.jacc.2016.03.593
14. **Dorbala S, Ando Y, Bokhari S, et al.** ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: Part 1 of 2—evidence base and standardized methods of imaging. J Nucl Cardiol 2019; 26(6):2065–2123. doi:10.1007/s12350-019-01760-6
15. **Poterucha TJ, Elias P, Bokhari S, et al.** Diagnosing transthyretin cardiac amyloidosis by technetium Tc 99m pyrophosphate: a test in evolution. JACC Cardiovasc Imaging 2021; 14(6):1221–1231. doi:10.1016/j.jcmg.2020.08.027
16. **Adam RD, Coriu D, Jercan A, et al.** Progress and challenges in the treatment of cardiac amyloidosis: a review of the literature. ESC Heart Fail 2021; 8(4):2380–2396. doi:10.1002/ehf2.13443
17. **Damy T, Garcia-Pavia P, Hanna M, et al.** Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. Eur J Heart Fail 2021; 23(2):277–285. doi:10.1002/ejhf.2027
18. **Hanna M, Damy T, Grogan M, et al.** Tafamidis and quality of life in people with transthyretin amyloid cardiomyopathy in the study ATTR-ACT: a plain language summary. Future Cardiol 2022; 18(3):165–172. doi:10.2217/fca-2021-0095

19. **Rosenblum H, Castano A, Alvarez J, Helmke S, Maurer MS.** Improved survival in patients with transthyretin cardiac amyloidosis treated with TTR stabilizers. J Card Fail 2017; 23(8):S20. doi:10.1016/j.cardfail.2017.07.039
20. **Carroll A, Dyck PJ, de Carvalho M, et al.** Novel approaches to diagnosis and management of hereditary transthyretin amyloidosis. J Neurol Neurosurg Psychiatry 2022; 93(6):668–678. doi:10.1136/jnnp-2021-327909
21. **Mehra MR, Uriel N, Naka Y, et al.** A fully magnetically levitated left ventricular assist device—final report. N Engl J Med 2019; 380(17):1618–1627. doi:10.1056/NEJMoa1900486

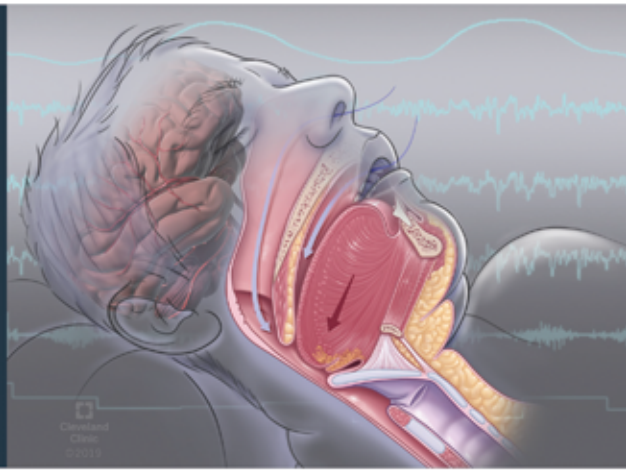
Address: *David Snipelisky, MD, FACC, Department of Cardiology and Cardiothoracic Surgery, Cleveland Clinic Florida, 2950 Cleveland Clinic Boulevard, Weston, FL 33331; snipeld@ccf.org*

Cleveland Clinic

Obstructive Sleep Apnea:

A Cleveland Clinic State-of-the-Art Review

CME-Certified Online Series



Participate in the complimentary Obstructive Sleep Apnea: A Cleveland Clinic State-of-the-Art Review online series for an in-depth review of OSA, including screening, diagnosis, and therapy. Via on-demand webcasts and text-based articles, learn how Cleveland Clinic faculty quickly and effectively identify OSA and treat patients.

Watch the webcasts and read the Cleveland Clinic Journal of Medicine Online Journal Supplement

Obstructive Sleep Apnea Basics

Want to know the symptoms, risk factors and prevalence of OSA? **Jessica Vensel Rundo, MD, MS,** discusses screening tools that can be used to assess for OSA risk.

Sleep Apnea and the Heart

Are you able to identify the physiology of sleep-heart interactions? **Reena Mehra, MD, MS**, describes the association of OSA and cardiovascular health.

Beyond Heart Health: Consequences of Obstructive Sleep Apnea

Ever wondered about the relationship between OSA and metabolic disease, and OSA and cognitive impairment? **Harneet K. Walia, MD**, presents OSA's impact on one's quality of life.

Positive Airway Pressure: Making an Impact on Sleep Apnea

Do you know the newest clinical trials and large observational studies related to PAP therapy for OSA? **Colleen G. Lance, MD**, discusses advanced PAP therapies, as well as the problem achieving PAP adherence.

Treatment of Obstructive Sleep Apnea: Alternatives to PAP Therapy

Want to know alternatives to PAP therapy? **Tina Waters, MD**, highlights conservative option, surgical interventions, oral appliance therapy, and nasal expiratory positive airway pressure therapy.

View Today!

ccfcme.org/sleepapnea

These activities have been approved for *AMA PRA Category 1 Credit™*.

19-EDU-1751626

REVIEW

John A. Morren, MD
Staff, Neuromuscular Center, and Program Director, Neuromuscular Medicine Fellowship, Neurological Institute, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Yuebing Li, MD, PhD
Neuromuscular Center, Department of Neurology, Neurological Institute, Cleveland Clinic, Cleveland, OH; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

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.

doi:10.3949/ccjm.90a.22017

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

Disorder	Similarities to myasthenia gravis	Differences from myasthenia gravis
Lambert-Eaton myasthenic syndrome	Weakness and fatigue	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-frequencey repetitive nerve stimulation testing shows an incremental response (ie, a progressive increase in motor amplitude)
Botulism	Ocular findings (diplopia and ptosis), bulbar dysfunction, generalized weakness	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
Amyotrophic lateral sclerosis	Bulbar dysfunction and weakness	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
Myopathy	Proximal limb weakness	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
Guillain-Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy	Generalized weakness	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
Thyroid eye disease	Diplopia	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
Oculopharyngeal muscular dystrophy	Ptosis, diplopia, dysphagia	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

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 dropped-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.

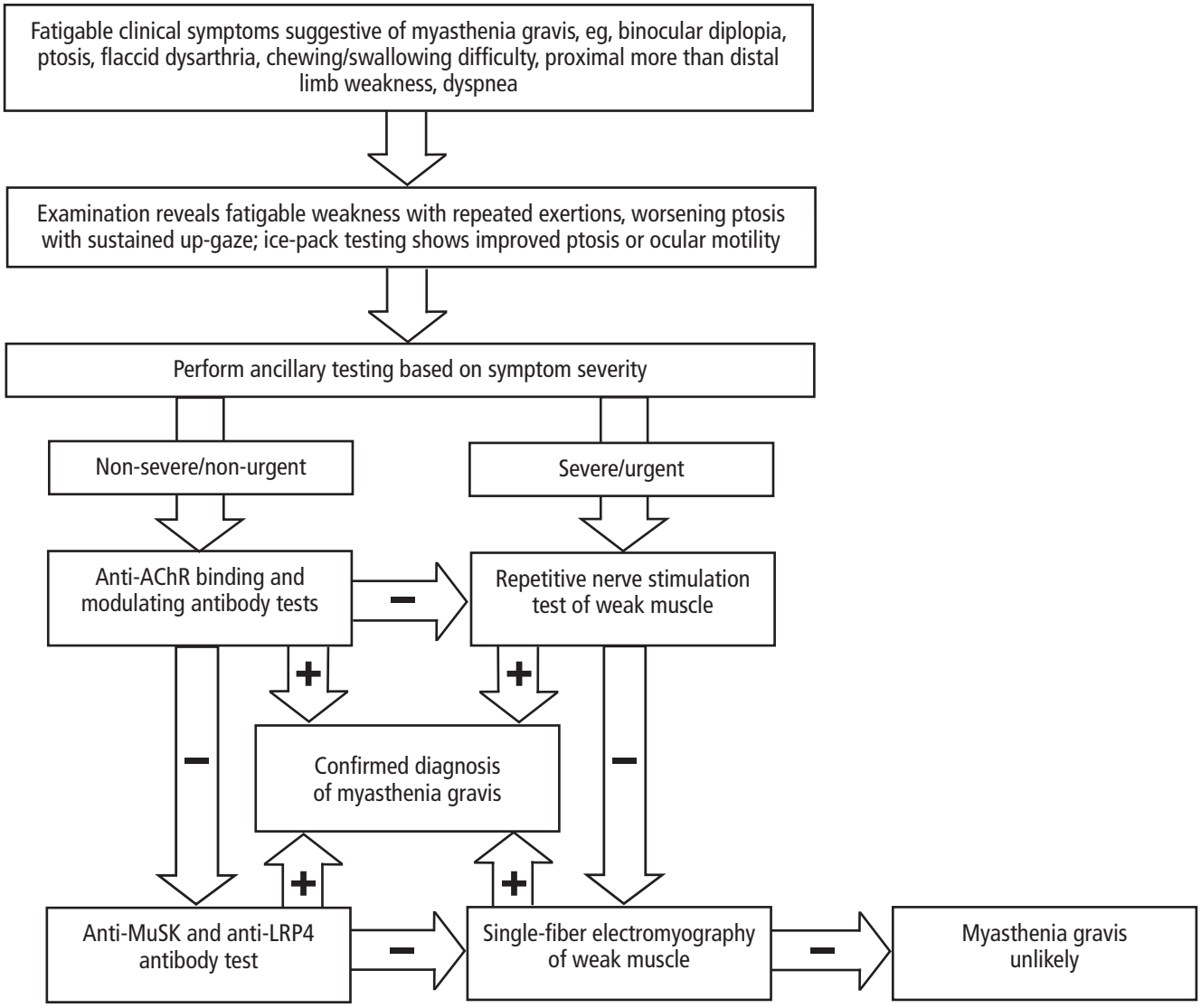


Figure 1. Diagnostic algorithm for myasthenia gravis. If the anti-AChR binding and modulating antibody tests are negative, two options are reasonable, as indicated.

AChR = acetylcholine receptor; LRP4 = lipoprotein-related protein 4; MuSK = muscle-specific tyrosine kinase

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.[15] 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

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]

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

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)[28]
- 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.[29]

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.[29]

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).[30,31]

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.[32]

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.[33] 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,[34] 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 hyoscyamine 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.[8]

WHEN SHOULD CORTICOSTEROIDS BE USED?

According to consensus guidelines,[30] 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.[35,36] However, retrospective studies of oral steroids (prednisone or prednisolone) as the main myasthenia gravis treatment also provide evidence that these drugs are effective.[37] 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.[37]

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.[38] Data suggest that patients over age 40, and especially those over age 60, are more likely to be good responders compared with younger patients.[37]

Corticosteroids help nearly all patients with all subtypes of myasthenia gravis, resulting in marked improvement in more than 80%

When starting corticosteroids, be alert for corticosteroid "dipping," ie, an exacerbation in myasthenic symptoms, seen in up to half of patients and usually occurring within the first week of starting treatment. Most cases are mild, and the worsening does not lead to the need for intubation or assisted ventilation. Dipping does not predict a poor long-term response to corticosteroid therapy.[39] Titrating the dose upward more gradually appears to reduce the occurrence of corticosteroid dipping.[40]

Once significant improvement is seen after starting corticosteroid therapy, there is no need to wait for maximum improvement to occur before starting to taper these drugs. Weaning should be slow and usually starts after several weeks of high-dose therapy. Initial steroid tapering typically involves reducing the daily dose of prednisone by about 5 to 10 mg per month.

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.[8] 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.[47] 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 transthoracic approach, and extended transcervical thymectomy through a low horizontal neck incision. Retrospective studies have shown similar clinical outcomes from the different surgical techniques.[51,52] 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.[30] 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.[53]

A screening test that can be done at the bedside or over the telephone is the single-breath counting test.[54] 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.[53] 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 H_2O, or if the maximal expiratory pressure falls below 40 cm H_2O. 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.

TABLE 2
Treatments on the horizon for myasthenia gravis

Complement inhibitor
Zilucoplan
Neonatal Fc receptor inhibitors
Batoclimab
Nipocalimab
Rozanolixizumab
B-lymphocyte depletion therapy
Obinutuzumab
Ofatumumab
Ublituximab
Blinatumomab
Inebilizumab
Cytokine inhibitor
Tocilizumab
Janus kinase inhibitors
Ruxolitinib
Baricitinib
Tofacitinib
Hematopoietic stem cell transplantation
Chimeric antigen receptor T-cell therapy

Managing myasthenic crisis

Managing myasthenic crisis entails optimizing medical management of intercurrent medical illness (including infections), removing any culprit medications, and giving aggressive immunotherapies aimed at quickly improving neuromuscular junction transmission.

The main therapies are plasmapheresis (also known as plasma exchange) and intravenous immunoglobulin, but usually not both. Both plasmapheresis and intravenous immunoglobulin may begin to produce clinical improvements within several days. However, since their efficacy may start to wane within a few weeks, concomitant augmentation of baseline immunotherapy (eg, corticosteroids) is needed. Anticholinesterase medications are generally withheld during a myasthenic crisis, especially if the patient has to be intubated, since discontinuation will reduce oropharyngeal secretions and aspiration risk.

Although general principles of weaning and extubation apply to those intubated and mechanically ventilated for myasthenic crisis, one should be mindful of more specific considerations. In particular, there should be a consistent reassuring trend in oropharyngeal secretion clearance and pulmonary function parameters (vital capacity > 15 to 20 mL/kg, maximal inspiratory pressure more negative than –25 to –30 cm H_2O) before weaning and attempted extubation. The best approach utilizes daily spontaneous breathing trials after initiation of intravenous immunoglobulin or plasmapheresis treatment.[55] Persistent neck flexor weakness may indicate a lower likelihood of successful extubation.

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 rozanolixizumab 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.

REFERENCES

1. **Liu FC, Kuo CF, See LC, Tsai HI, Yu HP.** Familial aggregation of myasthenia gravis in affected families: a population-based study. Clin Epidemiol 2017; 9:527–535. doi:10.2147/CLEP.S146617
2. **Keesey JC.** Clinical evaluation and management of myasthenia gravis. Muscle Nerve 2004; 29(4):484–505. doi:10.1002/mus.20030
3. **Grob D, Brunner N, Namba T, Pagala M.** Lifetime course of myasthenia gravis. Muscle Nerve 2008; 37(2):141–149. doi:10.1002/mus.20950950
4. **Pakzad Z, Aziz T, Oger J.** Increasing incidence of myasthenia gravis among elderly in British Columbia, Canada. Neurology 2011; 76(17):1526–1528. doi:10.1212/WNL.0b013e318217e735
5. **Sanders DB, Raja SM, Guptill JT, Hobson-Webb LD, Juel VC, Massey JM.** The Duke myasthenia gravis clinic registry: I. Description and demographics. Muscle Nerve 2021; 63(2):209–216. doi:10.1002/mus.27120
6. **Nair AG, Patil-Chhablani P, Venkatramani DV, Gandhi RA.** Ocular myasthenia gravis: a review. Indian J Ophthalmol 2014; 62(10): 985–991. doi:10.4103/0301-4738.145987
7. **Finnis MF, Jayawant S.** Juvenile myasthenia gravis: a paediatric perspective. Autoimmune Dis 2011; 2011:404101. doi:10.4061/2011/404101
8. **Morren J, Li Y.** Myasthenia gravis with muscle-specific tyrosine kinase antibodies: a narrative review. Muscle Nerve 2018; 58(3): 344–358. doi:10.1002/mus.26107
9. **Phillips LH 2nd, Torner JC, Anderson MS, Cox GM.** The epidemiology of myasthenia gravis in central and western Virginia. Neurology 1992; 42(10):1888–1893. doi:10.1212/wnl.42.10.1888
10. **Oh SJ, Morgan MB, Lu L, et al.** Racial differences in myasthenia gravis in Alabama. Muscle Nerve 2009; 39(3):328–332.doi:10.1002/mus.21191
11. **Dresser L, Wlodarski R, Rezania K, Soliven B.** Myasthenia gravis: epidemiology, pathophysiology and clinical manifestations. J Clin Med 2021; 10(11):2235. doi:10.3390/jcm10112235
12. **Mao ZF, Yang LX, Mo XA, et al.** Frequency of autoimmune diseases in myasthenia gravis: a systematic review. Int J Neurosci 2011; 121(3):121–129. doi:10.3109/00207454.2010.539307
13. **Christensen PB, Jensen TS, Tsiropoulos I, et al.** Associated autoimmune diseases in myasthenia gravis. A population-based study. Acta Neurol Scand 1995; 91(3):192–195. doi:10.1111/j.1600-0404.1995.tb00432.x
14. **Carr AS, Cardwell CR, McCarron PO, McConville J.** A systematic review of population based epidemiological studies in myasthenia gravis. BMC Neurol 2010; 10:46. doi:10.1186/1471-2377-10-46
15. **Beloor Suresh A, Asuncion RMD.** Myasthenia Gravis. In: StatPearls. Treasure Island, FL: StatPearls Publishing; December 15, 2021.
16. **Lamb CJ, Rubin DI.** Sensitivity and specificity of repetitive nerve stimulation with lower cutoffs for abnormal decrement in myasthenia gravis. Muscle Nerve 2020; 62(3):381–385. doi:10.1002/mus.26999
17. **Morren JA, Levin KH, Shields RW.** Diagnostic accuracy of single fiber electromyography for myasthenia gravis in patients followed longitudinally. J Clin Neurophysiol 2016; 33(5):469–474. doi:10.1097/WNP.0000000000000285

18. **Keesey J, Aarli J.** Something in the blood? A history of the autoimmune hypothesis regarding myasthenia gravis. J Hist Neurosci 2007; 16(4):395–412. doi:10.1080/09647040600675322
19. **Simpson JA.** An evaluation of thymectomy in myasthenia gravis. Brain 1958; 81(1):112–144. doi:10.1093/brain/81.1.112
20. **Oosterhuis HJ.** The natural course of myasthenia gravis: a long term follow up study. J Neurol Neurosurg Psychiatry 1989; 52(10): 1121–1127. doi:10.1136/jnnp.52.10.1121
21. **Grob D, Arsura EL, Brunner NG, Namba T.** The course of myasthenia gravis and therapies affecting outcome. Ann N Y Acad Sci 1987; 505:472–499. doi:10.1111/j.1749-6632.1987.tb51317.x
22. **Monsul NT, Patwa HS, Knorr AM, Lesser RL, Goldstein JM.** The effect of prednisone on the progression from ocular to generalized myasthenia gravis. J Neurol Sci 2004; 217(2):131–133. doi:10.1016/j.jns.2003.08.017
23. **Mazzoli M, Ariatti A, Valzania F, et al.** Factors affecting outcome in ocular myasthenia gravis. Int J Neurosci 2018; 128(1):15–24. doi:10.1080/00207454.2017.1344237
24. **Peeler CE, De Lott LB, Nagia L, Lemos J, Eggenberger ER, Cornblath WT.** Clinical utility of acetylcholine receptor antibody testing in ocular myasthenia gravis. JAMA Neurol 2015; 72(10):1170–1174. doi:10.1001/jamaneurol.2015.1444
25. **Mantegazza R, Beghi E, Pareyson D, et al.** A multicentre follow-up study of 1152 patients with myasthenia gravis in Italy. J Neurol 1990; 237(6):339–344. doi:10.1007/BF00315656
26. **Salins S, Teter B, Kavak K, Wolfe GI, Silvestri NJ.** Low-dose medication and long-term outcome in myasthenia gravis. J Clin Neuromuscul Dis 2016; 18(2):61–66. doi:10.1097/CND.0000000000000122
27. **Sanders DB, Evoli A.** Immunosuppressive therapies in myasthenia gravis. Autoimmunity 2010; 43(5–6):428–435. doi:10.3109/08916930903518107
28. **Gummi RR, Kukulka NA, Deroche CB, Govindarajan R.** Factors associated with acute exacerbations of myasthenia gravis. Muscle Nerve 2019; 60(6):693–699. doi:10.1002/mus.26689
29. **O'Connor L, Westerberg E, Punga AR.** Myasthenia gravis and physical exercise: a novel paradigm. Front Neurol 2020; 11:675. doi:10.3389/fneur.2020.00675
30. **Sanders DB, Wolfe GI, Benatar M, et al.** International consensus guidance for management of myasthenia gravis: executive summary. Neurology 2016; 87(4):419–425. doi:10.1212/WNL.0000000000002790
31. **Narayanaswami P, Sanders DB, Wolfe G, et al.** International consensus guidance for management of myasthenia fravis: 2020 update. Neurology 2021; 96(3):114–122. doi:10.1212/WNL.0000000000011124
32. **Dubey D, David WS, Reynolds KL, et al.** Severe neurological toxicity of immune checkpoint inhibitors: growing spectrum. Ann Neurol 2020; 87(5):659–669. doi:10.1002/ana.25708
33. **Maggi L, Mantegazza R.** Treatment of myasthenia gravis: focus on pyridostigmine. Clin Drug Investig 2011; 31(10):691–701. doi:10.2165/11593300-000000000-00000
34. **Engel AG, Lambert EH, Santa T.** Study of long-term anticholinesterase therapy. Effects on neuromuscular transmission and on motor end-plate fine structure. Neurology 1973; 23(12):1273–1281. doi:10.1212/wnl.23.12.1273
35. **Howard FM Jr, Duane DD, Lambert EH, Daube JR.** Alternate-day prednisone: preliminary report of a double-blind controlled study. Ann N Y Acad Sci 1976; 274:596-607. doi:10.1111/j.1749–6632.1976.tb47718.x
36. **Lindberg C, Andersen O, Lefvert AK.** Treatment of myasthenia gravis with methylprednisolone pulse: a double blind study. Acta Neurol Scand 1998; 97(6):370–373. doi:10.1111/j.1600-0404.1998.tb05968.x
37. **Morren J, Li Y.** Maintenance immunosuppression in myasthenia gravis, an update. J Neurol Sci 2020; 410:116648. doi:10.1016/j.jns.2019.116648
38. **Utsugisawa K, Suzuki S, Nagane Y, et al.** Health-related quality-of-life and treatment targets in myasthenia gravis. Muscle Nerve 2014; 50(4):493–500. doi:10.1002/mus.24213
39. **Pascuzzi RM, Coslett HB, Johns TR.** Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. Ann Neurol 1984; 15(3):291–298. doi:10.1002/ana.410150316
40. **Seybold ME, Drachman DB.** Gradually increasing doses of prednisone in myasthenia gravis. Reducing the hazards of treatment. N Engl J Med 1974; 290(2):81–84. doi:10.1056/NEJM197401102900204
41. **Howard JF Jr, Utsugisawa K, Benatar M, et al.** Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody-positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study [published correction appears in Lancet Neurol 2017; 16(12):954]. Lancet Neurol 2017; 16(12):976-986. doi:10.1016/S1474-4422(17)30369-1
42. **Vu T, Meisel A, Mantegazze R, et al.** Terminal complement inhibitor ravulizumab in generalized myasthenia gravis. NEJM Evid 2022; 1(5). doi:10.1056/EVIDoa2100066
43. **Howard JF Jr, Bril V, Vu T, et al.** Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial [published correction appears in Lancet Neurol 2021; 20(8):e5]. Lancet Neurol 2021; 20(7):526–536. doi:10.1016/S1474-4422(21)00159-9
44. **Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ.** Treatment of myasthenia gravis. Neurol Clin 2018; 36(2):311–337. doi:10.1016/j.ncl.2018.01.011
45. **Nagane Y, Suzuki S, Suzuki N, Utsugisawa K.** Early aggressive treatment strategy against myasthenia gravis. Eur Neurol 2011; 65(1):16–22. doi:10.1159/000322497
46. **Mantegazza R, Antozzi C.** When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies [published correction appears in Ther Adv Neurol Disord 2018; 11:1756286418765591]. Ther Adv Neurol Disord 2018; 11:1756285617749134. doi:10.1177/1756285617749134
47. **Nishino M, Ashiku SK, Kocher ON, Thurer RL, Boiselle PM, Hatabu H.** The thymus: a comprehensive review [published correction appears in Radiographics 2017; 37(3):1004]. Radiographics 2006; 26(2):335–348. doi:10.1148/rg.262045213
48. **Hohlfeld R, Wekerle H.** Reflections on the "intrathymic pathogenesis" of myasthenia gravis. J Neuroimmunol 2008; 201–202:21–27. doi:10.1016/j.jneuroim.2008.05.020
49. **Wolfe GI, Kaminski HJ, Aban IB, et al.** Randomized Trial of Thymectomy in Myasthenia Gravis [published correction appears in N Engl J Med 2017; 376(21):2097]. N Engl J Med 2016; 375(6):511–522. doi:10.1056/NEJMoa1602489
50. **Guillermo GR, Téllez-Zenteno JF, Weder-Cisneros N, et al.** Response of thymectomy: clinical and pathological characteristics among seronegative and seropositive myasthenia gravis patients. Acta Neurol Scand 2004; 109(3):217–221. doi:10.1034/j.1600-0404.2003.00209.x
51. **Meyer DM, Herbert MA, Sobhani NC, et al.** Comparative clinical outcomes of thymectomy for myasthenia gravis performed by extended transsternal and minimally invasive approaches. Ann Thorac Surg 2009; 87(2):385–391. doi:10.1016/j.athoracsur.2008.11.040
52. **Bachmann K, Burkhardt D, Schreiter I, et al.** Long-term outcome and quality of life after open and thoracoscopic thymectomy for myasthenia gravis: analysis of 131 patients. Surg Endosc 2008; 22(11):2470–2477. doi:10.1007/s00464-008-9794-2
53. **Dhar R.** Neuromuscular respiratory failure. Critical Care Neurol 2009; 15(3):40–67. doi:10.1212/01.CON.0000348809.76308.c0
54. **Kukulka K, Gummi RR, Govindarajan R.** A telephonic single breath count test for screening of exacerbations of myasthenia gravis: a pilot study. Muscle Nerve 2020; 62(2):258-261. doi:10.1002/mus.26987
55. **Wu JY, Kuo PH, Fan PC, Wu HD, Shih FY, Yang PC.** The role of non-invasive ventilation and factors predicting extubation outcome in myasthenic crisis. Neurocrit Care 2009; 10(1):35–42. doi:10.1007/s12028-008-9139-y
56. **UCB presents efficacy and safety results for zilucoplan and rozanolixizumab in generalized myasthenia gravis.** https://www.ucb.com/stories-media/Press-Releases/article/UCB-presents-efficacy-and-safety-results-for-zilucoplan-and-rozanolixizumab-in-generalized-myasthenia-gravis. Accessed January 11, 2023.

Address: *Yuebing Li, MD, PhD, Neurological Institute, S90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; Liy@ccf.org*

Cleveland Clinic

Neuro Pathways Podcast

Explore the latest advances in neurological practice.

A sampling of episode topics includes:

- Managing complex chronic back pain
- Diagnosing psychogenic non-epileptic seizures
- Evaluating Lewy body dementia
- Incorporating sleep management into routine care
- Managing patients in the opioid crisis era

Access these episodes and more at **clevelandclinic.org/neuropodcast**.

REVIEW

CME MOC

Jordana Yahr, DO
Department of Internal Medicine, Cleveland Clinic, Cleveland, OH

George Thomas, MD
Director, Center for Blood Pressure Disorders, Department of Kidney Medicine, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH; Co-principal Investigator for SPRINT and SYMPLICITY HTN-3

Juan Calle, MD
Department of Kidney Medicine, Glickman Urological and Kidney Institute Cleveland Clinic, Cleveland, OH; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Jonathan J. Taliercio, DO
Program Director, Nephrology and Hypertension Fellowship, Department of Kidney Medicine, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH; Co-principal Investigator for SYMPLICITY HTN-3

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.

doi:10.3949/ccjm.90a.22046

Most patients with hypertension do not achieve current recommended blood pressure targets. It is imperative that physicians recognize risk factors associated with resistant hypertension in order to better control it. In this article, we discuss the epidemiology, diagnosis, evaluation, and treatment of resistant hypertension and a stepwise approach (**Figure 1**)[1,2] to getting patients to their goal blood pressure.

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.[1]

This is stricter than the 2003 guidelines from the Seventh Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure,[3] 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%.[4]

Hypertension is a leading cause of cardiovascular disease and death.[5] Its management costs the US healthcare system approximately $131 billion annually.[6]

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.

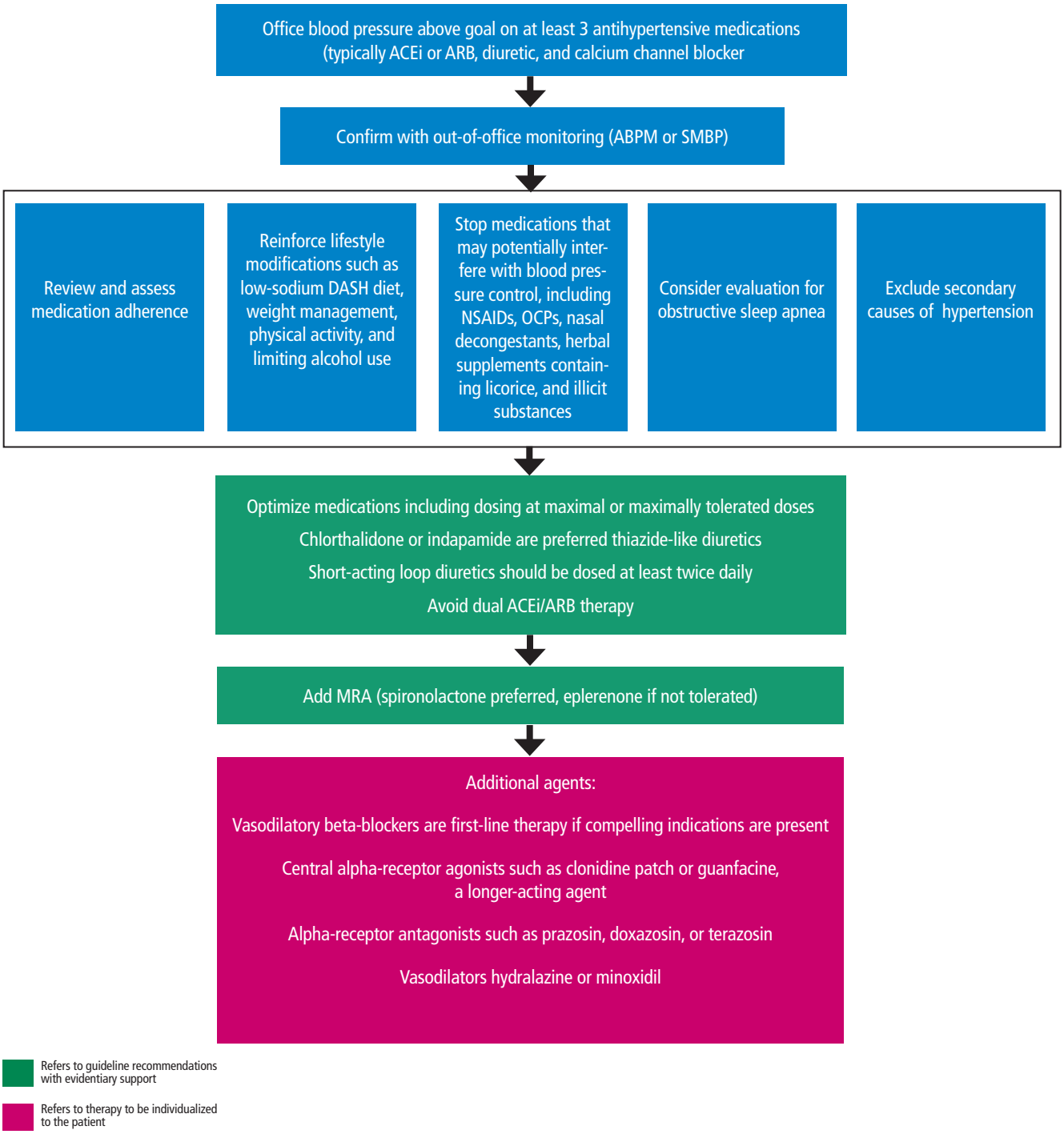


Figure 1. Management of resistant hypertension, recommendations adapted from the American Heart Association scientific statement on resistant hypertension, reference 2.

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."[1]

In patients at lower risk, the ACC-AHA guidelines say the same goal "may be reasonable."[1]

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.[7] This recommendation is based largely on the cardiovascular benefits of this lower goal demonstrated in the Systolic Blood Pressure Intervention Trial,[8] 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 m^2 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.[8,9]

In patients with diabetes, the American Diabetes Association recommends a target blood pressure lower than 130/80 mm Hg.[10]

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.[11] The control rate was 62.8% using the old threshold of less than 140/90 mm Hg.[11]

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.[2]

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%.[12] In hypertensive patients in the Chronic Renal Insufficiency Cohort, the prevalence of apparent treatment-resistant hypertension using the same definition was 40.4%.[13] Other comorbidities associated with resistant hypertension include older age, obesity, diabetes mellitus, and obstructive sleep apnea.[14,15]

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.[14–16] 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.[16] 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).[15]

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.

TABLE 1
Proper blood pressure measurement

Patients should sit, relaxed, for at least 5 minutes, with an empty bladder, without talking; they should not have consumed caffeine, smoked, or exercised in the last 30 minutes.
Use a device that has been properly calibrated, and a proper-sized cuff: the bladder should wrap around 80% of the patient's arm; a small cuff will result in higher blood pressure readings.
Take measurements in both arms, on bare skin, with the patient's arm supported; use the arm with the higher reading for subsequent readings, and repeat measurements 1 to 2 minutes apart.
Use the average of at least 2 readings obtained on at least 2 occasions to estimate blood pressure.

Based on information in reference 1.

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.[2] 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.[17]

Medication adherence can also be difficult to address, but several techniques have been studied.[18,19] Some laboratories offer serum and urine assays to detect metabolites of antihypertensive drugs, and pharmacy-based assessments include pharmacy fill history and pill counting.[18] Directly observed therapy has been shown to reduce resistant hypertension by 29%.[19] 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.[20]

Are the measurements accurate?

Measuring blood pressure accurately requires proper technique, proper cuff size, and use of validated devices (**Table 1**).[1]

Automated office blood pressure monitoring devices are favored over conventional manual auscultatory devices for office use.[1,7] 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.[21]

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.[1,7] 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.[22] 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.[22]

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**).[7] In contrast, the white-coat effect is the same pattern in a person who

TABLE 2
Patterns of in-office and out-of-office blood pressure in treated hypertension

		Out-of-office blood pressure (by daytime ambulatory or home blood pressure monitoring)	
		Normal	High[a]
In-office blood pressure	High[a]	White-coat effect	Uncontrolled hypertension
	Normal	Controlled hypertension	Masked uncontrolled hypertension

[a]Blood pressure 130/80 mm Hg or higher.

Adapted from information in reference 7.

is receiving treatment for hypertension.[23] The white-coat effect may be seen in 28% to 39% of those with resistant hypertension.[2]

Untreated white-coat hypertension is associated with a higher risk of cardiovascular events compared with sustained normotension.[23] 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.[24]

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.[24]

DOES THE PATIENT HAVE LIFESTYLE FACTORS THAT RAISE BLOOD PRESSURE?

Obesity

The relationship between increased adiposity and elevated blood pressure has been well established.[25] NHANES participants who had a body mass index of 30 kg/m^2 or higher were twice as likely to have resistant or apparent treatment-resistant hypertension.[12,26]

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.[25] 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,[27] 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.[28] 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.[1]

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).[29] 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.[28]

Recommended exercise

Aerobic exercise has been shown to reduce blood pressure in patients with hypertension and resistant hypertension.[30] 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).[30] 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 Hg[34,35]; importantly, low-dose aspirin is not associated with blood pressure elevation[36]
- 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

with the renin-angiotensin-aldosterone system, the cutoff values used, the time of testing, and the body positioning at the time of testing (morning preferred, after being seated for 15 minutes). The Endocrine Society guidelines[43] recommend initial testing with the aldosterone-renin ratio followed by a confirmatory test (intravenous or oral salt-loading test) for patients with hypertension who are at risk of primary aldosteronism.[43] Patients at risk include those with resistant hypertension on optimal therapy, those with hypertension with spontaneous or diuretic-induced hypokalemia, and those with hypertension with adrenal incidentaloma, as well as hypertensive first-degree relatives of patients with primary aldosteronism.

An aldosterone-renin ratio of 20 or higher should warrant further investigation if the plasma aldosterone concentration is 15 ng/dL or higher.[40] Patients with very low renin levels, spontaneous hypokalemia, and a plasma aldosterone concentration higher than 20 ng/dL likely do not require confirmatory testing and should move forward with adrenal imaging.

Primary aldosteronism is treated with surgery if a unilateral aldosterone-secreting adenoma is found, or is treated with mineralocorticoid receptor antagonists such as spironolactone or eplerenone in bilateral adrenal disease and in patients who are not candidates for surgery.

A full discussion of primary aldosteronism is beyond the scope of this article, but screening and diagnosis according to current guidelines may detect only a fraction of patients with primary aldosteronism, and a revamping of current practice guidelines is needed.

Obstructive sleep apnea

Obstructive sleep apnea is very common in patients with resistant hypertension.[44] Proposed mechanisms by which it could cause or worsen hypertension include increased upper-airway resistance, hypoxia, and hypercapnia.[45] These cause endothelial reactivity, inflammation, oxidative stress, and increased sympathetic and renin-angiotensin-aldosterone system activity, which ultimately lead to increased vascular tone and hypertension.[2,45]

Treating obstructive sleep apnea with continuous positive airway pressure (CPAP) in patients with resistant hypertension has been shown to decrease 24-hour ambulatory blood pressure, and the more hours per night that patients actually use it, the greater the effect on blood pressure.[46] However, although treating 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.[47] 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.[48]

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.[49] (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/m^2, **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.)[49]

Renovascular hypertension

Renovascular hypertension is a syndrome of elevated blood pressure due to diminished renal arterial blood flow resulting in kidney ischemia.[2] 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.[50]

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.[51] Symptoms that should prompt screening include paroxysmal headaches, diaphoresis, and tachycardia.[52]

The 2014 Endocrine Society guidelines[51] 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 inhibitors[54])
- A long-acting dihydropyridine calcium channel blocker
- A diuretic.

In patients with preserved glomerular filtration rate, the preferred first-line diuretic is either chlorthalidone 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 m^2. 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 m^2, 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 trial[57] 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 with reduced ejection fraction.[2] Finally, minoxidil may be used if hydralazine is not tolerated. Hydralazine and minoxidil are associated with fluid retention and reflex tachycardia.

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 (SYMPLICITY 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

1. **Whelton PK, Carey RM, Aronow WS, et al.** 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in J Am Coll Cardiol 2018; 71(19):2275–2279]. J Am Coll Cardiol 2018; 71(19):e127–e248. doi:10.1016/j.jacc.2017.11.006
2. **Carey RM, Calhoun DA, Bakris GL, et al.** Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension 2018; 72(5):e53–e90. doi:10.1161/HYP.0000000000000084
3. **Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee.** The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003; 289(19):2560–2572. doi: 10.1001/jama.289.19.2560. Erratum in: JAMA. 2003 Jul 9; 290(2):197. PMID: 12748199
4. **Muntner P, Carey RM, Gidding S, et al.** Potential US population impact of the 2017 ACC/AHA high blood pressure guideline. Circulation 2018; 137(2):109–118 doi:10.1161/CIRCULATIONAHA.117.032582
5. **Centers for Disease Control and Prevention.** About multiple causes of death, 1999–2020. https://wonder.cdc.gov/mcd-icd10.html. Accessed December 28, 2022.
6. **Kirkland EB, Heincelman M, Bishu KG, et al.** Trends in healthcare expenditures among US adults with hypertension: national estimates, 2003–2014. J Am Heart Assoc 2018; 7(11):e008731 doi:10.1161/JAHA.118.008731
7. **Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group.** KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int 2021; 99(3S):S1–S87. doi:10.1016/j.kint.2020.11.003
8. **SPRINT Research Group, Wright JT Jr, Williamson JD, et al.** A randomized trial of intensive versus standard blood-pressure control [published correction appears in N Engl J Med 2017; 377(25):2506]. N Engl J Med 2015; 373(22):2103–2116. doi:10.1056/NEJMoa1511939
9. **Cheung AK, Rahman M, Reboussin DM, et al.** Effects of intensive BP control in CKD. J Am Soc Nephrol 2017; 28(9):2812–2823. doi:10.1681/ASN.2017020148
10. **ElSayed NA, Aleppo G, Aroda VR, et al.** Summary of revisions: standards of care in diabetes—2023. Diabetes Care 2023; 46[suppl1]: S5–S9. https://doi.org/10.2337/dc23-Srev
11. **Centers for Disease Control and Prevention.** Estimated hypertension prevalence, treatment, and control among US adults. https://millionhearts.hhs.gov/data-reports/hypertension-prevalence.html. Accessed December 28, 2022.
12. **Persell SD.** Prevalence of resistant hypertension in the United States, 2003–2008. Hypertension 2011; 57(6):1076–1080. doi:10.1161/HYPERTENSIONAHA.111.170308
13. **Thomas G, Xie D, Chen HY, et al.** Prevalence and prognostic significance of apparent treatment resistant hypertension in chronic kidney disease: report from the Chronic Renal Insufficiency Cohort study. Hypertension 2016; 67(2):387–396. doi:10.1161/HYPERTENSIONAHA.115.06487

14. **ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group.** The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [published correction appears in JAMA 2003; 289(2):178] [published correction appears in JAMA 2004; 291(18):2196]. JAMA 2002; 288(23):2981–2997. doi:10.1001/jama.288.23.2981
15. **Muntner P, Davis BR, Cushman WC, et al.** Treatment-resistant hypertension and the incidence of cardiovascular disease and end-stage renal disease: results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertension 2014; 64(5):1012–1021. doi:10.1161/HYPERTENSIONAHA.114.03850
16. **Bangalore S, Fayyad R, Laskey R, et al.** Prevalence, predictors, and outcomes in treatment-resistant hypertension in patients with coronary disease. Am J Med 2014; 127(1):71–81.e1. doi:10.1016/j.amjmed.2013.07.038
17. **Durand H, Hayes P, Morrissey EC, et al.** Medication adherence among patients with apparent treatment-resistant hypertension: systematic review and meta-analysis. J Hypertens 2017; 35(12): 2346–2357. doi:10.1097/HJH.0000000000001502
18. **de Souza WA, Sabha M, de Faveri Favero F, Bergsten-Mendes G, Yugar-Toledo JC, Moreno H.** Intensive monitoring of adherence to treatment helps to identify "true" resistant hypertension. J Clin Hypertens (Greenwich) 2009; 11(4):183–191. doi:10.1111/j.1751-7176.2009.00102.x
19. **Ruzicka M, Leenen FHH, Ramsay T, et al.** Use of directly observed therapy to assess treatment adherence in patients with apparent treatment-resistant hypertension. JAMA Intern Med 2019; 179(10):1433–1434. doi:10.1001/jamainternmed.2019.1455
20. **Naik AD, Kallen MA, Walder A, Street RL Jr.** Improving hypertension control in diabetes mellitus: the effects of collaborative and proactive health communication. Circulation 2008; 117(11):1361–1368. doi:10.1161/CIRCULATIONAHA.107.724005
21. **Beckett L, Godwin M.** The BpTRU automatic blood pressure monitor compared to 24 hour ambulatory blood pressure monitoring in the assessment of blood pressure in patients with hypertension. BMC Cardiovasc Disord 2005; 5(1):18. doi:10.1186/1471-2261-5-18
22. **Shimbo D, Abdalla M, Falzon L, Townsend RR, Muntner P.** Role of ambulatory and home blood pressure monitoring in clinical practice: a narrative review. Ann Intern Med 2015; 163(9):691–700. doi:10.7326/M15-1270
23. **Cohen JB, Lotito MJ, Trivedi UK, Denker MG, Cohen DL, Townsend RR.** Cardiovascular events and mortality in white coat hypertension: a systematic review and meta-analysis. Ann Intern Med 2019; 170(12):853–862. doi:10.7326/M19-0223
24. **Stergiou GS, Asayama K, Thijs L, et al.** Prognosis of white-coat and masked hypertension: international database of home blood pressure in relation to cardiovascular outcome. Hypertension 2014; 63(4):675–682. doi:10.1161/HYPERTENSIONAHA.113.02741
25. **Landsberg L, Aronne LJ, Beilin LJ, et al.** Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment: a position paper of the Obesity Society and the American Society of Hypertension. J Clin Hypertens (Greenwich) 2013; 15(1):14–33. doi:10.1111/jch.12049
26. **Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC.** Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation 2011; 124(9):1046–1058. doi:10.1161/CIRCULATIONAHA.111.030189
27. **Parikh JS, Randhawa AK, Wharton S, Edgell H, Kuk JL.** The association between antihypertensive medication use and blood pressure is influenced by obesity. J Obes 2018; 2018:4573258. doi:10.1155/2018/4573258
28. **Sacks FM, Svetkey LP, Vollmer WM, et al.** Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 2001; 344(1):3–10. doi:10.1056/NEJM200101043440101
29. **Pimenta E, Gaddam KK, Oparil S, et al.** Effects of dietary sodium reduction on blood pressure in subjects with resistant hypertension: results from a randomized trial. Hypertension 2009; 54(3):475–481. doi:10.1161/HYPERTENSIONAHA.109.131235
30. **Dimeo F, Pagonas N, Seibert F, Arndt R, Zidek W, Westhoff TH.** Aerobic exercise reduces blood pressure in resistant hypertension. Hypertension 2012; 60(3):653–658. doi:10.1161/HYPERTENSIONAHA.112.197780
31. **Guimarães GV, Cruz LG, Tavares AC, Dorea EL, Fernandes-Silva MM, Bocchi EA.** Effects of short-term heated water-based exercise training on systemic blood pressure in patients with resistant hypertension: a pilot study. Blood Press Monit 2013; 18(6):342–345. doi:10.1097/MBP.0000000000000000
32. **Puddey IB, Beilin LJ.** Alcohol is bad for blood pressure. Clin Exp Pharmacol Physiol 2006; 33(9):847–852. doi:10.1111/j.1440-1681.2006.04452.x
33. **Piano MR, Benowitz NL, Fitzgerald GA, et al.** Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention, and treatment: a policy statement from the American Heart Association. Circulation 2010; 122(15):1520–1544 doi:10.1161/CIR.0b013e3181f432c3
34. **Warner TD, Mitchell JA.** COX-2 selectivity alone does not define the cardiovascular risks associated with non-steroidal anti-inflammatory drugs. Lancet 2008; 371(9608):270–273. doi:10.1016/S0140-6736(08)60137-3
35. **Johnson AG, Nguyen TV, Day RO.** Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994; 121(4):289–300. doi:10.7326/0003-4819-121-4-199408150-00011
36. **Zanchetti A, Hansson L, Leonetti G, et al.** Low-dose aspirin does not interfere with the blood pressure-lowering effects of antihypertensive therapy. J Hypertens 2002; 20(5):1015–1022. doi:10.1097/00004872-200205000-00038
37. **Bidani AK, Griffin KA.** Pathophysiology of hypertensive renal damage: implications for therapy. Hypertension 2004; 44(5):595–601. doi:10.1161/01.HYP.0000145180.38707.84
38. **Muntner P, Anderson A, Charleston J, et al.** Hypertension awareness, treatment, and control in adults with CKD: results from the Chronic Renal Insufficiency Cohort (CRIC) study. Am J Kidney Dis 2010; 55(3):441–451. doi:10.1053/j.ajkd.2009.09.014
39. **Huan Y, Cohen DL, Townsend RR.** Pathophysiology of hypertension in chronic kidney disease. In: Kimmel PL, Rosenberg ME. Chronic renal disease. Elsevier; 2014.
40. **Vaidya A, Mulatero P, Baudrand R, Adler GK.** The expanding spectrum of primary aldosteronism: implications for diagnosis, pathogenesis, and treatment. Endocr Rev 2018; 39(6):1057–1088. doi:10.1210/er.2018-00139
41. **Calhoun DA, Nishizaka MK, Zaman MA, Thakkar RB, Weissmann P.** Hyperaldosteronism among black and white subjects with resistant hypertension. Hypertension 2002; 40(6):892–896. doi:10.1161/01.hyp.0000040261.30455.b6
42. **Mulatero P, Stowasser M, Loh KC, et al.** Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centers from five continents. J Clin Endocrinol Metab 2004; 89(3):1045–1050. doi:10.1210/jc.2003-031337
43. **Funder JW, Carey RM, Fardella C, et al.** Case detection, diagnosis, and treatment of patients with primary aldosteronism: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2008; 93(9):3266–3281. doi:/10.1210/jc.2008-0104
44. **Logan AG, Perlikowski SM, Mente A, et al.** High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens 2001; 19(12):2271–2277. doi:10.1097/00004872-200112000-00022
45. **Dudenbostel T, Calhoun DA.** Resistant hypertension, obstructive sleep apnoea and aldosterone. J Hum Hypertens 2012; 26(5): 281–287. doi:10.1038/jhh.2011.47
46. **Martínez-García MA, Capote F, Campos-Rodríguez F, et al.** Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA 2013; 310(22):2407–2415. doi:10.1001/jama.2013.281250
47. **Bazzano LA, Khan Z, Reynolds K, He J.** Effect of nocturnal nasal continuous positive airway pressure on blood pressure in obstructive sleep apnea. Hypertension 2007; 50(2):417–423. doi:10.1161/HYPERTENSIONAHA.106.085175

48. **Kuna ST, Townsend RR, Keenan BT, et al.** Blood pressure response to treatment of obese vs non-obese adults with sleep apnea. J Clin Hypertens (Greenwich) 2019; 21(10):1580–1590. doi:10.1111/jch.13689
49. **Chung F, Yegneswaran B, Liao P, et al.** STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology 2008; 108(5):812–821. doi:10.1097/ALN.0b013e31816d83e4
50. **Ritchie J, Green D, Chrysochou C, Chalmers N, Foley RN, Kalra PA.** High-risk clinical presentations in atherosclerotic renovascular disease: prognosis and response to renal artery revascularization. Am J Kidney Dis 2014; 63(2):186–197. doi:10.1053/j.ajkd.2013.07.020
51. **Lenders JW, Duh QY, Eisenhofer G, et al.** Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2014; 99(6):1915–1942. doi:10.1210/jc.2014-1498
52. **Lenders JW, Eisenhofer G, Mannelli M, Pacak K.** Phaeochromocytoma. Lancet 2005; 366(9486):665–675. doi:10.1016/S0140-6736(05)67139-5
53. **Martins LC, Conceição FL, Muxfeldt ES, Salles GF.** Prevalence and associated factors of subclinical hypercortisolism in patients with resistant hypertension. J Hypertens 2012; 30(5):967–973. doi:10.1097/HJH.0b013e3283521484
54. **Messerli FH, Bangalore S, Bavishi C, Rimoldi SF.** Angiotensin-converting enzyme inhibitors in hypertension: to use or not to use? J Am Coll Cardiol 2018; 71(13):1474–1482. doi:10.1016/j.jacc.2018.01.058
55. **Ernst ME, Carter BL, Goerdt CJ, et al.** Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. Hypertension 2006; 47(3):352–358. doi:10.1161/01.HYP.0000203309.07140.d3
56. **Agarwal R, Sinha AD, Cramer AE, et al.** Chlorthalidone for hypertension in advanced chronic kidney disease. N Engl J Med 2021; 385(27):2507–2519. doi:10.1056/NEJMoa2110730
57. **Williams B, MacDonald TM, Morant S, et al.** Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015; 386(10008):2059–2068. doi:10.1016/S0140-6736(15)00257-3
58. **Acelajado MC, Hughes ZH, Oparil S, Calhoun DA.** Treatment of resistant and refractory hypertension. Circ Res 2019; 124(7): 1061–1070. doi:10.1161/CIRCRESAHA.118.312156
59. **Freeman MW, Halvorsen YD, Marshall W, et al.** Phase 2 trial of baxdrostat for treatment-resistant hypertension. N Engl J Med 2022; 10.1056/NEJMoa2213169. doi:10.1056/NEJMoa2213169
60. **Schlaich MP, Bellet M, Weber MA, et al.** Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial. Lancet 2022; 400(10367):1927–1937. doi:10.1016/S0140-6736(22)02034-7
61. **Bhatt DL, Kandzari DE, O'Neill WW, et al.** A controlled trial of renal denervation for resistant hypertension. N Engl J Med 2014; 370(15):1393–1401. doi:10.1056/NEJMoa1402670
62. **Azizi M, Sanghvi K, Saxena M, et al.** Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial. Lancet 2021; 397(10293):2476–2486. doi:10.1016/S0140-6736(21)00788-1

Address: *Jonathan J. Taliercio, DO, Program Director, Nephrology and Hypertension Fellowship, Department of Kidney Medicine, Glickman Urological and Kidney Institute, Q7, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; talierj@ccf.org*

Cleveland Clinic | Comprehensive COVID Care

Participate in an interdisciplinary educational resource for the care of COVID-19 patients

Learn best practices in current therapy and rapidly evolving management strategies for COVID-19 patients

Review new safety protocols and procedures that ensure the safety of caregivers and patients in a COVID-19 environment

Attain key concepts pertinent to inpatient management of COVID and Non-COVID medical care for physicians preparing for redeployment

Access Just-in-Time care management guides for quick and easy referencesvon diagnosis and strategies for patient care treatment.

Participate Today! **healthcareedu.ccf.org**

These activities have been approved for *AMA PRA Category 1 Credit™*

How to earn *AMA PRA Category 1 Credit*™ and ABIM MOC points

AMA/PRA Category 1 Credit™

To read articles as CME activities and claim credit, go to www.ccjm.org, click on the "CME/MOC" menu, and then "Articles." Find the articles that you want to read as CME activities and click on the appropriate links. After reading an article, click on the link to complete the activity. You will be asked to log in to your MyCME account (or to create an account). Upon logging in, select "CME," complete the activity evaluation, and print your certificate.

Call 216-444-2661 or e-mail ccjm@ccf.org with questions.

Maintenance of Certification (MOC) Points

All *Cleveland Clinic Journal of Medicine* CME activities are eligible for ABIM MOC points. Physicians may claim MOC points in addition to CME credit.

Follow the instructions for completing and claiming credit for CME activities.

When you log into your MyCME account, select "CME & MOC" and enter your ABIM identification number and your date of birth. The system will store this information after you enter it the first time.

Complete the quiz and evaluation and print your CME certificate.

February 2023 CME/MOC activity

Estimated time to complete the activity: up to 1 hour

Resistant hypertension: A stepwise approach

Release date: February 1, 2023
Expiration date: January 31, 2024

FINANCIAL DISCLOSURES: In accordance with the Standards for Integrity and Independence issued by the Accreditation Council for Continuing Medical Education (ACCME), The Cleveland Clinic Center for Continuing Education mitigates all relevant conflicts of interest to ensure CE activities are free of commercial bias.

AUTHOR AND STAFF DISCLOSURES: Authors' potential conflicts of interest are disclosed within their articles. *Cleveland Clinic Journal of Medicine's* staff disclose the following financial relationships that may be relevant to their editorial roles: Dr. Brian F. Mandell (Editor in Chief) reports teaching and speaking for Genentech; and consulting for Horizon Pharma. Dr. Kristin Highland (Associate Editor) has disclosed financial interests (consulting, research, teaching, and speaking) with Actelion Pharmaceuticals, Bayer Healthcare, Boehringer Ingelheim, Eiger Biopharmaceuticals, Gententech, Gossamer Bio, Lilly, Reata Pharmaceuticals, United Therapeutics, and Viela Bio. Dr. Christian Nasr (Associate Editor) reports service on advisory committees or review panels for Exelixis, Horizon Pharma, Neurogastrx, and Nevro Corp.; and consulting for Siemens.

DISCLAIMER: The information in these educational activities is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient's medical condition. The viewpoints expressed in these CME activities are those of the authors. They do not represent an endorsement by The Cleveland Clinic Foundation. In no event will The Cleveland Clinic Foundation be liable for any decision made or action taken in reliance upon the information provided through these CME activities.

CME ACCREDITATION:
In support of improving patient care, Cleveland Clinic Center for Continuing Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Cleveland Clinic Center for Continuing Education designates this journal-based CME activity for a maximum of *1.0 AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Participants claiming CME credit from this activity may submit the credit hours to the American Osteopathic Association for Category 2 credit.

AMERICAN BOARD OF INTERNAL MEDICINE (ABIM):
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Please Note: To receive MOC you must select the MOC option during the online credit claiming process and complete the required steps. ABIM MOC points will be reported within 30 days of claiming credit.