Accordant
A CVS Caremark Company

Clinical Practice Guidelines

Myasthenia Gravis

Program Update: 07/31/2013

Approved by:
Andrew Krueger, MD
Donald B. Sanders, MD
Mark B. Bromberg, MD, PhD

Accordant Clinical Practice Guidelines:
Myasthenia Gravis

Table of Contents

INTRODUCTION

The AccordantCare™ program works with health plans to assess, monitor, and support those with certain complex, chronic conditions. The focus of the program is to improve health outcomes and prevent or limit disease-related complications. AccordantCare offers unique services at no additional charge to the patients, putting them in a strong position to adhere to their treatment plan.

There are several ways AccordantCare augments physicians' efforts. Through regular telephone contact, AccordantCare nurses:

- Keep patients informed about the disease process
- Coach patients in self-motivation and self-care skills
- Encourage patients to alert their physician when new symptoms arise
- Direct patients to resources that help pay for medication, transportation, home modifications, etc.
- Ensure preventive and screening measures are accomplished
- Provide emotional support to patients and caregivers
- Screen for depression
- Find local support groups

We invite physicians to make use of the services offered by AccordantCare and to suggest ways we can further patients' treatment goals. To offer feedback, get more information, ask questions, or voice concerns, call toll-free 1-800-948-2497 to speak with a program representative from 8 a.m. to 9 p.m., Monday through Thursday, and from 8 a.m. to 5 p.m. on Friday, Eastern Time. Messages left after hours will be returned the next business day.

Intent of Guidelines

The purpose of this Clinical Practice Guideline is to describe current patterns of practice where there is no fully established national guideline for diagnosis and management. It is not meant to dictate care of patients. Decisions about care are made by the physician and the patient based on the individual needs of that patient.

A patient's health plan may or may not pay for the all medicines, tests, equipment, or services mentioned in this document. Benefits should be checked with the individual's health plan to assure payment.

DISEASE OVERVIEW

Myasthenia gravis (MG) is a chronic autoimmune disease in which autoantibodies prevent normal communication between nerve and muscle cells. Autoantibodies block or destroy acetylcholine receptors (AChR) on the muscle endplate, which prevents binding of the neurotransmitter acetylcholine. In a different type of MG, autoantibodies block another element of the neuromuscular junction, muscle-specific tyrosine kinase

(MuSK). Some patients with myasthenia gravis have no detectable antibodies. The major symptom of myasthenia gravis is a weakness or fatigue of voluntary skeletal muscles. This weakness increases during periods of activity and improves after periods of rest.

The prevalence of MG is estimated at between 10 to 20 per 100,000 population.

The pharmacologic treatment of MG must be individualized and can be expensive. In a 2011 study of the costs associated with MG, pharmacy costs accounted for 43% of the total medical and pharmacy costs. The use of IVIG accounted for 85% of the MG-related pharmacy costs. IVIG was used by 12% of the patients in the cohort, some of whom received more than 20 IVIG infusions during the two-year study period—despite the fact that there is little evidence supporting the use of IVIG for chronic management of MG. The high costs of IVIG demand that cost analysis be performed when IVIG is used frequently.[1]

Types of Disease

In autoimmune generalized myasthenia gravis, weakness may affect almost all voluntary muscles. Ocular myasthenia gravis is the term used to describe autoimmune MG when it is restricted to the striated muscles that control the eye and eyelids.[2,3] Bulbar myasthenia gravis is the term used to describe autoimmune MG when it is restricted to striated muscles that control speech and swallowing. Generalized MG is the least common pattern and refers to weakness of limb muscles, and at times the diaphragm. With generalized MG, ocular and bulbar symptoms may also occur. In transient neonatal myasthenia gravis the transfer of AChR antibodies from the mother to the fetus produces symptoms similar to autoimmune MG, but the baby's symptoms usually go away after 18 days to a few months.[4,5]

Congenital myasthenic syndromes are a group of genetic disorders in which one or more of the proteins needed for neuromuscular transmission is missing or unable to function properly; it is not an autoimmune disease.[5] Accordant only enrolls members with autoimmune generalized, ocular, and bulbar MG.

DIAGNOSIS OF DISEASE

Pharmacologic Tests[6]

Edrophonium (Tensilon®, Enlon®)
Neostigmine (Prostigmin®)
Pyridostigmine (Mestinon®)

Electrophysiologic Tests[6]

Repetitive nerve stimulation (RNS)
Single fiber electromyography (SFEMG)

Immunologic Tests[6]
AChR-binding antibody assay
AChR-blocking antibody test
AChR-modulating antibody test
Striated muscle antibodies
MuSK antibodies

Miscellaneous tests[3,6]
Ice, sleep, and rest tests

APPROACH TO MANAGEMENT OF PRIMARY CONDITION

Treatment Goals
The main goal in treating MG is to effect a sustained or permanent remission.[5] Other goals are to prevent a myasthenic crisis, to avoid progression from ocular to generalized myasthenia, and to improve the patient's quality of life.[3] Once weakness is improved, a major goal is to reduce medications to the least amount that maintains the maximal benefit.[7]

Recommended Drug Therapies

Acetylcholinesterase inhibitors (ACIs)[8]
- pyridostigmine (Mestinon®, Mestinon Timespan[9])
- neostigmine (Prostigmin®)
- Regonol Solution for Injection®[9]

Immunosuppressants (when required, corticosteroids are usually the first choice[8])
Systemic corticosteroids
- prednisone (Prednisone®, Deltasone®, Sterapred®, Orasone®)
- prednisolone
- hydrocortisone
- methylprednisolone
- dexamethasone

Azathioprine[7,8] (Imuran®)
Mycophenolate mofetil (CellCept®)[7,8,10,11]
Cyclosporine[7,8] (Gengraf®, Neoral®, Sandimmune®, or SangCya®)
Tacrolimus[7,8]
Consider methotrexate[12]
Cyclophosphamide[7,8]

Temporary therapy[8,13,14]
Plasmapheresis/plasma exchange
Intravenous immunoglobulin (IVIG)
- Bivigam™ 10%
- Carimune® NF

- Flebogamma® 5% & 10% DIF
- Gammagard Liquid™ 10%
- Gammagard® S/D IgA <1 µg/mL
- Gammaked™ 10%
- Gammaplex® 5%
- Gamunex®-C 10%
- Octagam® 5%
- Privigen® 10%

Surgical therapies

Thymectomy[15]:

- Transsternal, or sternotomy (full or partial)
- Transcervical thymectomy
- Video assisted thoracoscopic surgery (VATS)

PREVENTION AND MANAGEMENT OF COMPLICATIONS

Accordant helps patients prevent and manage complications by teaching early warning signs, encouraging adherence to treatment plans, offering supportive care, and recommending physician contact where needed. The goals and cooperative interventions below do not represent a comprehensive list of complications but reflect some of the more common clinical situations specific to myasthenia gravis. General health topics (e.g., age-appropriate cancer screening) are beyond the scope of this document.

Goal: Control general myasthenia gravis

- Effect a sustained or permanent remission[5]
- Minimize the adverse effects of therapy[16]
- Prevent a myasthenic crisis[3]
- Control symptoms and improve the patient's quality of life[3]
- Address comorbidities

Cooperative interventions include teaching patients to:

- recognize the symptoms of MG and understand the natural history of the disease[17]
- understand any adverse side effects of medications and improve patient compliance[5]
- understand the nonpharmacologic and pharmacologic treatment options[16]
- reduce physical activity when such activity increases weakness, including bulbar or respiratory weakness[18]
- plan activities to take advantage of energy peaks[19]
- get yearly flu vaccination, especially if taking immunosuppressants[20,21]
- have infections treated promptly[17]
- avoid drugs known to increase myasthenic weakness[17,22]
- avoid temperature extremes[22]
- use the One-Breath Count to assess and monitor breathing function

- know the signs and symptoms of myasthenic and cholinergic crises[23]
- eat well-balanced meals that consist of high protein and low carbohydrates and low salt
- understand and effectively manage comorbidities

Goal: Control ocular and bulbar myasthenia gravis and prevent progression to generalized myasthenia[3]

- Effect a sustained or permanent remission[5]
- Minimize the adverse effects of therapy[16]
- Control symptoms and improve the patient's quality of life[3]

Cooperative interventions include teaching patients to:

- understand the nonpharmacologic and pharmacologic treatment options.[16]
- understand the complications of therapy with acetylcholinesterase inhibitors or corticosteroids.[16]
- conserve energy and prevent excessive fatigue.[24]
- plan activities to take advantage of energy peaks.[19]
- recognize the symptoms of generalized MG.
- understand the importance of medication compliance

Goal: Avoid a myasthenic crisis, prevent recurrence of a crisis, or manage crisis so the patient can return to normal function as quickly as possible

Cooperative interventions include teaching patients to:

- understand the signs and symptoms of impending myasthenic crisis
- avoid medicines that increase muscle weakness in MG patients, especially anti-infective agents, including aminoglycosides and fluoroquinolones[25]
- perform the one-breath count test
- inform their doctor immediately about any severe bulbar or respiratory problems
- understand the importance of pneumonia and flu shots, especially if taking immunosuppressants.[20]
- avoid live vaccines
- have infections treated promptly[17]
- avoid temperature extremes and emotional stress[22,26]
- wear a medical alert bracelet and carry a contraindicated medication card

Goal: Avoid a cholinergic crisis

Cooperative interventions include teaching patients to:

- perform the one-breath count test
- take ACIs on time and exactly as prescribed[23]
- recognize the signs and symptoms of cholinergic crisis, particularly weakness that worsens after ACI doses or at least does not get better
- report the signs and symptoms of cholinergic crisis to a nurse, doctor, or emergency room immediately[23]
- wear a medical alert bracelet and carry a contraindicated medication card

Goal: Minimize chewing and swallowing problems to:

- maintain adequate nutrition
- avoid coughing or choking when eating
- avoid aspiration pneumonia

Cooperative interventions include teaching patients to:

- alert their doctor to any of the symptoms of chewing or swallowing problems
- schedule meals close to medication peaks
- use compensatory techniques that may help prevent aspiration
- understand the importance of good oral care
- periodically take their temperature and report any increases to their doctor

Goal: Improve the chances of successful pregnancy in the female MG patient
Cooperative interventions include teaching patients to:

- help coordinate care among neurologist, obstetrician, and neonatologist
- understand the risks and complications of pregnancy
- understand the fetal complications of MG (neonatal MG and arthrogryposis multiplex congenita)[18]
- understand that medication dosage may need frequent adjustment during pregnancy
- report weakening of bulbar and respiratory muscles
- inform their doctor about any other medications they are using[27]
- conserve energy and prevent excessive fatigue[24]
- plan activities to take advantage of energy peaks[19]
- have infections treated promptly[17]
- avoid temperature extremes[22]
- eat well-balanced meals that consist of high protein and low carbohydrates and low salt[28]
- get the annual flu vaccine, especially if taking immunosuppressants[18]
- understand that worsening may occur days to weeks after delivery
-

PATIENT FOLLOW-UP

Follow patients to determine response to therapy and to monitor for treatment side effects.[18]
Screen pregnant women with myasthenia gravis for fetal development of AMC.[18]

PATIENT EDUCATION

Myasthenia Gravis Foundation of America, Inc.

- www.myasthenia.org

References

1. Guptill JT, Marano A, Krueger A, Sanders DB. Cost analysis of myasthenia gravis from a large U.S. insurance database. *Muscle Nerve*. 2011;44(6):907-911.
2. Ocular Myasthenia Gravis: Myasthenia Gravis Foundation of America Web site. http://www.myasthenia.org/LinkClick.aspx?fileticket=uT52jMdiL6I%3d&tabid=84. Accessed April 15, 2013.
3. Elrod RD, Weinberg DA. Ocular myasthenia gravis. *Ophthamol Clin N Amer*. 2004;17(3):275-309.
4. *Myasthenia Gravis Fact Sheet.* Bethesda, MD: National Institutes of Health, National Institute of Neurological Disorders and Stroke; updated December 4, 2012. NIH Publication No. 10-768. http://www.ninds.nih.gov/disorders/myasthenia_gravis/detail_myasthenia_gravis.htm . Accessed April 15, 2013.
5. Nicolle MW. Myasthenia gravis. *Neurologist*. 2002;8(1):2-21.
6. Meriggioli MN, Sanders DB. Advances in the diagnosis of neuromuscular junction disorders. *Am J Phys Med Rehabil*. 2007;84(8):627-638.
7. Sanders DB, Evoli A. Immunosuppressive therapies in myasthenia gravis. *Autoimmunity*. 2010;43(5-6):428-435.
8. Skeie GO, Apostolski S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol*. 2010;17(7):893-902.
9. Pyridostigmine (Mestinon): Myasthenia Gravis Foundation of America Web site. http://www.myasthenia.org/LinkClick.aspx?fileticket=UZBynNVARTc%3d&tabid=84. Accessed April 15, 2013.
10. Hehir MK, Burns TM, Alpers J, Conaway MR, Sawa M, Sanders DB. Mycophenolate mofetil in AChR-antibody-positive myasthenia gravis: outcomes in 102 patients. *Muscle Nerve*. 2010;41(5):593-598.
11. Chan JW. Mycophenolate mofetil for ocular myasthenia. *J Neurol*. 2008;255(4):510-513.
12. Heckmann JM, Rawoot A, Bateman K, Renison R, Badri M. A single-blinded trial of methotrexate versus azathioprine as steroid-sparing agents in generalized myasthenia gravis. *BMC Neurol*. 2011;11(PMC3170595):97.
13. Gajdos P, Chevret S, Toyka K. Plasma exchange for generalized myasthenia gravis. *Cochrane Database Syst Rev*. 2011;(Issue 4):CD002275.
14. Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. *Cochrane Database Syst Rev*. 2012;12:CD002277.
15. Thymectomy: Myasthenia Gravis Foundation of America Web site. http://www.myasthenia.org/LinkClick.aspx?fileticket=BIVoreOXJGo%3d&tabid=84. Accessed April 15, 2103.
16. Kusner LL, Puwanant A, Kaminski HJ. Ocular myasthenia: diagnosis, treatment, and pathogenesis. *Neurologist*. 2006;12(5):231-239.
17. Harrison T. Myasthenia Gravis. In: Ferri FF, ed. *Ferri's Clinical Advisor 2007: Instant Diagnosis and Treatment.* 9th ed. Philadelphia, PA: Mosby Elsevier; 2007.
18. Lisak, R.P.; Sanders, D.B.; Meriggioli, M.N. ACP PIER: Myasthenia Gravise. American College of Physicians Web site.

http://pier.acponline.org/physicians/diseases/d999/d999.html [available with subscription]. Accessed March 28, 2011.
19. Barry L. The patient with myasthenia gravis really needs you. *Nursing (Lond)*. 1982;12(7):50-53.
20. Zinman L, Thoma J, Kwong JC, Kopp A, Stukel TA, Juurlink DN. Safety of influenza vaccination in patients with myasthenia gravis: a population-based study. *Muscle Nerve*. 2009;40(6):947-951.
21. Auriel E, Regev K, Dori A, Karni A. Safety of influenza and H1N1 vaccinations in patients with myasthenia gravis, and patient compliance. *Muscle Nerve*. 2011;43(6):893-894.
22. Myasthenia Gravis. In: Ferri FF, ed. *Practical Guide to the Care of the Medical Patient.* 7th ed. Philadelphia, PA: Mosby Elsevier; 2007.
23. Armstrong SM, Schumann L. Myasthenia gravis: diagnosis and treatment. *J Am Acad Nurse Pract*. 2003;15(2):72-78.
24. O'Donnell L. Caring for patients with myasthenic gravis. *Nursing (Lond)*. 1995;25(3):60-61.
25. Jones SC, Sorbello A, Boucher RM. Fluoroquinolone-associated myasthenia gravis exacerbation: evaluation of postmarketing reports from the US FDA adverse event reporting system and a literature review. *Drug Saf*. 2011;34(10):839-847.
26. Hetherington KA, Losek JD. Myasthenia gravis: myasthenia vs cholinergic crisis. *Pediatr Emerg Care*. 2005;21(8):546-551.
27. Cyclosporine: Myasthenia Gravis Foundation of America Web site. http://www.myasthenia.org/LinkClick.aspx?fileticket=OeAU34faAKU%3d&tabid=84. Accessed April 16, 2013.
28. Prednisone: Myasthenia Gravis Foundation of America Web site. http://www.myasthenia.org/LinkClick.aspx?fileticket=spFjsIzdtOE%3d&tabid=84. Accessed April 15, 2013.

