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Nevertheless, clinically silent involvement of other organs is likely, and vasculitis is frequently found in muscle biopsied at the same time as nerve.

Vasculitic neuropathy may also be seen as part of the vasculitis syndrome occurring in the course of other connective tissue disorders. The most frequent is rheumatoid arthritis, but ischemic neuropathy due to involvement of vasa nervorum may also occur in mixed cryo globulinemia, Sjögren's syndrome, granulomatosis with polyangiitis (formerly known as Wegener's), hypersensitivity angiitis, SLE, and progressive systemic sclerosis. Some vasculitides are associated with antineutrophil cytoplasmic antibodies (ANCAs), which in turn are subclassified as cytoplasmic (cANCA) or perinuclear (pANCA). cANCAs are directed against proteinase 3 (PR3), whereas pANCAs target myeloperoxidase (MPO). PR3/cANCAs are associated with eosinophilic granulomatosis with polyangiitis, whereas MPO/pANCAs are typically associated with microscopic polyangiitis, CSS, and less commonly PAN. Of note, MPO/pANCA has also been seen in minocycline-induced vasculitis. PART 13 Neurologic Disorders Management of these neuropathies, including the "nonsystemic" vasculitic neuropathy, consists of treatment of the underlying condi tion as well as the aggressive use of glucocorticoids and cyclophospha mide. Use of these immunosuppressive agents has resulted in dramatic improvements in outcome, with 5-year survival rates now >80%. Clini cal trials found that the combination of rituximab and glucocorticoids is not inferior to cyclophosphamide and glucocorticoids. Thus, com bination therapy with glucocorticoids and rituximab is recommended as the standard initial treatment, particularly for ANCA-associated vasculitis. Mepolizumab, an anti–interleukin 5 monoclonal antibody, when added to standard care, is also effective for treatment of eosino philic granulomatosis with polyangiitis. ANTI-Hu PARANEOPLASTIC NEUROPATHY (Chap. 99) This uncommon immune-mediated disorder manifests as a sensory neuronopathy (i.e., selective damage to sensory nerve bodies in dorsal root ganglia). The onset is often asymmetric with dysesthesias and sensory loss in the limbs that soon progress to affect all limbs, the torso, and the face. Marked sensory ataxia, pseudoatheto sis, and inability to walk, stand, or even sit unsupported are frequent features and are secondary to the extensive

deafferentation. Subacute sensory neuronopathy may be idiopathic, but more than half of cases are paraneoplastic, primarily related to lung cancer, and most of those are small-cell lung cancer (SCLC). Diagnosis of the underlying SCLC requires awareness of the association, testing for the paraneoplastic antibody, and often positron emission tomography (PET) scanning for the tumor. The target antigens are a family of RNA-binding proteins (HuD, HuC, and Hel-N1) that in normal tissues are only expressed by neurons. The same proteins are usually expressed by SCLC, triggering in some patients an immune response characterized by antibodies and cytotoxic T cells that cross-react with the Hu proteins of the dor sal root ganglion neurons, resulting in immune-mediated neuronal destruction. An encephalomyelitis may accompany the sensory neu ronopathy and presumably has the same pathogenesis. Neurologic symptoms usually precede, by ≤6 months, the identification of SCLC. The sensory neuronopathy runs its course in a few weeks or months and stabilizes, leaving the patient disabled. Most cases are unrespon sive to treatment with glucocorticoids, IVIg, PE, or immunosuppres sant drugs. ■ ■FURTHER READING Amato AA, Ropper AH: Sensory ganglionopathy. N Engl J Med 383:1657, 2020. Cortese A et al: Antibodies to neurofascin, contactin-1, and contactinassociated protein 1 in CIDP: Clinical relevance of IgG isotype. Neurol Neuroimmunol Neuroinflamm 7:E639, 2020. Gwathmey KG et al: Peripheral nerve vasculitis: Classification and disease associations. Neurol Clin 37:303, 2019. Keh RYS et al: COVID-19 vaccination and Guillain-Barré syn drome: Analyses using the National Immunoglobulin Database. Brain 146:739, 2023.

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Myasthenia Gravis and

Other Diseases of the Neuromuscular Junction Myasthenia gravis (MG) is a neuromuscular junction (NMJ) disorder characterized by weakness and fatigability of skeletal muscles. The under lying defect is a decrease in the number of available acetylcholine recep tors (AChRs) at NMJs due to an antibody-mediated autoimmune attack. Available treatments for MG are highly effective, although side effects can limit their use and a cure has remained elusive. ■ ■PATHOPHYSIOLOGY At the NMJ (Fig. 459-1, Video 459-1), acetylcholine (ACh) is syn thesized in the motor nerve terminal and stored in vesicles (quanta). When an action potential travels down a motor nerve and reaches the nerve terminal, ACh from 150 to 200 vesicles is released and com bines with AChRs that are densely packed at the crests of postsynaptic folds on skeletal muscle. The AChR consists of five subunits (2α, 1β, 1δ, 1γ, or ε) arranged around a central pore. When ACh combines with the binding sites on α subunits of the AChR, the channel in the AChR opens, permitting the rapid entry of cations, chiefly sodium, which produces depolarization at the end-plate region of the muscle

fiber. If the depolarization is sufficiently large, it initiates an action potential that is propagated along the muscle fiber, triggering muscle contraction. This process is rapidly terminated by hydrolysis of ACh by acetylcholinesterase, which is present within the synaptic cleft, and by diffusion of ACh away from the receptor. Muscle-specific tyrosine kinase (MuSK) is a postsynaptic trans membrane protein that helps stabilize postsynaptic clustering of AChRs. Agrin is released from the presynaptic motor nerve terminal and binds low-density lipoprotein receptor-related protein 4 (LRP4). This agrin-LRP4 complex activates MuSK. This facilitates recruitment of cytoplasmic proteins, including downstream of tyrosine kinase 7 (DOK7) and rapsyn, to assist in clustering AChR. These various pro teins are important in the pathogenesis of not only MG but also some of the hereditary congenital myasthenic syndromes. In MG, the fundamental defect is a decrease in the number of available AChRs at the postsynaptic muscle membrane. In addition, the postsynaptic folds are flattened, or “simplified.” These changes result in decreased efficiency of neuromuscular transmission. There fore, although ACh is released normally, it produces small end-plate

potentials that may fail to trigger muscle action potentials. Failure of transmission results in muscle weakness. The amount of ACh released per impulse normally declines on repeated activity (termed presynaptic rundown). In myasthenic patients, reduced efficiency of neuromuscular transmission, combined with this normal rundown, results in activation of fewer and fewer muscle fibers by successive nerve impulses, and hence increasing weakness, or myasthenic fatigue. This mechanism also accounts for the decremental response to repetitive nerve stimulation seen on electro diagnostic testing. MG is an autoimmune disorder most commonly caused by antiAChR antibodies. The anti-AChR antibodies reduce the number of available AChRs at NMJs by three distinct mechanisms: (1) accelerated turnover of AChRs by a mechanism involving cross-linking and rapid endocytosis of the receptors; (2) damage to the postsynaptic muscle membrane through antibody-mediated complement activation; and (3) blockade of the active site of the AChR (i.e., the site that normally binds ACh). An immune response to MuSK, a protein involved in AChR clustering at the NMJ (as noted above), also results in MG, with reduction of AChRs demonstrated experimentally. Anti-MuSK anti body occurs in ~10% of patients (~40% of AChR antibody–negative patients with generalized MG), whereas 1–3% have antibodies to Myelin sheath Acetate Choline Ca+ ions AChE Voltage-gated Na+ channels A FIGURE 459-1 Illustrations of (A) a normal presynaptic neuromuscular junction, (B) a normal postsynaptic terminal, and (C) a myasthenic neuromuscular junction. AChE, acetylcholinesterase. See text for description of normal neuromuscular transmission. The myasthenia gravis (MG) junction demonstrates a reduced number of acetylcholine receptors (AChRs); flattened, simplified postsynaptic folds; and a widened synaptic space. See Video 459-1 also. (Reproduced with permission from AA Amato, J Russell: Neuromuscular Disorders, 2nd ed. New York, McGraw-Hill; 2016.)

another protein at the NMJ—LRP4—that, as mentioned, is also important for clustering of AChRs. These pathogenic antibodies are IgG and are T-cell dependent. Thus, immunotherapeutic strategies directed against either the antibody-producing B cells or helper T cells, directly reducing the pathogenic antibodies, or blocking complementmediated destruction of the AChRs are all effective in anti-AChRpositive MG. MuSK antibodies exert their pathogenic effect by directly inhibiting binding between MuSK and LRP4, leading to loss of AChRs and other functions of MuSK. Of note, MuSK antibodies are of the IgG4 subtype and, as such, do not activate complement. As a result, anti-MuSK-positive MG does not respond to complement inhibition. LRP4 antibodies are of the IgG1

subclass and also cause complementmediated destruction, similar to AChR antibodies, and possibly inter rupt agrin-induced MuSK activation.

Although MG is caused by autoantibodies, a significant contribution exists from T cells, including T regulatory (Treg) cells. These Tregs are critical in suppressing activation of other immune cells that have escaped negative selection in the thymus. Because these other cells have not been deleted by negative selection or suppressed in the periphery, they attack “self” antigens. Deficiency or dysfunction of Tregs contrib utes to the pathogenesis not only of MG but of many other autoim mune diseases. The primary source of Treg cells is the thymus, which CHAPTER 459 Myasthenia Gravis and Other Diseases of the Neuromuscular Junction SNARE proteins Syntaxin-1 SNAP 25 Synaptotagmin Synaptobrevin ChAT Choline acetyltransferase Acetylcholine receptor Axon Voltage-gated K+ channel ChAT Agrin Active zone Voltage-gated Ca+ channel Myofibril

ACh (acetylcholine) Vesicle SNARE proteins Syntaxin-1 SNAP 25 Synaptotagmin Synaptobrevin Vesicle fusion Agrin ACh receptor AChE Dystroglycan β δ α α γ Rapsyn PART 13 Neurologic Disorders Dok-7 MuSK Lrp4 Na+ channels Myofibril B FIGURE 459-1 (Continued) is abnormal in ~75% of patients with AChR antibody–positive MG. In ~65%, the thymus is “hyperplastic,” with the presence of active germi nal centers detected histologically. The hyperplastic thymus may be but is not necessarily enlarged. An additional 10% of patients have thymic tumors (thymomas). Muscle-like cells within the thymus (myoid cells), which express AChRs on their surface, may serve as a source of auto antigen and trigger the autoimmune reaction within the thymus gland. ■ ■CLINICAL FEATURES MG has an incidence ranging from 6.3 to 29 per million and a preva lence ranging from 100 to 361 per million. It affects individuals in all age groups, but peak incidence occurs in women in their twenties and thirties and in men in their fifties and sixties. Overall, women are affected more frequently than men, in a ratio of ~3:2. Cardinal features are weakness and fatigability of muscles. Myasthenic weakness often worsens during repeated use (fatigue) and/or late in the day and may improve following rest or sleep. The course of MG is variable. Exacerbations and remissions may occur, particularly during the first 1–3 years after disease onset. In ~85% of patients, myasthenic weakness becomes generalized, affecting facial, bulbar, axial, or limb muscles in addition to ocular muscles. If weakness remains restricted to ocular muscles for 3 years, future generalization is unlikely, and these patients are said to have ocular MG. However, we have seen rare patients generalize >5 years after onset of ocular MG. Unrelated infections, systemic disorders, or tapering of MG therapies can lead to increased myasthenic weakness and may precipitate myasthenic exacerbation or “crisis” (see below). Some exacerbations occur without any identifiable precipitating factors. The distribution of muscle weakness often has a characteristic pat tern. Cranial muscles, particularly extraocular and eyelid muscles, are frequently involved early in the course of MG; diplopia and ptosis are common initial symptoms. Facial weakness produces a “snarling”

Vesicle SNARE proteins ACh Syntaxin-1 SNAP 25 Synaptotagmin Synaptobrevin Vesicle fusion Agrin AChR autoantibody Dystroglycan Complement AChE α α α α Lysis of ACh receptors Na+ channel Myofibril C expression when the patient attempts to smile. Weakness in chewing is most noticeable after prolonged effort or chewing hard or tough foods like meat. Speech may have a nasal timbre caused by weakness of the palate or a dysarthric “mushy” quality due to tongue weakness. Hoarseness can occur from laryngeal weakness. Difficulty in swallow ing (dysphagia) may occur as a result of weakness of the palate, tongue, or pharynx, giving rise to nasal regurgitation or

aspiration of liquids or food. Bulbar, neck, and ventilatory weakness can be especially promi nent in MuSK antibody–positive MG. Weakness in neck extensor muscles can lead to head drop. Limb weakness in MG is often proximal and may be asymmetric. Nonetheless, some patients manifest with mainly distal weakness (finger and wrist drop or foot drop). Deep ten don reflexes are typically preserved. Sensory symptoms, sensory loss, and pain are absent. If ventilatory weakness necessitates intubation or noninvasive ventilation to avoid intubation, the patient is said to be in MG crisis. All other worsening is termed exacerbation. ■ ■DIAGNOSIS AND EVALUATION (TABLE 459-1) The diagnosis is suspected based on weakness and fatigability in the typical distribution described above, without loss of deep tendon reflexes or sensory signs or symptoms or abnormality of other neuro logic functions. The suspected diagnosis should be confirmed defini tively before treatment is undertaken; this is essential because (1) other treatable conditions may closely resemble MG and (2) the treatment of MG may involve surgery and the prolonged use of drugs with potential side effects. Ice-Pack Test If a patient has ptosis, application of a pack of ice over a ptotic eye for 2 min often results in improvement if the ptosis is due to an NMJ defect. A lid rise of 2 mm following this cooling is considered a positive result. This is hypothesized to be due to less depletion of quanta of AChR in the cold and reduced activity of

TABLE 459-1 Diagnosis of Myasthenia Gravis (MG) History Diplopia, ptosis, dysarthria, dysphagia, dyspnea Weakness in characteristic distribution: proximal limbs, neck extensors, generalized Fluctuation and fatigue: worse with repeated activity, improved by rest Effects of previous treatments Physical examination Evaluation for ptosis at rest and following 1 min of exercise, extraocular muscles and subjective diplopia, orbicularis oculi and oris strength, jaw opening and closure Assessment of muscle strength in neck and extremities Weakness following repeated shoulder abduction Vital capacity measurement Absence of other neurologic signs Laboratory testing Anti-AChR radioimmunoassay: ~85% positive in generalized MG; 50% in ocular MG; definite diagnosis if positive; negative result does not exclude MG; ~40% of AChR antibody–negative patients with generalized MG have anti-MuSK antibodies and ~2% have LRP4 antibodies Repetitive nerve stimulation: decrement of >10% at 3 Hz: highly probable Single-fiber electromyography: blocking and jitter, with normal fiber density; confirmatory, but not specific Edrophonium chloride (Enlon) 2 mg + 8 mg IV; highly probable diagnosis if unequivocally positive Ice-pack test looking for improvement in ptosis is very sensitive For ocular or cranial MG: exclude intracranial lesions by CT or MRI Abbreviations: AChR, acetylcholine receptor; CT, computed tomography; LRP4, lipoprotein receptor-related protein 4; MRI, magnetic resonance imaging; MuSK, muscle-specific tyrosine kinase. acetylcholinesterase at the NMJ. It is a quick and easy test to do in the clinic or at the bedside of a hospitalized patient. Autoantibodies Associated with MG As previously mentioned, anti-AChR antibodies are detectable in the serum of ~85% of all myas thenic patients but in only ~50% of patients with weakness confined to the ocular muscles. The presence of anti-AChR antibodies is virtually diagnostic of MG, but a negative test does not exclude the disease. The measured level of anti-AChR antibody does not correspond well with the severity of MG in different patients. Antibodies to MuSK are pres ent in up to 40% of AChR antibody–negative patients with generalized MG depending on the population. MuSK antibodies are rarely present in AChR antibody–positive patients or in patients with MG limited to ocular muscles. A small proportion of MG patients without antibodies to AChR or MuSK have antibodies to LRP4. Sending LRP4 antibodies has a low specificity. As such, we only check them in patients with clear MG by phenotype and electrodiagnostic testing but absent AChR and MuSK antibodies. Additionally, antibodies against agrin also have been found in rare patients with MG, but it is unclear if they are pathogenic, and

they are not currently tested in clinical practice. Additionally, anti-striated muscle antibodies directed against titin and other skeletal muscle components have been identified in some patients. However, they are not pathogenic, and their presence does not confirm the diagnosis of MG or the presence of a thymoma. Given their limited utility and potential for misinterpretation, we do not order them. Furthermore, antibodies directed against Caspr2 (contactin-associated protein-like 2) may coexist primarily in patients with thymoma who have MG and neuromyotonia or Morvan's syndrome. The presence of these antibodies can help confirm the diagnosis of a second paraneo plastic syndrome in these clinical situations. Electrodiagnostic Testing Repetitive nerve stimulation may provide helpful diagnostic evidence of MG. Medications that inhibit acetylcholinesterase should be stopped 12–24 h or for as long as pos sible before testing. It is best to test weak muscles or proximal muscle groups. Electrical stimulation is delivered at a rate of two or three per

second to the appropriate nerves, and action potentials are recorded from the muscles. In normal individuals, the amplitude of the evoked muscle action potentials does not change by >10% at these rates of stimulation. However, in myasthenic patients, there is a rapid reduc tion of >10% in the amplitude of the evoked responses. If repetitive nerve stimulation is normal and/or symptoms are exclusively ocular, single-fiber electromyography (EMG), a specialized more sensitive test typically done at MG referral centers, is performed.

Anticholinesterase Test Drugs that inhibit the enzyme ace tylcholinesterase allow ACh to interact repeatedly with the limited number of AChRs in MG, producing improvement in muscle strength. Edrophonium was most commonly used historically for diagnostic testing because of the rapid onset (30 s) and short duration (~5 min) of its effect, with an objective endpoint such as ptosis typically measured. Edrophonium is no longer used due to potential for side effects and lack of availability. CHAPTER 459 Pulmonary Function Tests (Chap. 295) Measurements of ven tilatory function are valuable because of the frequency and seriousness of respiratory impairment in myasthenic patients. Differential Diagnosis Other conditions that cause weakness of the cranial and/or somatic musculature include nonautoimmune congenital myasthenia, drug-induced myasthenia, Lambert-Eaton myasthenic syndrome (LEMS), hyperthyroidism (Graves' disease), botulism, intracranial mass lesions, oculopharyngeal dystrophy, and mitochondrial myopathy (Kearns-Sayre syndrome, progressive exter nal ophthalmoplegia). Treatment with immune checkpoint inhibitors (ICIs) for cancer may also result in autoimmune MG. Myositis and myocarditis are also often found in combination with MG as a compli cation of ICIs (Chap. 377). Symptoms typically begin after the first or second cycle of treatment, with ptosis, diplopia, bulbar, neck, extrem ity weakness, and respiratory weakness. ICI-related myositis without disordered neuromuscular transmission can mimic MG, itself causing a similar pattern of weakness including ocular and bulbar weakness, which is uncommon in other autoimmune myopathies. Patients usu ally improve when the ICI is discontinued and a short course of gluco corticoids is given, with intravenous immunoglobulin (IVIg) or plasma exchange depending on severity; however, with fulminant disease, the fatality rate remains high, mainly due to the concurrent myocarditis. Treatment with penicillamine (used for scleroderma or rheumatoid arthritis) has also been associated with MG. Aminoglycoside, quino lone and macrolide antibiotics, intravenous magnesium, or procain amide can also cause exacerbation of weakness in myasthenic patients; very large doses can cause neuromuscular weakness in normal indi viduals. Botulinum toxin injections should be avoided in MG patients. Myasthenia Gravis and Other Diseases of the Neuromuscular Junction The congenital myasthenic syndromes (CMS) comprise a rare het

erogeneous group of disorders of the NMJ that are not autoimmune but rather are due to mutations in >30 identified genes. Virtually any component of the NMJ may be affected. Alterations in function of the presynaptic nerve terminal, in the various subunits of the AChR, acetylcholinesterase, or the other molecules involved in end-plate development or maintenance, have been identified in the different forms of CMS. These disorders share many of the clinical features of autoimmune MG, including weakness and fatigability of proximal or distal extremity muscles and often involving extraocular and eyelid muscles similar to the distribution in autoimmune MG. CMS is most often suspected when symptoms of myasthenia began in infancy or childhood; however, some patients initially present in adulthood. As in autoimmune MG, repetitive nerve stimulation is often associated with a decremental response. Some forms of CMS (e.g., acetylcholinesterase deficiency, prolonged open channel syndrome) have a feature of afterdischarges that are not seen in MG. An additional clue is the absence of AChR and MuSK antibodies, although these are absent in ~10% of generalized MG patients (so-called double seronegative MG). The prevalence of CMS is estimated at ~3.8 per 100,000. The most common genetic defects occur in the ε subunit of the AChR, account ing for ~50% of CMS cases, with mutations in the genes encoding for rapsin, COLQ, DOK7, agrin, and GFPT together accounting for ~40%.

In most of the recessively inherited forms of CMS, the mutations are heteroallelic; that is, different mutations affecting each of the two alleles are present. Features of the most common forms of CMS are summarized in Table 459-2. Molecular analysis is required for precise elucidation of the defect; this may lead to helpful treatment as well as genetic counseling. Some forms of CMS improve with acetylcholines terase inhibitors, while others (e.g., slow channel syndrome, acetylcho linesterase deficiency, DOK7-related CMS) actually worsen. Fluoxetine and quinidine can be useful for slow channel syndrome, and albuterol for mutations affecting acetylcholinesterase, DOK7, rapsyn, and agrin. Additionally, ephedrine and 3,4-diaminopyridine (3,4-DAP) may be of benefit in some forms of CMS.

LEMS is a presynaptic disorder of the NMJ that causes skeletal muscle weakness; however, the pattern of involvement differs from that in MG. The proximal muscles of the lower limbs are most commonly affected, although other muscles may be involved as well. Cranial and bulbar weakness, including ptosis of the eyelids, diplopia, dysarthria, and dysphagia may occur but are not typically the presenting or prominent symptoms. However, LEMS can be further distinguished from MG because patients with LEMS often have depressed or absent reflexes and experience autonomic symptoms such as dry mouth, orthostasis, and impotence (Chap. 451). Nerve stimulation produces an initial low-amplitude compound muscle action potential and, at low rates of repetitive stimulation (2–3 Hz), a decremental response as seen in MG; however, at high rates (20–50 Hz) or following brief exer cise, incremental responses occur. LEMS is caused by autoantibodies directed against P/Q-type calcium channels at the presynaptic motor nerve terminals detected in ~85% of LEMS patients. These autoan tibodies impair the release of ACh from nerve terminals. In young adults, particularly women, LEMS is less commonly associated with an underlying cancer. However, in older adults, LEMS is associated with malignancy, most commonly small-cell lung cancer (SCLC), and virtually all of these patients have P/Q-type calcium channel autoanti bodies. The tumor cells may express calcium channels that stimulate the autoimmune response. Initial management requires comprehensive evaluation for malignancy and reassessment if the initial malignancy evaluation is negative. Treatment of LEMS symptoms involves therapy first with 3,4-DAP and

pyridostigmine. 3,4-DAP acts by blocking potassium channels, which results in prolonged depolarization of the motor nerve terminals, thus enhancing ACh release. Pyridostigmine prolongs the action of ACh, allowing repeated interactions with AChRs. If symptoms are severe or life-threatening or if symptomatic therapy is insufficient, immunomodulatory therapy including IVIg or plasma exchange can be used. PART 13 Neurologic Disorders Botulism (Chap. 158) is due to potent bacterial toxins produced by any of eight different strains of Clostridium botulinum. The toxins enzymatically cleave specific proteins essential for the release of ACh from the motor nerve terminal, thereby interfering with neuromuscu lar transmission. Most commonly, botulism is caused by ingestion of improperly prepared food containing toxin. Rarely, the nearly ubiq uitous spores of C. botulinum may germinate in wounds. In infants, the spores may germinate in the gastrointestinal (GI) tract and release toxin, causing muscle weakness. Patients present with myasthenia-like bulbar weakness (e.g., diplopia, dysarthria, dysphagia) and lack sensory symptoms and signs. Weakness may generalize to the limbs and may result in respiratory failure. Reflexes are present early, but they may be diminished as the disease progresses. Mentation is normal. Auto nomic findings include paralytic ileus, constipation, urinary retention, dilated or poorly reactive pupils, and dry mouth. The demonstration of toxin in serum by bioassay is definitive, but the results usually take a relatively long time to be completed and may be negative. Nerve stimulation studies reveal reduced compound muscle action potential (CMAP) amplitudes that increase following high-frequency repetitive stimulation. Treatment includes ventilatory support and aggressive inpatient supportive care (e.g., nutrition, deep-vein thrombosis pro phylaxis) as needed. Antitoxin should be given as early as possible to be effective and can be obtained through the Centers for Disease Control and Prevention. A preventive vaccine is available for laboratory work ers or other highly exposed individuals.

Hyperthyroidism is readily diagnosed or excluded by tests of thyroid function, which should be carried out routinely in patients with suspected MG. Abnormalities of thyroid function (hyper- or hypothyroidism) may increase myasthenic weakness. Diplopia resem bling that in MG may occasionally be due to an intracranial mass lesion that compresses nerves to the extraocular muscles (e.g., sphenoid ridge meningioma), but magnetic resonance imaging (MRI) of the head and orbits usually reveals the lesion. Progressive external ophthalmoplegia is a rare condition resulting in weakness of the extraocular muscles and often symmetric ptosis, which may be accompanied by weakness of the proximal muscles of the limbs and other systemic features. Most patients with this condition have mitochondrial disorders that can be detected by genetic testing or with muscle biopsy (Chap. 460). Search for Associated Conditions (Table 459-3) Myasthenic patients have an increased incidence of several associated disorders. Thymic abnormalities occur in ~75% of AChR antibody–positive patients, as noted above. Neoplastic change (thymoma) may produce enlargement of the thymus, which is detected by chest computed tomography (CT) or MRI. A thymic shadow on CT scan may normally be present through young adulthood, but enlargement of the thymus in a patient age >40 years is highly suspicious for thymoma. Approxi mately 10–15% of patients with MG have thymoma, and therefore, chest imaging to evaluate this possibility is performed at diagnosis. Hyperthyroidism occurs in 3–8% of patients and may aggravate the myasthenic weakness. Thyroid function tests should be obtained in all patients with suspected MG. Other autoimmune disorders, most com monly systemic lupus erythematosus and rheumatoid arthritis, can coexist with MG; associations also occur with neuromyelitis optica, multiple sclerosis, neuromyotonia, Morvan’s syndrome (encephalitis, insomnia, confusion, hallucinations, autonomic dysfunction, and neuromyotonia), rippling muscle disease, granulomatous myositis/ myocarditis,

and chronic inflammatory demyelinating polyneuropathy. An infection of any kind can exacerbate typical MG and should be sought carefully in patients with relapses. Because of the side effects of glucocorticoids and other immunotherapies used in the treatment of MG, a thorough medical investigation should be undertaken, searching specifically for evidence of chronic or latent infection (such as tubercu losis or hepatitis), hypertension, diabetes, renal disease, and glaucoma. TREATMENT Myasthenia Gravis The prognosis of MG has improved strikingly as a result of advances in treatment. Nearly all myasthenic patients can be returned to full productive lives with proper therapy. Common treatments for MG include anticholinesterase medications, glucocorticoids and other immunosuppressive agents, thymectomy, plasmapheresis, IVIg, rituximab, and the recently approved complement inhibitors and neonatal Fc receptor (FcRn) antagonists (Fig. 459-2). ANTICHOLINESTERASE MEDICATIONS Anticholinesterase medication produces at least partial improve ment in most myasthenic patients, although improvement is com plete in only a few. Patients with anti-MuSK MG generally obtain less benefit from anticholinesterase agents than those with AChR antibodies and may actually worsen. Pyridostigmine is the most widely used anticholinesterase drug and is initiated at a dosage of 30–60 mg three to four times daily. The beneficial action of oral pyridostigmine begins within 15–30 min and lasts for 3–4 h, but individual responses vary. The frequency and amount of the dose should be tailored to the patient’s individual requirements through out the day. For example, patients with weakness in chewing and swallowing may benefit by taking the medication before meals so that peak strength coincides with mealtimes. Long-acting pyr idostigmine may occasionally be useful to get the patient through the night but should not be used for daytime medication because of variable absorption. The maximum useful dose of pyridostigmine

TABLE 459-2 Congenital Myasthenic Syndromes (CMS) CMS SUBTYPE GENE CLINICAL FEATURES Presynaptic Disorders CMS with paucity of ACh release CHAT; CHT AR; early onset, respiratory failure at birth, episodic apnea, improvement with age Synaptic Disorders AChE deficiency COLQ AR; early onset; variable severity; axial weakness with scoliosis; apnea; +/– EOM involvement, slow or absent pupillary responses Postsynaptic Disorders Involving AChR Deficiency or Kinetics Primary AChR deficiency AChR subunit genes AR; early onset; variable severity; fatigue; typical MG features AChR kinetic disorder: slow channel syndrome AChR subunit genes AD; onset childhood to early adult; weak forearm extensors and neck; respiratory weakness; variable severity AChR kinetic disorder: fast channel syndrome AChR subunit genes AR; early onset; mild to severe; ptosis, EOM involvement; weakness and fatigue Postsynaptic Disorders Involving Abnormal Clustering/Function of AChR DOK 7 AR; limb girdle weakness with ptosis but no EOM involvement Rapsyn AR; early onset with hypotonia, respiratory failure, and arthrogryposis at birth to early adult onset resembling MG Agrin AR; limb girdle or distal weakness, apnea Decremental response to RNS MuSK AR; congenital or childhood onset of ptosis, EOM and progressive limb girdle weakness LRP4 AR; congenital onset with hypotonia; ventilatory failure, mild ptosis, and EOM weakness Other Postsynaptic Disorders Limb-girdle CMS with tubular aggregates GFPT1; DPAGT1; ALG2; ALG14; DPAGT1 AR; limb-girdle weakness usually without ptosis or EOM weakness; onset in infancy or early adult Congenital muscular dystrophy with myasthenia Plectin AR; infantile or childhood onset of generalized weakness including ptosis and EOM; epidermolysis bullosa simplex; elevated CK Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; AChR, acetylcholine receptor; AD, autosomal dominant; AR, autosomal recessive; CHAT, choline acetyl transferase; CHT, sodium-dependent high-affinity choline transport 1; CK, creatine kinase; CMA, congenital myasthenic syndrome; COLQ, collaganic tail of endplate acetylcholinesterase; 3,4-DAP, 3,4-diaminopyridine;

Dok7, downstream of tyrosine kinase 7; DPAGT1, UDP-N-acetylglucosamine-dolichyl-phosphate N-acetylglucosamine phosphotransferase; EOM, extraocular muscle; GFPT1, glutamine-fructose-6-phosphate aminotransferase 1; LRP4, lipoprotein receptor-related protein 4; MG, myasthenia gravis; MuSK, muscle specific kinase; RNS, repetitive nerve stimulation. Source: Reproduced with permission from AA Amato, et al (eds): Amato and Russell's Neuromuscular Disorders, 3rd ed. New York: McGraw Hill; 2025. rarely exceeds 360–480 mg daily. Overdosage with anticholines terase medication may cause increased weakness and other side effects. In some patients, muscarinic side effects of the anticholin esterase medication (diarrhea, abdominal cramps, excess salivation, nausea) may limit the dose tolerated. Atropine/diphenoxylate or loperamide is useful for the treatment of gastrointestinal symptoms. THYMECTOMY Two separate issues should be distinguished: (1) surgical removal of thymoma, and (2) thymectomy as a treatment for MG. Surgical removal of a thymoma is necessary because of the possibility of local tumor spread, although most thymomas are histologically benign. A large international study (the MGTX trial) of extended transsternal thymectomy in nonthymomatous, AChR antibody–positive, gener alized MG demonstrated that participants who underwent thymec tomy had improved strength and function, required less prednisone and fewer additions of second-line agents (e.g., azathioprine), and

ELECTROPHYSIOLOGIC FEATURES RESPONSE TO ACHE INHIBITORS TREATMENT Decremental response to RNS Improve AChE inhibitors; 3,4-DAP After discharges on nerve stimulation and decrement on RNS Worsen Albuterol; ephedrine; 3,4-DAP; avoid AChE inhibitors Decremental response to RNS Improve AChE inhibitors; 3,4-DAP After discharges on nerve stimulation and decrement on RNS Worsen Fluoxetine and quinidine; avoid AChE inhibitors CHAPTER 459 Decremental response to RNS Improve AChE inhibitors; caution with 3,4-DAP Myasthenia Gravis and Other Diseases of the Neuromuscular Junction Decremental response to RNS Variable Albuterol; ephedrine; may worsen with AChE inhibitors Decremental response to RNS Variable Albuterol Variable Albuterol; may worsen with AChE inhibitors Decremental response to RNS Variable Variable response to AChE inhibitors and 3,4-DAP Positive response to albuterol Decremental response to RNS Worsen Worsen with AChE inhibitors Decremental response to RNS Variable Albuterol; ephedrine; variable response to AChE inhibitors and 3,4DAP; albuterol Decremental response to RNS Variable No response to AChE and 3,4-DAP had fewer hospitalizations for exacerbations lasting at least 5 years. Whether or not less invasive thymectomy provides identical ben efit is unknown; however, less invasive techniques are now used in most thymectomies at many institutions. Importantly, patients with ocular myasthenia, MuSK-positive, and seronegative MG were all excluded from the MGTX study; retrospective and anecdotal evidence suggests that these patients may not benefit from thymec tomy. Thymectomy should never be carried out as an emergency procedure, but only when the patient is adequately prepared. If nec essary, treatment with IVIg or plasmapheresis may be used before surgery to maximize strength in weak patients. IMMUNOTHERAPY The choice of immunotherapy should be guided by the relative benefits and risks for the individual patient and the urgency of treatment. It is helpful to develop a treatment plan based on shortterm, intermediate-term, and long-term objectives. For example,

TABLE 459-3 Disorders Associated with Myasthenia Gravis and Recommended Laboratory Tests Associated disorders Disorders of the thymus: thymoma, hyperplasia Other autoimmune neurologic disorders: chronic inflammatory demyelinating polyneuropathy, neuromyelitis optica Other autoimmune disorders: Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis, systemic

lupus erythematosus, skin disorders, family history of autoimmune disorder Disorders or circumstances that may exacerbate myasthenia gravis: hyperthyroidism or hypothyroidism, occult infection, medical treatment for other conditions (see Table 459-5) Disorders that may interfere with therapy: tuberculosis, diabetes, peptic ulcer, gastrointestinal bleeding, renal disease, hypertension, asthma, osteoporosis, obesity Recommended laboratory tests or procedures CT or MRI of chest PART 13 Neurologic Disorders Tests for antinuclear antibodies, rheumatoid factor Thyroid function tests Testing for tuberculosis Fasting blood glucose, hemoglobin A1c Pulmonary function tests Bone densitometry Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging. Establish diagnosis unequivocally (see Table 459-1) Search for associated conditions (see Table 459-3) Ocular only Crisis Generalized MRI of brain (if positive, reassess) Anticholinesterase (pyridostigmine) Anticholinesterase (pyridostigmine) Intensive care (tx respiratory infection; fluids) Evaluate for thymectomy (indications: thymoma or generalized MG with anti-AChR antibodies); evaluate surgical risk, FVC Good risk (good FVC) Poor risk (low FVC) Plasmapheresis or intravenous Ig then If unsatisfactory Thymectomy Improved If not improved Evaluate clinical status; if indicated, go to immunosuppression Immunosuppression See text for short-term, intermediate, and long-term treatments FIGURE 459-2 Algorithm for the management of myasthenia gravis. FVC, forced vital capacity; MRI, magnetic resonance imaging.

if immediate improvement is essential typically because of the severity of weakness, IVIg should be administered or plasmapher esis should be undertaken as “rescue” therapy. For the intermediate term, glucocorticoids, cyclosporine or tacrolimus, rituximab, and the newer complement inhibitors and FcRn antagonists generally produce clinical improvement within a period of 1–3 months. They can be used for bridging until other immunotherapies become effective or in refractory patients. The beneficial effects of other nonsteroidal immunosuppressive therapies, azathioprine and myco phenolate mofetil, usually begin after many months (and as long as 1–1.5 years), However, these drugs have advantages over glucocor ticoids for the long-term treatment of patients with MG. Rituximab is highly effective in patients with MuSK antibody–positive MG. Glucocorticoid Therapy Glucocorticoids, when used properly, produce improvement in myasthenic weakness in the great major ity of patients. To minimize adverse side effects, prednisone should be given in a single morning dose rather than in divided doses throughout the day. In patients with only ocular or mild general ized weakness, the initial dose can be relatively low (15–25 mg/d). The dose is increased stepwise, as tolerated by the patient (usually by 5 mg/d at 7- to 14-day intervals), until there is marked clinical improvement or a dose of 50–60 mg/d is reached. The full effect of a particular dose of prednisone often takes 2–3 weeks to observe. In patients with more severe weakness and those already in the hospital and/or intubated, starting at a high dose is reasonable, typically after pretreatment with IVIg or plasma exchange to protect against early steroid-associated worsening. Patients are maintained for about a month on the dose that controls their symptoms, and then the dosage is slowly tapered (no faster than 10 mg a month until on 20 mg daily and then by 2.5–5 mg every 1–3 months until on 10 mg daily, and more slowly thereafter) to determine the minimum effective dose. Close monitoring both for side effects and for efficacy is essential. Some patients can be managed with out the addition of other immunotherapies. Patients on long-term glucocorticoid therapy must be followed carefully to prevent or treat adverse side effects. The most common errors include (1) an insufficient duration or dose of prednisone—improvement may be delayed and gradual; (2) tapering the dosage too early, too rapidly, or excessively; and (3) lack of attention to prevention and treatment of side effects. Other Immunotherapies Mycophenolate mofetil, azathioprine, cyclosporine, tacrolimus, rituximab, and rarely, cyclophospha mide are

effective in many patients, either alone or in various combinations. Mycophenolate mofetil is widely used because of its presumed effectiveness and relative lack of side effects. A dose of 1–1.5 g bid is recommended. Its mechanism of action involves inhibition of purine synthesis by the de novo pathway. Since lymphocytes have only the de novo pathway, but lack the alternative salvage pathway that is present in all other cells, mycophenolate inhibits proliferation of lymphocytes but not proliferation of other cells. It does not kill or eliminate preexisting autoreactive lymphocytes, and therefore, clinical improvement may be delayed for many months to a year, until the preexisting autoreactive lymphocytes die spontaneously. The advantage of mycophenolate lies in its relative paucity of adverse side effects. The primary side effect is diarrhea or other GI symptoms. Rare side effects are development of leukopenia and very small risks of malignancy or progressive multifocal leukoencephalopathy inherent in nearly all immu nosuppressive treatments. Although two published studies did not show positive outcomes, most experts attribute the negative results to flaws in the trial designs, and mycophenolate is widely used and supported in many guidelines for long-term treatment of myasthenic patients. Azathioprine has long been used for MG, and a randomized, clinical trial demonstrated that it was effective in reducing the dos age of prednisone necessary to control MG symptoms. However, the beneficial effect can take a year or more to become evident.

Approximately 10–15% of patients are unable to tolerate aza thioprine because of idiosyncratic reactions consisting of flulike symptoms (e.g., fever and malaise, abdominal pain), bone marrow suppression, or abnormalities of liver function. An initial dose of 50 mg/d is given for about a week to test for these side effects. If this dose is tolerated, it is increased by 50 mg weekly to 150 mg daily. Some patients require additional increases to reach a dose of ~2–3 mg/kg of total body weight or until the white blood count falls to 3000–4000/μL. Allopurinol should never be used in combination with azathioprine because the two drugs share a common degrada tion pathway; the result may be severe bone marrow suppression due to increased effects of the azathioprine. The calcineurin inhibitors cyclosporine and tacrolimus are effec tive in MG and work more rapidly than azathioprine and mycophe nolate. However, both, and cyclosporin in particular, are associated with more frequent severe side effects including hypertension, nephrotoxicity, and drug interactions. The usual dose of cyclo sporine is 4–5 mg/kg per d, and the average dose of tacrolimus is 0.07–0.1 mg/kg per d, given in two equally divided doses. “Trough” blood levels are measured 12 h after the evening dose. The thera peutic range for the trough level of cyclosporine is 150–200 ng/L, and for tacrolimus, it is 5–15 ng/L. Rituximab is a monoclonal antibody that binds to the CD20 mol ecule on B lymphocytes. It is widely used for the treatment of B-cell lymphomas and has also proven successful in the treatment of several autoimmune diseases including rheumatoid arthritis, pem phigus, and some IgM-related neuropathies. Rituximab can induce prolonged remissions in MuSK antibody–positive MG, which was previously more difficult to treat than anti-AChR–positive MG. We treat MuSK antibody–positive MG patients with 1 g IV on two occasions 2 weeks apart. Periodically, a repeat course needs to be administered; some MuSK patients can go up to 2–3 years between infusions. A large National Institutes of Health–sponsored randomized trial of rituximab in AChR antibody–positive generalized MG failed to demonstrate efficacy, but many of the participants had longstanding MG that failed other therapies. However, a more recent randomized, placebo-controlled trial from Sweden of new-onset MG (<1 year) reported that a single infusion of 500 mg IV ritux imab resulted in greater likelihood of participants achieving mini mal MG manifestations and reduced need for rescue medications compared with placebo at 48 weeks. Further studies are needed, however, to determine how long this improvement may last and the need for retreatment.

For the rare refractory MG patient, a course of high-dose cyclophosphamide may induce long-lasting benefit. At high doses, cyclophosphamide eliminates mature lymphocytes but spares hematopoietic precursors (stem cells), because they express the enzyme aldehyde dehydrogenase, which hydrolyzes cyclophospha mide. This procedure is reserved for refractory patients and should be administered only in a facility fully familiar with this approach. Maintenance immunotherapy after treatment is usually required to sustain the beneficial effect. NEWLY APPROVED TREATMENTS Special attention needs to be given to the newly approved therapies for MG. Complement inhibitors and FcRn inhibitors have revolu tionized treatment of patients with MG (Table 459-4). Because they work quickly in most patients, they may be used as bridge therapies until other immunotherapies can “kick in” or in those who are refractory to standard treatments. Complement Inhibitors Currently, three complement inhibitors are U.S. Food and Drug Administration (FDA) approved for AChR antibody–positive generalized MG based on positive clinical trial results. Most patients who will improve on these agents will do so within the first 12 weeks, and improvement is appreciated in many within the first 1–4 weeks. These drugs each work by inhibiting the cleavage of C5 in the terminal complement cascade. Eculizumab

was shown to be effective in a positive phase 3 study, which led to FDA approval in 2017. Subsequently, ravulizumab was approved in 2021. Both eculizumab and ravulizumab are monoclonal antibod ies given intravenously; ravulizumab has a longer effect. Zilucoplan is the latest complement inhibitor and was approved in 2023. Unlike eculizumab and ravulizumab, zilucoplan is a subcutaneously administered macrocyclic peptide inhibitor of C5. Because it is not a monoclonal antibody like eculizumab and ravulizumab, it can be coadministered with plasma exchange, IVIg, or FcRn antagonists. An additional benefit is that patients can self-administer zilucoplan with a prefilled syringe. In practice, we typically reassess efficacy at 12 weeks in patients treated with C5 inhibitors and decide whether or not to continue treatment.

Complement inhibition increases the risk of meningococcal infection. Therefore, a first series of vaccinations with both quadri valent and MenB vaccines is given at least 14 days prior to initiation of treatment and then again 1–2 months later. Those patients in whom treatment needs to be started sooner than this initial vac cination series is complete should receive antibiotic prophylaxis (penicillin). Vaccination reduces, but does not eliminate, the risk of meningitis. Physicians must enroll in drug-specific risk evaluation and mitigation strategy programs for all complement inhibitors and counsel patients regarding the risk and signs and symptoms of men ingitis. Patients are recommended to carry a safety/alert wallet card. CHAPTER 459 Myasthenia Gravis and Other Diseases of the Neuromuscular Junction Neonatal Fc Receptor (FcRn) Antagonists FcRns on endothelial cells salvage IgG and albumin from degradation by lysosomes, lead ing to longer IgG half-lives. Blocking the FcRn results in increased catabolism of IgG, thereby reducing IgG (and pathogenic antibody) levels. The potential benefits over plasma exchange include the ease of administration, increased availability, and reduced risk in patients with coagulopathies or limited peripheral venous access. Efgartigimod and rozanolixizumab are now approved for clinical use based on their efficacy in clinical trials (Table 459-4). Efgar tigimod can be given intravenously or subcutaneously, whereas rozanolixizumab is given via a subcutaneous infusion. Importantly, only rozanolixizumab is approved for both anti-AChR and antiMuSK generalized myasthenia. As with complement inhibitors, the FcRn inhibitors usually are effective within the first 3 months of treatment, again often within the first month. Side effects are some what variable and include increased risk of respiratory and urinary infections, headaches (including aseptic meningitis with

rozano lixizumab), and hypoalbuminemia (FcRn also prevents lysosomes from degrading albumin). Comparative efficacy with one another or with complement inhibitors cannot be readily ascertained with existing clinical trial data. One potential benefit of FcRn antagonists over complement inhibitors is that guidance from clinical trials exists on how to ramp up or ramp down administration frequency based on clinical response. PLASMAPHERESIS AND INTRAVENOUS IMMUNOGLOBULIN Plasmapheresis has long been used therapeutically in MG. Plasma, which contains the pathogenic antibodies, is mechanically sepa rated from the blood cells, which are then returned to the patient. A course of five or six exchanges (3–4 L per exchange) is generally administered over a 10- to 14-day period. Plasmapheresis produces a short-term reduction in anti-AChR antibodies, with clinical improvement in many patients. It is most useful as a temporary treatment in severely affected patients or to improve the patient's condition prior to surgery (e.g., thymectomy). The indications for the use of IVIg are the same as those for plasma exchange: to produce rapid improvement to help the patient through a difficult period of myasthenic weakness or prior to sur gery. This treatment has the advantages of not requiring special equipment or large-bore venous access. The usual dose is 2 g/kg, which is typically administered over 2–5 days. Improvement occurs in ~70% of patients, beginning during treatment or within a week and continuing for weeks to months. The exact mechanism of

TABLE 459-4 Comparison of New Complement Inhibitors and FcRn Inhibitors for Generalized Myasthenia DRUG/MECHANISM TRIAL(S) FDA APPROVED DOSING CLINICAL TRIAL POPULATION NOTES Approved Complement Inhibitors Eculizumab (humanized monoclonal Ab anti-C5, inhibits terminal complement/MAC activation) Phase 2 REGAIN : 26 weeks REGAIN open-label extension: 22.7 months (median), up to 3 years Loading: 900 mg IV weekly × 4 Maintenance: 1200 mg IV on week 5 then q2 weeks Ravulizumab (humanized monoclonal Ab anti-C5, inhibits terminal complement/MAC activation) Phase 2 CHAMPION MG: 26 weeks CHAMPION MG open-label extension Actual body weight–based dosing Loading: 40 to <60 kg: 2400 mg IV; 60 to <100 kg: 2700 mg IV; ≥100 kg: 3000 mg IV Maintenance (14 days after loading and then q8 weeks): 40 to <60 kg: 3000 mg IV; 60 to <100 kg: 3300 mg IV; ≥100 kg: 3600 mg IV PART 13 Neurologic Disorders Zilucoplan (synthetic macrocyclic peptide targeting C5/C5b, inhibits terminal complement/MAC activation) Phase 2 RAISE: 12 weeks RAISE-XT open-label extension Phase 3 dosing 0.3 mg/kg SC daily Label dosing (prefilled syringes): Actual body weight–based daily SC injections <56 kg: 16.6 mg daily; 56 kg to <77 kg: 23 mg; ≥77 kg: 32.4 mg Approved FcRn Inhibitors Efgartigimod IV/SC (human anti-FcRn IgG1 Fc fragment; reduces autoantibody levels and IgG recycling) Phase 2 ADAPT: 26 weeks ADAPT open-label extension: up to 3 years ADAPT-SC noninferiority study, open-label parallel-group: 12 weeks with open-label extension Weight-based IV: 10 mg/kg IV (up to 1200 mg) weekly × 4 = 1 cycle Fixed dose SC: 1,008 mg SC

weekly × 4 = 1 cycle Rozanolixizumab (human anti-FcRn IgG4 monoclonal antibody; reduces autoantibody levels and IgG recycling) Phase 2 MycarinG: 18 weeks Open-label extension: completed Phase 3 included 7 and 10 mg/ kg given as SC infusion weekly for 6 weeks followed by 8 weeks off. Patients averaged 4 treatment cycles per year (range 1–7) Clinical dosing: <50 kg: 420 mg; 50 to <100 kg: 560 mg; ≥100 kg: 840 mg given as a weekly health care provider–administered SC infusion for 6 weeks (1 cycle) Abbreviations: AChR, acetylcholine receptor; Ab, antibody; FcRn, neonatal Fc receptor; FDA, Food and Drug Administration; gMG, generalized myasthenia gravis; IVIg, intravenous immunoglobulin; MAC, membrane attack complex; MGADL, Myasthenia Gravis Activities of Daily Living; MuSK, muscle-specific tyrosine

kinase; NSIST, nonsteroidal immunosuppressant therapy; PLEX, plasma exchange; QMG, quantitative myasthenia gravis. Source: Reproduced with permission from AA Amato et al (eds): Amato and Russell's Neuromuscular Disorders, 3rd ed. New York: McGraw Hill; 2025. action of IVIg in MG is unknown; the treatment has no consistent long-term effect on the measurable amount of circulating AChR antibody. Adverse reactions are generally not serious but may include headache, fluid overload, and rarely aseptic meningitis, renal failure, hemolytic anemia, and embolic or thrombotic events. IVIg or plasma exchange is occasionally used in combination with other immunosuppressive therapy for maintenance treatment of difficult MG, though this is less common in the contemporary era since the advent of C5 inhibitors and FcRn antagonists. INVESTIGATIONAL TREATMENTS Several trials of different complement and FcRn inhibitors are underway. Inhibitors of interleukin 6 and CD19 targets on B cells are also being studied. Notably, CD19-targeting chimeric antigen

AChR ab + gMG (class II–IV) Refractory (at least 2 NSISTs or at least 1 NSIST and PLEX/IVIg) MGADL score ≥6 Did not reach statistical significance for primary MGADL endpoint Reached significance for multiple secondary endpoints Requires meningococcal vaccination Adults with AChR ab + gMG (class II–IV) MGADL score ≥6 Requires meningococcal vaccination Adults with AChR ab + gMG (class II–IV) MGADL score ≥6 QMG ≥12 Requires meningococcal vaccination Self-administered SC Adults with gMG regardless of Ab status, MGADL at least 5 with 50% nonocular ADAPT was designed to observe wearing off – cycles repeated at return of symptoms and no sooner than every

8 weeks Number of infusions per cycle and time between cycles can be individualized (as was done in the open-label extension) Efgartigimod SC is not currently approved for selfinjection; health care provider administered; refrigeration required Adults with AChR or MuSK Ab + gMG (11% of participants) MGADL score ≥3 QMG score ≥11 Headache occurred in 38–45% of treatment group and 19% of placebo, including rare aseptic meningitis Infection rate higher in

10 mg/kg dosing group; efficacy equivalent Shorter mean disease duration than other phase 3 trials

(5–6 years) Hypoalbuminemia and peripheral edema receptor (CAR) therapy and chimeric autoantibody receptor T (CAART) therapy targeting the antibody ligand on T cells are also in clinical trials for MG. MANAGEMENT OF MYASTHENIC CRISIS Myasthenic crisis is defined as an exacerbation of weakness suf ficient to endanger life; it usually includes ventilatory failure caused by diaphragmatic and intercostal muscle weakness. Treatment should be carried out in intensive care units staffed with teams experienced in the management of MG. The possibility that dete rioration could be due to excessive anticholinesterase medica tion ("cholinergic crisis") is unlikely given that very high doses of cholinesterase inhibitors are rarely used but is considered in the differential. The most common cause of crisis is intercurrent

infection. This should be treated immediately because the mechani cal and immunologic defenses of the patient can be assumed to be compromised. The myasthenic patient with fever and early infec tion should be treated like other immunocompromised patients. Early and effective antibiotic therapy, ventilatory assistance, and pulmonary physiotherapy are essentials of the treatment program. As discussed above, plasmapheresis or IVIg is frequently helpful in hastening recovery. MANAGEMENT OF MYASTHENIA ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITOR THERAPY MG is

a rare complication of ICI therapy for cancer. It can develop de novo or as an exacerbation of preexisting diagnosed or undiag nosed disease. Patients usually manifest with ocular, bulbar, neck, and respiratory weakness within the first one to four cycles of ICI therapy. Compared to idiopathic MG, ICI-associated MG is more likely to be seronegative and overlap with myositis and myocarditis. The mortality rate is 20–50%, most often because of severe myocar ditis. Importantly, ICI-associated myositis is more common than immune-related MG. It can resemble MG clinically, with prominent or exclusively ocular weakness but without evidence for a decre menting response on repetitive nerve stimulation. The mainstay of treatment for ICI-associated MG is glucocorticoids, including IV solumedrol (which differs from idiopathic MG), and with plasma exchange or IVIg added for severe weakness. Complement inhibi tors have recently been reported as effective in AChR antibody– positive ICI-associated MG with myositis and myocarditis. DRUGS TO AVOID IN MYASTHENIC PATIENTS Many drugs can potentially exacerbate weakness in patients with MG (Table 459-5). As a rule, the listed drugs should be avoided whenever possible. TABLE 459-5 Drugs with Interactions in Myasthenia Gravis (MG) Drugs That May Exacerbate Weakness in Patients with MG Antibiotics Aminoglycosides: e.g., streptomycin, tobramycin, kanamycin Quinolones: e.g., ciprofloxacin, levofloxacin, ofloxacin, gatifloxacin Macrolides: e.g., erythromycin, azithromycin Nondepolarizing muscle relaxants for surgery d-Tubocurarine (curare), pancuronium, vecuronium, atracurium Beta-blocking agents Propranolol, atenolol, metoprolol Local anesthetics and related agents Procaine, Xylocaine in large amounts Procainamide (for arrhythmias) Botulinum toxin Botox exacerbates weakness Quinine derivatives Quinine, quinidine, chloroquine, mefloquine (Lariam) Magnesium Decreases acetylcholine release Penicillamine May cause MG Checkpoint inhibitors May cause MG and other autoimmune neuromuscular disorders (e.g., myositis, inflammatory neuropathy) Drugs with Important Interactions in MG Cyclosporine and tacrolimus Broad range of drug interactions, which may raise or lower levels Azathioprine Avoid allopurinol—combination may result in myelosuppression

■ ■PATIENT ASSESSMENT To evaluate the effectiveness of treatment as well as drug-induced side effects, it is important to assess the patient’s clinical status systemati cally at baseline and on repeated interval examinations. Following the patient with spirometry with determination of forced vital capacity and mean inspiratory and expiratory pressures is important.

PROGNOSIS Approximately 20% of patients with MG achieve a sustained remission and can be tapered off all immunotherapies. There does not appear to be a correlation between disease severity and likelihood of remis sion. Thymectomy may increase the chance of achieving remission in anti-AChR MG, but the large, randomized MGTX trial was too short in duration to examine this endpoint; rather, the results revealed only that thymectomy was efficacious and led to less use of glucocorticoids and second-line agents. Mortality from MG diminished greatly during the twentieth century, changing from a “grave” illness with mortality of nearly 70% a century ago, to 2–30% by the 1950s, with contemporary estimates in the 1–5% range. Anti-MuSK patients generally were more difficult to treat than anti-AChR MG in the past. However, recent series suggest that rituximab is effective in this subgroup, thereby reducing these risks and improving the prognosis. Nonparaneoplastic LEMS is usually responsive to immunotherapy and symptomatic treatment with pyridostigmine and 3,4-DAP. In older adults, LEMS is most often paraneoplastic, and screening for an underlying tumor is indicated (Chap. 99). Recent studies suggest that survival in patients with LEMS has improved, for uncertain reasons and likely not due to earlier diag nosis and treatment of the tumor. There is wide variability in age of onset, severity, and prognosis of the many types of CMS.

ISSUES The incidence of MG and its subtypes varies in different populations, for example, occurring in ~2–10/106 individuals in the United States and the Netherlands and up to 20/106 individuals in Spain. Estimates of prevalence in different parts of the world range widely from 2–360/106. The age of onset may also be influenced by geographic and/or ethnic differences. Juvenile-onset MG is uncommon in Western popula tions but may represent more than half of cases in Asians. MuSK MG appears to be more common in the Mediterranean area of Europe than in northern Europe and is also more common in the northern regions of East Asia than in the southern regions. A concern during the COVID-19 pandemic is whether MG patients on immunosuppressive therapies might be at increased risk of infection or developing a more severe course. Furthermore, flares of MG can be triggered by infection, and contracting COVID-19 may lead to an exacerbation, including MG crisis. We have not reduced the dosage of immunosuppressive medications in MG patients who are doing well but have been more likely to manage worsening disease by treating with IVIg rather than increasing the dosage of, or adding new, immunosuppressive agents. Patients are strongly advised to receive the COVID-19 vaccine, wear masks, and maintain social distancing, particularly when infection levels are high in their communities. An international panel published guidelines for management of MG patients during the pandemic. ■ ■FURTHER READING Amato AA et al: Amato and Russell’s Neuromuscular Disorders, 3rd ed. New York, McGraw Hill, 2025. Guidon AC: Lambert-Eaton myasthenic syndrome, botulism, and immune checkpoint inhibitor-related myasthenia gravis. Continuum (Minneap Minn) 25:1785, 2019. Gwathmey KG et al: How should newer therapeutic agents be incor porated into the treatment of patients with myasthenia gravis? Muscle Nerve 69:389, 2024. Hehir MK 2nd, Li Y: Diagnosis and management of myasthenia gra vis. Continuum (Minneap Minn) 28:1615, 2022. International mg/covid-19 working group et al: Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myas thenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci 412:116803, 2020.

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