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MYASTHENIA GRAVIS

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BACKGROUND– In myasthenia gravis (MG), the prototypic autoimmune disease, antibodies against acetylcholine receptors impair neuromuscular transmission and produce weakness. Although recognized for several hundred years, it has only been over the last three decades that effective treatments have become available for MG.

REVIEW SUMMARY– This review summarizes the principles of normal neuromuscular transmission, the clinical features of MG, and the tests available for its diagnosis. The current treatments for MG are discussed, including possible mechanisms of action and a discussion of potential adverse effects. When available, evidence-based justification for individual treatment options is given, and areas of controversy identified.

CONCLUSIONS– Significant improvements in the diagnosis and management of MG have been made over the last several decades. The available treatments either improve neuromuscular transmission directly, or suppress or modulate the pathogenic immune response in MG. Treatment is highly individualized and must take into account the severity of disease, the presence of other diseases, and the kinetics of response for the available treatments. This requires detailed knowledge of the mechanisms of action and possible adverse effects for each treatment. However, despite an optimistic outlook with modern treatment, the management of MG continues to be plagued by lack of efficacy in some, and significant adverse effects in most MG patients.

KEY WORDS *myasthenia gravis, immunosuppression, autoimmunity, neuromuscular junction, electrodiagnosis*

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In the human autoimmune disease myasthenia gravis (MG) autoantibodies directed against acetylcholine receptors (AChR) at the neuromuscular junction interfere with neuromuscular transmission, producing muscle weakness. Much is known about the pathogenesis of MG, and there are several treatment options. The management of a patient with MG can be a very rewarding experience and is highly individualized, requiring a constant balance between the therapeutic benefits, kinetics of treatment response, and adverse effects.

EPIDEMIOLOGY AND CLASSIFICATION

The prevalence of MG is between 1 in 10,000 to 15,000 (1,2). However, the prevalence is likely higher, because individuals with more subtle symptoms may go unrecognized. As with most other autoimmune diseases, females are more commonly affected (2). MG can occur at any age and affects all races, although juvenile MG may be more common in Orientals (3).

It is useful to consider the various clinical subgroups of MG (Table 1). In neonatal MG, the transfer of AChR antibodies from mother to fetus produces a self-limited disorder of neuromuscular transmission (2,4,5). The congenital myasthenic syndromes are hereditary disorders in which one or more of the proteins needed for neuromuscular transmission are absent or improperly formed (6). These disorders are not autoimmune, and therefore immunosuppression is not indicated. Juvenile MG, arbitrarily defined as onset before the age of 18, reflects the early onset of immune-mediated MG, and more commonly affects postpubertal females (7). Cases of ocular seronegative MG may be more common in Oriental children, who generally follow a benign course (3). In seronegative MG, AChR antibodies are not detected in serum (8). Early-onset MG is more common in females, and is

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Table 1.
Subgroups in Myasthenia Gravis

Nonimmune	
Congenital myasthenic syndrome [131]	Presynaptic, synaptic, or postsynaptic defects in proteins at the neuromuscular junction
Immune	
Neonatal myasthenia gravis	Transplacental passage of AChR antibodies
Juvenile myasthenia gravis	Onset before 18 years of age
Early-onset myasthenia gravis	Onset from 18 to 50 years of age
Late-onset myasthenia gravis	Onset after 50 years of age
Seronegative myasthenia gravis	No detectable AChR antibodies

arbitrarily defined as onset after 18 years of age but before 50. Late-onset MG is more common in males, with onset after age 50 (2,9). There is an increased incidence of an underlying thymoma in late-onset MG (9). These subgroups are associated with different sensitivities of the diagnostic tests, and in some instances with different responses to treatment (Table 2).

NEUROMUSCULAR TRANSMISSION AND THE PATHOGENESIS OF MYASTHENIA GRAVIS

It is important for the clinician to understand normal neuromuscular transmission and how the antiacetylcholine antibody acts, because these are the basis of diagnostic tests and treatments (10).

In normal neuromuscular transmission (Figure 1), depolarization of the presynaptic nerve terminal produces an influx of calcium through voltage-gated calcium channels. Vesicles containing acetylcholine (ACh) then fuse with the presynaptic nerve terminal membrane. After release, ACh interacts with the acetylcholine receptor (AChR) on the muscle endplate surface. This opens the AChR channel, resulting in an influx of cations, largely sodium. Depolarization of the muscle surface produces an excitatory endplate potential, and if the endplate potential is of sufficient amplitude, muscle surface voltage-gated sodium channels are opened. This generates an action potential that eventually results in excitation-contraction coupling and muscle movement. Normally, an excess of ACh is released and there is an abundance of AChRs; the "safety margin" for neuromuscular transmission. ACh binds transiently to its receptor and then either diffuses from the neuromuscular junction or is hydrolyzed by acetylcholinesterase (AChE), providing a self-limited response to nerve depolarization. There is a steady state relationship between degradation and synthesis of mus-

Table 2.
Diagnostic Tests in Myasthenia Gravis

Test	Advantages	Disadvantages
Tensilon	Fast, easy to perform, inexpensive Sensitive (with appropriate end-point; 85%–90% in ocular) Excellent for suspected ocular	Adverse effects especially with cardiac disease Nonspecific Time-consuming for neurologist Not useful with less well-defined end-points (dysarthria, dysphagia, limb weakness)
Anti-acetylcholine receptor antibodies	Highly specific for myasthenia gravis Sensitive in the presence of generalized disease	Insensitive for ocular myasthenia gravis (positive in 29%–79%) Long delay for results Expensive
Electrodiagnosis		
Repetitive nerve stimulation	Technically easy Sensitive with generalized disease (90% in proximal muscle)	Insensitive for ocular myasthenia gravis (60% positive repetitive nerve stimulation) Nonspecific (false-positives) Patient discomfort
Single fiber electromyography	Highly sensitive for defect in neuromuscular transmission (90%–99%); best for suspected ocular when other tests are negative	Time-consuming and requires considerable patient cooperation Nonspecific (false-positives) Technically difficult

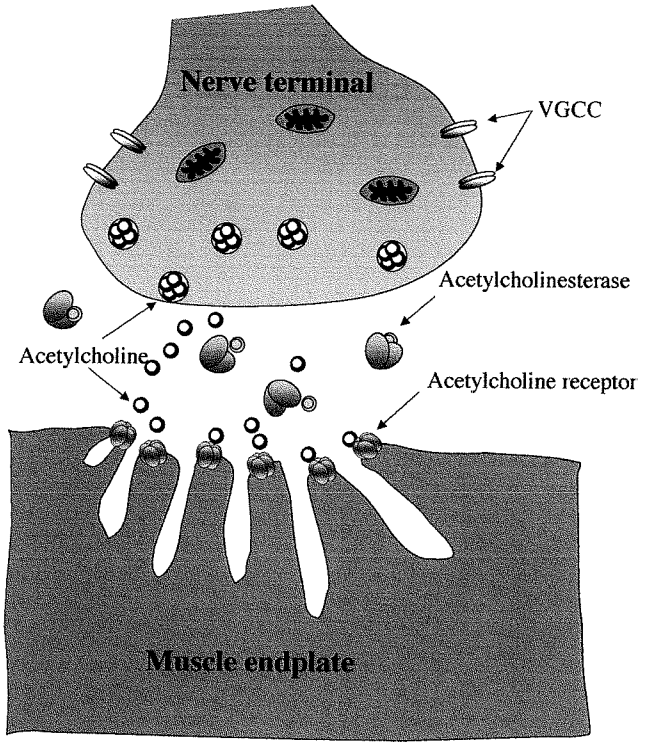

FIGURE 1.
The normal neuromuscular junction. This diagram depicts the neuromuscular junction, showing the presynaptic nerve terminal and postsynaptic muscle endplate. Important structures at the neuromuscular junction include the voltage-gated calcium channels (VGCC); acetylcholine, contained with vesicles in the presynaptic nerve terminal, as well as free within the neuromuscular junction; acetylcholine receptors on the muscle endplate; and acetylcholinesterase located in the basal lamina of the neuromuscular junction.

cle surface AChRs, with a half-life of 6 to 13 days for AChR turnover (11).

In MG, antibodies are directed against the acetylcholine receptors (AChR antibodies) (12,13). Evidence that MG is an immune-mediated disease is based upon its association with other autoimmune diseases in both patient and family members, the association of clinical subgroups with specific HLA types, and the frequent finding of thymic pathology (2,9,14,15). Pathologically, immunoglobulins, predominantly IgG, and complement are deposited at damaged neuromuscular junctions (16). In experimental autoimmune myasthenia gravis (EAMG), the animal model of MG, the immunization of a variety of species of animals with AChRs and Freund's adjuvant induces the clinical and electrophysiological features of MG (17).

Anti-AChR antibodies are detectable in most patients (75% to 94%) with generalized MG and many (29% to 79%) patients with ocular MG (9,12,13,18). Those without demonstrable AChR antibodies may have antibodies against other determinants at the neuromuscular junction. AChR antibodies are usually of the IgG class, and there is considerable variation within and between individuals as to the precise specificity of these antibodies (12,19). Across a population of MG patients, absolute titers correlate poorly with clinical severity, although in a single patient changes in AChR antibody titers correlate roughly with clinical changes (18). AChR antibodies interfere with neuromuscular transmission through one of three mechanisms, with the proportion of antibodies acting with each of these mechanisms varying between patients (20,21) (Figure 2). First, some bind to the AChR cholinergic binding site, blocking the binding of ACh. Second, some AChR antibodies cross-link muscle surface AChRs, increasing their rate of internalization into muscle and reducing the numbers of available AChRs. Third, and perhaps most importantly, AChR antibodies that bind complement result in destruction of the muscle endplate, and a more long-lasting loss of AChRs (22). Continuing AChR resynthesis allows some recovery from these processes. Differences in the mechanisms of antibodies between patients

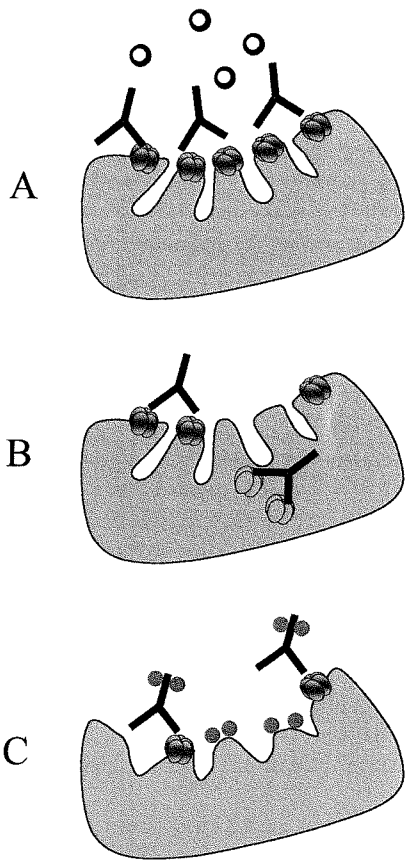

FIGURE 2.
Mechanisms of antiacetylcholine receptor antibodies. The three possible mechanisms for AChR antibodies are shown. (A) Acetylcholine receptor antibodies block the cholinergic binding site of the acetylcholine receptor, preventing acetylcholine from binding the receptor. (B) Acetylcholine receptor antibodies cross-link adjacent AChRs, increasing their rate of internalization into muscle. (C) Acetylcholine receptor antibodies that bind complement result in destruction of the muscle endplate and a reduction in the numbers of available AChRs.

may explain why in some patients diagnostic tests are negative or treatments ineffective. Thus, if the majority of antibodies produce a long-lasting reduction in available AChRs, pyridostigmine may be less effective.

Involvement of the thymus is important in the pathogenesis and treatment of MG (23,24). Pathological abnormalities of the thymus are found in 80% of MG patients. The thymus may expose autoreactive B and T lymphocytes to the AChR, or to AChR-like structures, on thymic myoid cells or cortical thymic epithelial cells (23,24). Most patients (65%) with early-onset generalized disease have a hyperplastic thymus, enriched for AChR-reactive B and T lymphocytes, and the site of considerable AChR antibody production (25). A thymoma occurs in 24% to 38% of late-onset patients, less commonly in early-onset MG patients, and can be discovered before or after the onset of MG (23,24). Thymomas are rarely if ever found in seronegative MG, and are less common in ocular MG (9). The presence of thymoma lessens the benefit of thymectomy and worsens the overall prognosis (26). In 10% to 20% of MG patients, the thymus is atrophic, in keeping with normal age-related involution (23,24).

CLINICAL FEATURES

The first presentation of MG is usually with weakness of the extraocular muscles, producing ptosis or diplopia (Figure 3). More subtle weakness may produce blurring of vision. Characteristically, the weakness of MG fluctuates and fatigues over the course of the day. On awakening, the symptoms have usually resolved or are minimal, but increase again toward the end of the day. There are exceptions, and occasionally myasthenics will describe maximal weakness first thing in the morning. Fatigue is suggested by increasing weakness with use of specific muscle groups. This history should be elicited by nondirected questioning, because a similar pattern of worsening toward the end of the day can be elicited in other neuropathic and myopathic disorders. Thus, a more specific history of fatigue is obtained by asking when the weakness is worse, and whether there are certain times of the day when the symptoms are likely to be much better or worse, rather than asking specifically whether the weakness is worse at the end of the day. Another often reported symptom of myasthenia gravis not emphasized in the literature is photophobia, with a worsening in double vision or ptosis on exposure to bright sunlight. The mechanism of this is unknown.

Bulbar symptoms are also common in MG, with 6% to 24% of individuals presenting with purely or predominantly oropharyngeal symptoms, consisting of painless dysphagia or dysphonia (27–30). Speech may be either hypernasal or hoarse. Dysphagia may present with repeated attempts necessary to swallow, regurgitation, choking, or aspiration. More subtle manifestations include excessive clearing of the throat during or after eating, or recurrent pneumonia suggesting aspiration. Dysphagia is also fatigable, and a history of little difficulty with breakfast, moderate difficulty with lunch, and

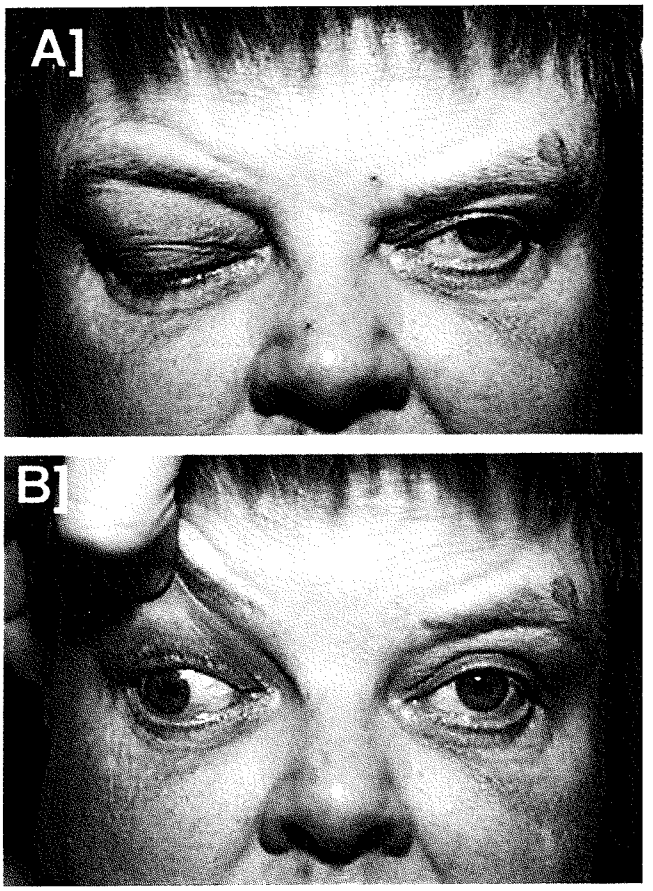

FIGURE 3.
Extraocular muscle involvement in myasthenia gravis. (A) Complete right-sided ptosis. (B) A pattern of extraocular muscle involvement mimicking a pupil-sparing third nerve palsy.

an inability to eat in the evening is highly suggestive of MG. The recognition of dysphagia is important for the diagnosis of MG, and its presence may interfere with treatment unless enteral or parenteral access is available. Facial weakness produces difficulty with eye closure or a change in facial appearance. Jaw fatigue produces painless difficulty with chewing, especially of harder foods such as meat. Significant bulbar weakness is more often associated with respiratory involvement, including exertional dyspnea or orthopnea. The latter is a result of abdominal contents pushing against a weak diaphragm. A similar mechanism likely accounts for a history of dyspnea on bending over to tie up shoes, typical for MG.

Although MG often begins with extraocular involvement, only 15% remain as ocular MG (9,31). Most eventually develop bulbar symptoms or symmetric weakness of the proximal extremities. MG can produce weakness of neck flexion or, less commonly, extension. Nevertheless, MG is one of a few neuromuscular conditions that can present as a head drop. In the arms, deltoids and triceps are characteristically weaker than biceps or distal muscles. Leg weakness is less common and generally consists of hip flexion weakness. Significant proximal leg weakness without ocular, bulbar, or

arm weakness should suggest a steroid myopathy in a treated MG patient. The muscle weakness in MG has a variable distribution and severity, with some muscles weak and others completely normal.

On examination, ptosis may be evident at rest, but often worsens after 60 to 90 seconds of sustained upgaze. The elevation of a severely ptotic eyelid may elicit more subtle ptosis on the opposite side, previously masked by contraction of the frontalis muscle to compensate for the more ptotic eyelid. Diplopia in MG can follow any pattern, including what appears to be an internuclear ophthalmoplegia or pupil-sparing third nerve palsy (Figure 3). Difficulties in mapping diplopia to a single muscle or cranial nerve should suggest MG. Commonly, on examining the extraocular movements the patient experiences subjective diplopia despite an absence of objective limitation in extraocular movements. When gaze is first directed to a peripheral object, there may be a single object, although with sustained gaze fatigue occurs and diplopia results. When severe, extraocular muscle involvement in MG may produce a virtually immobile eye, although this should raise the possibility of other conditions such as a mitochondrial myopathy or dysthyroid ophthalmopathy. An inability to bury the eyelashes suggests facial weakness, which, when severe, produces a myopathic or myasthenic snarl, caused by weakness of the orbicularis oris muscles. Weakness of jaw muscles in MG involves closure more than opening. There are several methods to demonstrate fatigue clinically. Five successive contractions of a muscle group against resistance will often elicit fatigue in MG, although care must be taken to maintain the same degree of resistance for each contraction. The presence of fatigue is not specific for MG, and its absence does not rule out the diagnosis. There are exceptions to the classical presentation of MG (32). A small number of patients present with a limb girdle pattern, without significant ocular or bulbar weakness. In some cases, the weakness may be highly asymmetric, and may selectively involve distal muscles. A recent document has put forth a new clinical classification system according to clinical involvement and severity, adapted from that originally described by Osserman (33) (Table 3).

The presence of pain, sensory disturbance, or pupillary involvement suggests another diagnosis. AChR antibodies do not affect central AChRs, which are of a different configuration, and cognitive difficulties are more likely attributed to the indirect effects of a chronic disease or of medications (34). The sensory exam is normal and deep tendon reflexes are unaffected in MG. Long tract findings suggest an intrinsic brain-stem lesion. Bowel and bladder function are preserved in MG, although a rare individual may describe urinary incontinence that improves with subsequent treatment (35).

Relapses in MG may occur at times of physical and emotional stress, when medications used for its treatment are being withdrawn, when other medications are added (see below), during or after pregnancy, or at times of infections, including pneumonia brought on by aspiration (36). Severe and increasing weakness of bulbar and/or respiratory muscles, a myasthenic crisis, is a medical emergency and requires prompt admission, treatment of any underlying precipitants (often an infection), and initiation or optimization of medical treatment for MG (36–38).

Table 3.
Myasthenia Gravis Foundation of America Clinical Classification*

Class I
Any ocular muscle weakness
May have weakness of eye closure
All other muscle strength is normal
Class II
Mild weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IIa—Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IIb—Predominantly affecting oropharyngeal respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class III
Moderate weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IIIa—Predominantly affecting limb, axial muscles, or both. May also have lesser involvement of oropharyngeal muscles.
IIIb—Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class IV
Severe weakness affecting other than ocular muscles. May also have ocular muscle weakness of any severity.
IVa—Predominantly affecting limb and/or axial muscles. May also have lesser involvement of oropharyngeal muscles.
IVb—Predominantly affecting oropharyngeal, respiratory muscles, or both. May also have lesser or equal involvement of limb, axial muscles, or both.
Class V
Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

*Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Neurology*. 2000;55:16–23.

DIAGNOSIS

The major hurdle to diagnosing myasthenia gravis is suspecting it clinically. The delay between symptom onset and diagnosis is often measured in years (9). This may reflect

fluctuation in the symptoms and signs pathognomonic of MG, so that what was severe weakness the previous evening has resolved when seen in a physician's office the following morning. Once suspected, there are several tests available for the diagnosis of MG (9,31,39–43). These differ in their sensitivity and specificity depending on the clinical subgroup (Table 2).

In the Tensilon test, an intravenous injection of the short-acting acetylcholinesterase inhibitor (AChEI) edrophonium transiently increases the amount of ACh available, improving weakness caused by impaired neuromuscular transmission (9,39,44). There are several protocols for performing this test. It is contraindicated in the presence of significant cardiac disease, especially in an elderly patient with a bradyarrhythmia, when additional cholinergic stimulation may further reduce the heart rate (45). Because edrophonium may also induce increased bronchial secretions and bronchoconstriction, it should be avoided in the presence of severe asthma or chronic obstructive pulmonary disease. The maximum dose of edrophonium administered is 10 mg. This should not be given all at once because the patient may experience significant adverse effects from excessive nicotinic and muscarinic cholinergic stimulation. A common protocol is to inject 2 mg, waiting several minutes to look for a response, followed by another 3 mg, again waiting several minutes, and finishing with the final 5 mg. A response occurs within 2 to 5 minutes, and generally lasts 5 to 10 minutes. A history of a Tensilon test that produced an immediate response lasting for weeks to months should be treated with skepticism. The test must be performed blinded, using a second vial containing sterile saline drawn up by an unblinded observer. This is especially important when the endpoint is less clear, for example when looking for improvement in dysarthria or in proximal arm weakness. Stable ptosis is the best situation to perform a Tensilon test. In a young individual with no history of cardiac disease, it is acceptable to perform a Tensilon test in an office setting, providing that atropine is available in case a significant bradyarrhythmia occurs. In an elderly individual, it is best performed in a hospital setting. The adverse effects of edrophonium include muscle fasciculations (nicotinic cholinergic stimulation), increased sweating and salivation, abdominal cramps, diarrhea, and bradycardia (muscarinic cholinergic stimulation) (9,46). Their occurrence may make it difficult to blind the test.

A Tensilon test is sensitive in diagnosing a defect in neuromuscular transmission, but is not specific for MG (Table 2). It is especially useful in ocular MG, when other diagnostic tests may be negative (9,31,39). Depending on the mechanism of AChRs antibodies, there may be insufficient numbers of AChRs available so that a negative Tensilon test does not negate the diagnosis of MG. Inexplicably, there is no correlation between results of the Tensilon test and the subsequent response to pyridostigmine (39). Indeed, although the Tensilon test is very sensitive for the diagnosis of ocular MG, a frequent clinical observation is that pyridostigmine is relatively ineffective for the ocular symptoms of MG.

The electrophysiological diagnosis of MG involves either repetitive nerve stimulation or single fiber electromyography (SFEMG) (10). In disorders of neuromuscular transmission repetitive stimulation of a nerve at 2 to 5 Hz (generally 3 Hz is used) produces a progressive decrease, or decrement, in the amplitude of the motor response. In stable patients, it may be advisable to discontinue pyridostigmine the evening before testing to increase the sensitivity of this test. The use of proximal target sites is more sensitive, although technically more difficult (10,40). Depending on the target muscle and nerve used, a decrement in excess of 10% is generally considered abnormal. The presence of decrement is sensitive but not specific for the diagnosis of MG (Table 2) (10,40).

A Tensilon test is sensitive in diagnosing a defect in neuromuscular transmission, but is not specific for MG.

SFEMG is the most sensitive way to detect impaired neuromuscular transmission. Abnormalities include either jitter (a difference in the timing of muscle fiber activation between two fibers in a single motor unit) or blocking (the complete failure of neuromuscular transmission at one muscle fiber in a pair). Although highly sensitive, abnormalities in SFEMG are not specific for MG (10,40,47). False-positives occur in a number of other disorders, including mitochondrial myopathies or oculopharyngeal muscular dystrophy (47). To maximize sensitivity, patients should not take AChE inhibitors before SFEMG.

Whether electrophysiological testing is useful to monitor the effects of treatment in MG is as yet undemonstrated. It may be useful to repeat studies in a known MG patient who later presents with atypical symptoms, or when the question of a steroid myopathy arises. Normal SFEMG in a clinically weak muscle is said to exclude a defect of neuromuscular transmission as a cause for this weakness (48).

The detection of serum AChR antibodies is highly specific for MG (49). Unfortunately, their sensitivity is low in the presence of ocular symptoms only (Table 2) (9). Although there is no need for serological testing in an otherwise characteristic clinical presentation, the absence of AChR antibodies should at least raise the possibility of other diagnoses. The absolute titer of AChR antibodies does not correlate with differences in disease severity between individuals, although there is a rough correlation between changes in AChR antibody titers and clinical status in a single individual (18). Repeat AChR antibody testing is rarely needed in the

management of MG, and much more useful is the history, neurological examination, and, occasionally, electrophysiological testing.

Depending on the situation other ancillary tests may also be useful. In late-onset seropositive MG, 30% of patients will have an underlying thymoma (23,24). Although occasionally detected on a plain radiograph of the chest, a CT scan of the chest is more sensitive and should be done in all late-onset seropositive patients. Thymomas occur less frequently in seropositive early-onset MG, and rarely if ever in seronegative MG (23,24). Because of the increased likelihood of other autoimmune diseases, clinical evidence of these diseases should be sought. Tests of thyroid function or vitamin B12 levels may be useful. Thyroid disease and MG may coexist. In patients with severe ocular involvement with significant proptosis or marked limitation in the extraocular movements, a CT scan of the orbits may be indicated to detect enlarged extraocular muscles in dysthyroid ophthalmopathy. If the diagnosis is unclear after investigations are complete, a muscle biopsy may be indicated.

MANAGEMENT

The goal in MG is to induce a sustained or permanent remission. It is particularly important to understand the mechanisms of each treatment. The therapy of MG is highly individualized, balancing the clinical severity against the efficacy, frequency of adverse effects, and the expense and convenience of each treatment. It is useful to educate the patient about potential adverse effects, as advance notice of what to expect may improve compliance and tolerance of drugs and procedures which may be at least initially unpleasant.

The treatment of MG is divided into several categories (46) (Table 4). Symptomatic treatments improve neuromuscular transmission, but do not affect the underlying immunopathogenesis. The suppression or modulation of the immune system affects the underlying problem. The long-term outlook may be improved by thymectomy. Treatment with intravenous immunoglobulin (IVIg) or plasma exchange is useful when there is significant and progressive weakness of either bulbar or respiratory muscles (myasthenic crisis). These treatments usually improve the clinical situation relatively quickly, and provide time for other immunosuppressive or symptomatic treatments to take effect.

Table 4.
Treatment of Myasthenia Gravis

Symptomatic
Acetylcholinesterase inhibitors
Pyridostigmine
Neostigmine
Immunosuppression
Corticosteroids
Prednisone, prednisolone
Hydrocortisone
Methylprednisolone
Dexamethasone
Azathioprine
Cyclosporine
Cyclophosphamide
Mycophenolate
Other
Operative
Thymectomy
Temporary
Plasma exchange
Intravenous immunoglobulin (IVIg)

Symptomatic—Acetylcholinesterase Inhibitors

A major advance in the treatment of MG was the demonstration that physostigmine was effective in reversing its clinical manifestations (50). Since then, the use of pyridostigmine has become a mainstay in the treatment of MG (46). Although other AChEI are available, they have a higher risk of adverse effects and shorter half-lives, with no demonstrated advantages to pyridostigmine (51). Pyridostigmine inhibits AChE, increasing the amount of ACh available to interact with available AChRs. As discussed above, antibodies that decrease available AChRs will reduce the efficacy of AChEI. The dose and interval of pyridostigmine treatment must be individualized, because its absorption and duration of action is highly variable between individuals (52). Peak plasma levels of pyridostigmine occur between 1 and 2 hours after ingestion, with a half-life of 60 to 90 minutes, longer than that seen with neostigmine (52,53). Neither pyridostigmine nor neostigmine bind significantly to serum proteins, so drug interactions are uncommon (52). Both are excreted by renal tubular secretion and a dose reduction is needed in severe renal failure (52,53).

The optimal dose of AChEIs is highly variable between individuals. This requires an initial empiric choice of dose, followed by a careful titration guided by the clinical response. One strategy is to begin with 30 mg orally taken four times over the course of the waking day, with increases every several days thereafter. Doses above 120 to 180 mg every 3 to 4 hours are rarely needed. The risk of a cholinergic crisis, when excessive stimulation of nicotinic AChRs results in weakness, is increased at higher doses. Most patients, after education and experience, are able to titrate the doses and timing of AChEIs themselves, providing that guidelines in terms of the maximum rate of increase and doses are given. Some patients benefit from a small dose of AChEI given on an as needed basis before predicted times of increased muscular effort. Although the peak effect of pyridostigmine occurs between 1 and 2 hours, its beneficial effects can begin within 30 to 45 minutes (54,55). Thus, with significant dysphagia, taking pyridostigmine 45 to 60 minutes before a meal may be helpful. The variation in duration of action after

a given dose of AChEI is large, commonly 3 to 6 hours for pyridostigmine and 2 to 4 hours for neostigmine (56). The requirements for AChEIs may change over time, and when immunosuppression has begun, the same dose of pyridostigmine may have an increased effect, so it can be reduced or discontinued. Any changes in dose or interval of AChEI ingestion should be based on a cumulative pattern of the subjective and objective observations of both patient and physician. The edrophonium test is usually not useful in making decisions about AChEI doses (51).

For patients with significant weakness first thing in the morning, a long-acting Mestinon Supraspan contains 60 mg for immediate release and 120 mg for more controlled release (56). Its use during the day is less effective than the regular 60-mg tablets because of even poorer bioavailability. Pyridostigmine may be prepared as a syrup, which is useful in the pediatric patient. It is available for parenteral infusion (intramuscularly or intravenously), useful in an intubated patient, although the 60-mg tablets can be crushed and given through a nasogastric or gastrojejunal tube. Neostigmine is available in 15-mg tablets, or in solution for parenteral use, with the dose used being approximately 1/30 to 1/60 of oral pyridostigmine (46).

Despite the excellent rationale for the use of AChEIs and abundant anecdotal evidence of their benefits, there are no controlled trials of AChEI use in MG. An improvement in respiratory function or reversal of electrophysiological abnormalities immediately after AChEI was demonstrated in small studies (51,52,57). Although often effective, AChEIs are rarely sufficient alone, and a common clinical observation is that they are even less effective for the ocular symptoms of MG, which are more responsive to corticosteroids (31,39,46,58).

Adverse effects to AChEIs occur in approximately one third of patients (9). In a few individuals they occur at very low doses. Some are a consequence of the stimulation of muscarinic AChRs at autonomic ganglia, and include increased sweating and salivation, bronchorrhea and bronchoconstriction, lacrimation, bradycardia, abdominal cramps, and diarrhea. They are rarely disabling and can be ameliorated with medications blocking muscarinic but not nicotinic AChRs. Diphenoxylate, loperamide, glycopyrrolate, ipratropium, propantheline, or scopolamine may be used (48). Bradycardia and hypotension are uncommon with oral preparations but can occur with parenteral AChEI (45). Stimulation of nicotinic AChRs may produce muscle fasciculations and cramps. With increased weakness after a recent increase in AChEI dose, a cholinergic crisis should be considered, although whether a true cholinergic crisis exists is controversial (51,55). Nevertheless, AChEIs are often discontinued in a myasthenic crisis because their muscarinic effects may complicate management. No clinical weakness has been described due to the long-term use of these agents, but there is experimental evidence in animals of endplate pathology with prolonged exposure to much higher doses than are normally used in humans (48,51).

Thus, AChEIs are useful for the symptomatic management of MG although they are often only partially effective. They do not have significant long-term adverse effects. Their utility is limited by the lack of efficacy in some individuals, by the wide variations in dose and interval required within and between patients, and by adverse effects. Importantly, they have no effect on the underlying pathogenic immune response in MG.

Immunosuppression

A variety of medications suppress the immune system and therefore the pathogenic immune response in MG. Although in theory any immunosuppressive medication could work in MG, in practice a relatively small number of agents are used, largely because of familiarity with doses, kinetics, and adverse effects.

Corticosteroids

A major era in the management of MG began with the use of corticosteroids, which seemed to correlate temporally with improved morbidity and mortality (5,46). Although used now for years, with considerable anecdotal and retrospective clinical evidence documenting their usefulness, controlled trials to demonstrate their benefit have not been done. However, this lack of evidence from controlled trials is common for most currently available therapies in MG, despite incontrovertable evidence of reduced morbidity and mortality as a result of these therapies. The benefits of corticosteroids must be balanced against a significant incidence of serious adverse effects (46,59,60).

The precise mechanisms of corticosteroids in MG are unknown. There are likely multiple effects on both humoral and cellular immune responses (46,61–63). AChR antibody levels are usually reduced after corticosteroid administration, correlating roughly with clinical improvement (46,63,64). Corticosteroids may have pharmacological effects on neuromuscular transmission, possibly responsible for the early clinical worsening seen after high-dose therapy is started (65,66). Either prednisone or prednisolone can be used for outpatients. Hydrocortisone, high-dose intravenous methylprednisolone, or dexamethasone have also been used for the inpatient management of MG patients. Prednisone is metabolized in the liver, so that medications (including cyclosporine) that stimulate the hepatic microsomal enzyme system may increase corticosteroid metabolism. This may reduce the efficacy of corticosteroids, and increase dose requirements (61).

There are many regimens for instituting corticosteroid therapy (5,61). High-dose therapy is effective earlier, but carries a greater risk of adverse effects (31,61,67,68). Starting low-dose alternate-day corticosteroids, followed by gradual increases until improvement is seen, reduces the risk of adverse effects but delays the onset of clinical improvement (68). The strategy used by many experienced clinicians is to

begin at 10 to 20 mg daily, increasing every few days by a similar amount until a therapeutic dose is reached. As a rule, doses exceeding 1 mg/kg are not needed. Which strategy is used depends on the urgency of the situation, and the implications of adverse effects should they occur. One possible concern of high-dose corticosteroid (1 to 1.5 mg/kg) at treatment onset is that of early worsening in weakness (58,63,65,68). This is seen in up to 48% of patients, and is especially likely in more severely affected patients. In less than 10% of patients, significant worsening may result in the need for respiratory support. It generally begins within 4 to 5 days of starting treatment (range 1 to 21 days) and lasts 4 to 7 days (range 1 to 20 days), even when corticosteroid therapy is continued (63,65). Electrophysiological evidence of worsened neuromuscular transmission is seen within hours of corticosteroid administration, suggesting a pharmacological effect (63,66). Therefore, in severe MG, especially if there is significant bulbar or respiratory weakness, the initial stages of corticosteroid therapy should be performed either in the hospital or under very close outpatient supervision. Beginning with low-dose alternate-day corticosteroid (e.g., 15 to 25 mg on alternate days) with gradual increases thereafter lessens the risk of early worsening but also delays the onset of benefit (68). Corticosteroid resistance may be a result of severe disease, suboptimal doses, insufficient treatment duration, noncompliance, overly aggressive tapering, or an erroneous diagnosis.

In severe MG, especially if there is significant bulbar or respiratory weakness, the initial stages of corticosteroid therapy should be performed either in the hospital or under very close outpatient supervision.

A common approach is to institute corticosteroid therapy until clinical improvement occurs, continue this therapy for a further 2 to 3 months to stabilize the situation, and then to gradually taper the dose of prednisone by 5 mg per month. Faster rates of tapering are associated with increased risks of relapse but significant adverse effects may force a more rapid rate of tapering, necessitating careful clinical monitoring (61,69). Azathioprine, discussed below, will often allow a more rapid and successful tapering of corticosteroids (69). Although alternate-day therapy is commonly used in the belief that this minimizes adverse effects, there is little evidence to support this.

In the only randomized controlled trial study of corticosteroids in MG there was a suggestion of benefit, although the number of patients studied was too small to permit statistical analysis (70). A more recent unblinded randomized controlled trial compared prednisone to a short course of prednisone followed by azathioprine alone (71). Although the time to first deterioration was similar in both treatment arms, early treatment failures in the prednisone alone group were three times more common than in the prednisone followed by azathioprine group. After 3 years, the likelihood of being in remission or minimally symptomatic was similar in both treatment arms. The remaining literature on corticosteroid use in MG, all uncontrolled and retrospective, suggests an improvement rate of 65% to 100% (48,55,58,63,67,68,72). Disparate schedules of administration and outcome measures makes comparison of these studies difficult. In ocular MG, corticosteroids, often at low doses, are usually more effective than AChEIs, with some evidence to suggest that corticosteroid use may reduce the risk of subsequent generalization (31,58,73).

It is important to recognize the timing of response to corticosteroids. Although the onset of benefit may occur within a month, significant improvement commonly takes 3 to 6 months, and maximal benefit may take 4 to 9 months (51,67,71). Therefore, a trial of at least 6 months is required to assess response (67)].

The adverse effects of corticosteroids are frequent, occurring in 20% to 80% of MG patients, and may be severe. They are more likely with chronic high-dose corticosteroid therapy and in the elderly (63,67,74,75). Common adverse effects (Table 5) include the development of a cushingoid appearance with weight gain (14% to 56%), infections (up to 50%), osteoporosis (3% to 30%), hypertension (3% to 12%), and cataracts (8% to 26%). Because long-term therapy is often required, strategies to reduce these risks should be put into place as early as possible (Table 5). Diabetes is not an absolute contraindication to corticosteroids, but a worsening in hyperglycemia should be anticipated and managed. Despite widespread practice, there is no evidence to support the routine use of H2 blockers or proton pump inhibitors with corticosteroids. To reduce the risk of infections and delayed wound healing, thymectomy should be performed before the institution of corticosteroid therapy. However, in a poorly controlled myasthenic, the risks of thymectomy are significant, and it may be preferable to first stabilize the disease with corticosteroids and then taper to a more acceptable dose before thymectomy.

Corticosteroids are highly effective in MG but chronic therapy is often required, producing a significant risk of adverse effects. They are inexpensive, and in most patients will form the mainstay of treatment for other than mild symptoms.

Table 5.
Adverse Effects of Corticosteroids

Adverse effect	Management*	Comment
Gastrointestinal		
Dyspepsia	take with food	higher risk with concurrent use of NSAIDS
Peptic ulcers	concomitant use of anti-ulcer agent (H_2 blocker, proton pump inhibitor, cytoprotective agent), especially if previous history of ulcer, or taking NSAIDs	
Changed Body Habitus		
Cushingoid	alternate-day dosage	reversible after dose reduction/discontinuation
Weight gain	diet exercise	
Skin		
Acne		reversible after dose reduction/discontinuation
Hirsutism		
Striae		
Alopecia		
Easy bruising		
Delayed wound healing		
Metabolic, Fluid, and Electrolyte		
Peripheral edema		reversible after dose reduction/discontinuation
Hypertension	monitor BP regularly, reduce sodium intake, diuretics	
Hypokalemia/muscle cramps	high potassium foods, potassium supplementation	
Hyperglycemia	oral hypoglycemic/insulin if necessary	
Menstrual changes	CHO/calorie-restricted diet	
Adrenal suppression	single morning dose/slow tapering alternate-day dosage	may be prolonged even after discontinuation requiring corticosteroid coverage at times of stress (surgery, illness, etc.)
Muscle		
Cramps	high K^+ diet	reversible after dose reduction/discontinuation, but may take up to a year
Myopathy	regular exercise	suspect with weakness of proximal legs despite improving MG otherwise, and if neck flexion preserved
Behavioral		
Anxiety	symptomatic treatment	more common with high dose, first time on steroids?
Insomnia		
Psychosis		reversible after dose reduction/discontinuation
Mania		
Depression		Psychosis not a contraindication to another trial of corticosteroid.
Psychosis		
Mania		
Depression		

Table 5.
Continued

Adverse effect	Management*	Comment
Bone		
Osteoporosis	alternate-day dosage monitor bone mineral density in high-risk patients prophylaxis with calcium/ biphosphonates/vitamin D if long-term use looks likely consider withdrawing steroids	
Avascular necrosis	alternate-day dosage prompt investigation of hip pain with plain radiographs, MRI, etc.	
Ocular		
Blurred vision	check for hyperglycemia	? Secondary to fluid, electrolyte changes
Cataracts	regular slit-lamp examination with long-term use	
Glaucoma	check intraocular pressure	
Growth		
Growth retardation	alternate-day dosage	in children
Infection	monitor for symptoms and signs of infection	immunosuppression reversible after dose reduction/discontinuation

*For all, use the lowest dose/duration possible to minimize adverse effects

Azathioprine

In comparison to many other immunosuppressive agents, azathioprine is a relatively weak immunosuppressive drug. It inhibits purine synthesis and is metabolized by xanthine oxidase (55,76,77). The exact mechanism of action is unknown but likely involves suppression of both humoral and cellular arms of the pathogenic immune response (76,78,79) A common treatment strategy is to begin at 50 mg per day, increasingly weekly by 50 mg until a therapeutic dose (generally in the range of 2 to 3.5 mg per kg per day) is achieved. It is given as a single morning dose, although if gastrointestinal upset occurs, the dose can be divided. The drug is well absorbed, with peak concentrations appearing in plasma at 1 to 2 hours (76,77). Because allopurinol inhibits xanthine oxidase, if both medications are used concurrently the dose of azathioprine used should be reduced (usually 0.5–1 mg/kg per day only) and monitoring must be vigilant (48,76,77)

Two randomized controlled trials have compared azathioprine to corticosteroids. In the first, azathioprine had a lower rate of treatment failures and fewer adverse effects, although both azathioprine- and prednisone-treated groups had a similar rate of improvement at 3 years (71). A more recent, although smaller study, showed an unusually high drop out rate in the azathioprine group, and a poor response in the remaining patients (80). Uncontrolled retrospective trials suggest efficacy in 70% to 90% of patients, with most patients achieving significant improvement or remission (5,48,75,76,78,79,81). Because of its steroid-sparing effects, azathioprine will often allow a more rapid rate of tapering and lower doses of corticosteroids (55,69,76,78,79). The onset of effect may take 2 to 10 months, with maximal benefit not occurring for 6 to 24 months (51,55,76,79,82) This long delay frequently precludes the use of azathioprine as a first-line drug, so that it is generally combined with corticosteroids, with which it might have synergism (48,75,78,82). Once remission occurs, tapering of azathioprine should occur over 12 to 24 months.

Adverse effects of azathioprine occur in roughly one third (10% to 54%) of MG patients (5,9,48,74–76,79). In some series, 10% to 25% of patients were unable to continue azathioprine because of gastrointestinal, hematological, or hepatic toxicity. As with all immunosuppressives, susceptibility to infections is increased. Transient gastrointestinal upset can occur shortly after beginning therapy, and is usually ameliorated by temporarily reducing the dose, by taking it with food, or by dividing the total dose over the day. Hepatotoxicity, relatively common, is generally mild and reversible. An increase in transaminase levels to greater than two times the upper limit of normal necessitates a dose reduction and vigilant monitoring of the liver enzymes (79). If they continue to increase, azathioprine should be discontinued. Subsequent trials of azathioprine must be carried out cautiously, starting at an even lower dose (25 mg per day) and increasing either biweekly or monthly. To a certain extent, bone marrow suppression is a desired and dose-related consequence of therapy, and increases in the red blood cell mean

corpuscular volume may correlate with benefit (55,76). However, excessive myelosuppression, with neutropenia or thrombocytopenia, should be avoided. Lymphopenia occurs commonly and is less concerning, although a significant reduction in the absolute lymphocyte count may necessitate a dose reduction. Doses that reduce the total white blood cell count below the lower limit of the normal range, or the total neutrophil count below 1×10^9/L, should be reduced.

This potential for hepatic and hematological toxicity necessitates vigilant monitoring after the institution of azathioprine therapy. Assessing the complete blood count and differential, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, bilirubin, and alkaline phosphatase levels weekly for the first 8 weeks, and monthly thereafter is one possible strategy for monitoring azathioprine. These adverse effects can occur at any time, and if detected early, are reversible with a dose decrease or complete discontinuation. The use of angiotensin-converting enzyme inhibitors may increase the risk of bone marrow suppression caused by azathioprine (83). Allopurinol, which inhibits xanthine oxidase, increases the possibility of toxicity. A relatively uncommon but early reaction consists of severe flu-like symptoms, beginning within the first week or two. This may represent an allergic reaction and almost always precludes the further use of azathioprine. Less common adverse effects include skin rash, alopecia, and pancreatitis.

The issue of whether chronic use of azathioprine results in an increased rate of malignancy, specifically lymphoma and dermatological, in MG is controversial (55,76,84). Although this has been shown in the renal transplant and rheumatoid arthritis populations, and perhaps in multiple sclerosis, there is no evidence for this in myasthenia gravis (84). Nevertheless, it is important to discuss this with the patient. It may be best to consider other treatments if there is a strong personal or family history of malignancies. Despite warnings perpetuated in the literature, there is no evidence of an increased rate of teratogenicity with azathioprine, and it is likely safe in pregnancy (85). However, the long latency before benefit means that it may not be reasonable to begin azathioprine for the first time during pregnancy. On the other hand, there is no need to discontinue azathioprine in a well-controlled patient who is either pregnant or is contemplating pregnancy, although this should be discussed with the patient beforehand.

Thus, although azathioprine is less useful as a primary therapy in MG because of its long latency before benefit, it is extremely useful in patients who are intolerant of corticosteroids and allows a more rapid and successful tapering of corticosteroids. It is as effective as corticosteroids and likely has fewer adverse effects, although requires vigilant monitoring for both hepatic and hematological toxicity.

Cyclosporine

Although less commonly used, cyclosporine is one of the few treatments for which there is randomized controlled trial evidence of efficacy in MG (86,87). Cyclosporine is a potent immunosuppressive agent. By interfering with the activation of T helper lymphocytes, cyclosporine inhibits B lymphocytes and therefore reduces the production of AChR antibodies (77,87).

Azathioprime is extremely useful in patients who are intolerant of corticosteroids and allows a more rapid and successful tapering of corticosteroids.

Cyclosporine is generally used when first-line treatments have failed or are contraindicated (87,88). A newer preparation, Neoral, has improved oral absorption and bioavailability (77). The initial dose is 2 to 5 mg/kg (lean body weight) given as a divided dose every 12 hours. The dose is highly individualized, and adjusted to maintain a serum trough concentration of 100 to 150 ng/mL (46,48,86,87). Higher serum levels may lead to early improvement but have an increased risk of toxicity (87). Peak concentrations of the drug occur within 1.3 to 4 hours after oral administration (77). Metabolism occurs mainly in the liver by the cytochrome P450 system (77). As a consequence, medications that inhibit this system increase serum levels and toxicity (77). These include a variety of commonly used drugs, such as the macrolide antibiotics, and even grapefruit juice. Patients should be counseled that the initiation or cessation of other medications may change serum levels and therefore efficacy or toxicity.

After the successful results of several small open trials in MG, a randomized controlled trial assessed cyclosporine in MG patients treated with AChEIs only. A favorable response was seen, but the use of cyclosporine was limited by significant toxicity (86). A second randomized controlled trial in MG patients who had failed corticosteroid therapy was also positive, with some improvement seen 1 to 2 months after beginning therapy, and significant benefit at 3 to 5 months (87). Most patients were on lower doses of corticosteroids by 6 months, and maximal benefit occurred at 12 months. In parallel to clinical improvement, AChR antibody titers were reduced. However patients often relapsed after discontinuation of cyclosporine.

Dose-related adverse effects, including nephrotoxicity and hypertension, limit cyclosporine use in MG (77,86,87). Other adverse effects include hepatotoxicity, hirsutism, nausea, gingival hyperplasia, tremor, headache, neuropathy, and psychiatric changes (77). Relative contraindications to the

use of cyclosporine include preexisting renal failure, poorly controlled hypertension, or significant hepatic dysfunction.

Thus, cyclosporine is of benefit in MG, as demonstrated by two randomized controlled trials, and may work faster than corticosteroids. However, its use is limited by its expense and toxicity, and by the need for vigilant monitoring of serum levels. Because of this, cyclosporine is used mainly in severe MG not responding to corticosteroids or azathioprine.

Cyclosporine is of benefit in MG, as demonstrated by two randomized controlled trials, and may work faster than corticosteroids.

Cyclophosphamide

Less commonly used in MG, cyclophosphamide interferes with DNA synthesis and may preferentially suppress B lymphocytes (77). Thus, it is theoretically advantageous in an antibody-mediated disorder such as MG. It has been used in MG patients refractory to other immunosuppressive agents (48,55). Daily doses of 1.5 to 5 mg/kg orally are used, although monthly intravenous pulse therapy may be less toxic (48,89). Cyclophosphamide was effective in EAMG, although the high doses required produced the need for subsequent bone marrow transplantation (90). Open trials in a small number of MG patients have shown a benefit in 70% to 86% of patients (89,91,92). The initial response is generally seen within 1 month, with most improvement occurring within 1 year. There may be a relationship between improvement and cumulative dose (89). As with all immunosuppressive agents, relapse may occur after discontinuation, although re-initiation of the drug is generally followed by recovery.

Although anecdotally effective in the treatment of MG, cyclophosphamide is also impressively toxic (76). Adverse effects include excessive myelosuppression, hepatotoxicity, alopecia, pancytopenia, nausea and vomiting, arthralgia, dizziness, susceptibility to infections, bladder fibrosis, interstitial pulmonary fibrosis, and hemorrhagic cystitis (76,77,89,92). It is also associated with an increased risk of bladder carcinoma and hematologic malignancies. High doses may produce cardiac toxicity. Regular monitoring of a complete blood count and differential, liver enzymes, and urine is needed. Cyclophosphamide is teratogenic and its long-term use may decrease fertility (76,85).

Other Medications

A variety of immunosuppressive agents including newer medications used for transplant recipients are being tried in MG. Evidence supporting their use in MG is limited to small number of case reports. In theory, there is no reason why any immunosuppressive agent would not be effective in MG. The specific agents described above are more commonly used largely because of familiarity with the expected response and adverse effects. Recently, mycophenolate has been used in small numbers of patients with myasthenia gravis. It appears to be well tolerated, and when used in combination with other standard immunosuppressive agents, in an uncontrolled nonrandomized trial, produced benefit in roughly two thirds of MG patients (93,94).

TEMPORARY TREATMENTS

In situations of rapidly worsening weakness, especially when bulbar or respiratory muscles are involved, the long latency before benefit from either corticosteroids or azathioprine is unacceptable. Two therapies, intravenous immunoglobulin (IVIg) and plasma exchange, are useful in this situation. Both produce temporary improvement only, with no long-term effects on the course of the disease.

Plasma Exchange

There is a solid rationale for the use of plasma exchange in MG, with several serological studies showing reductions in AChR titers by 50% to 70% (57,64,95,96). This temporarily improves neuromuscular transmission. Each exchange removes approximately 60% of serum components, so that a course of three to five exchanges removes 93% to 99% of serum IgG and other factors (97). Because the majority of AChR antibodies are IgG, with a half-life of 21 days, they return at a slower rate than non-IgG components, which have a shorter half-life (97). AChEIs are not significantly removed during plasma exchange (46). A common schedule consists of three to five exchanges, each exchanging 5% of body weight (50 mL/kg), over 3 to 10 days (48). There are no randomized controlled trials proving the efficacy of plasma exchange in MG. In one study, two exchanges were as effective as more intensive therapy (98). Plasma exchange is used primarily at times of significant weakness of respiratory and bulbar muscles, and also to reduce the risk of perioperative or postoperative complications of surgical procedures including thymectomy (95,99,100). It is also effective in seronegative MG (51,101). Plasma exchange may be useful to prevent or manage corticosteroid-induced early worsening.

After beginning plasma exchange, electrophysiological improvement in neuromuscular transmission is seen within 24 hours (102). Clinical benefit begins in 2 to 10 days and is maximal at 8 to 16 days (55,103,104). The duration of improvement is variable, ranging from 2 to 8 weeks (55,95). Thus, it is useful to warn patients that improvement after

thymectomy is likely attributable to plasma exchange, and that a return to baseline can be expected before the benefits of thymectomy occur. Although immunosuppression modifies the disease in the long-term, plasma exchange does not (97,104,105).

In uncontrolled trials, 60% to 88% of MG patients improved after plasma exchange (95,103,106). There was no correlation between AChR antibody titer and response. Significant complement-mediated endplate damage may explain the lack of response in some individuals. In one uncontrolled study, both plasma exchange and pyridostigmine produced benefit, although plasma exchange was superior, with improvement occurring on days 2 to 4 (57). In another retrospective series, patients receiving prethymectomy plasma exchange required less mechanical ventilation and had shorter stays in the intensive care unit (100). There are no prospective studies comparing plasma exchange to placebo. An randomized controlled trials comparing plasma exchange to IVIg in worsening MG showed similar benefit from both, although IVIg had fewer adverse effects (103).

Plasma exchange is generally well tolerated (96). Difficulty with venous access is often a limiting factor (55,96,97). More common adverse effects occur in 12% to 40% and require discontinuation in 2% to 10% of exchanges (98,103). These adverse effects include hypotension or hypertension, tachycardia, fever, chills, nausea, vomiting, citrate-induced hypocalcemia, hypoalbuminemia, and changes in clotting with thrombocytopenia or bleeding and catheter-related venous thrombosis. (55,96,97).

Despite a dearth of controlled studies of plasma exchange in MG, there is a compelling rationale for its use and considerable evidence from uncontrolled observations to support its efficacy in MG.

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Intravenous Immunoglobulin

IVIg is a more recent addition to the therapeutic armamentarium in MG. IVIg is prepared from the plasma of large numbers of healthy donors, and is rigorously prepared and screened for potential infectious agents (97,107). The principle active component in IVIg appears to be IgG itself (97). After infusion, the half-life of IgG is approximately 21 days (range 12 to 45 days) (97). Although employed successfully along with ACTH in MG in the early 1970s, it wasn't until after promising results in idiopathic thrombocytopenic purpura that IVIg was used in earnest in MG (5,108,109). There is no evidence to support a specific treatment schedule. The current regimens simply follow those used initially in ITP and consist of a course of 2 g/kg (total dose) given over 2 to 5 days.

In open trials, improvement was seen in 50% to 87% of MG patients (103,108–111). In the only randomized controlled trials published to date, IVIg was compared to plasma exchange (103). Although only three exchanges were used, arguably suboptimal, IVIg was equivalent in efficacy. Only 61% of patients improved, fewer than in most uncontrolled trials, probably reflecting more rigorous clinical analysis. Although IVIg appears to be as effective as plasma exchange, it may be better tolerated (97,103). The onset of benefit generally occurs within 4 days after beginning the infusion, is optimal at 8 to 15 days, and lasts 40 to 106 days (103,107,110,111).

There has been no convincing demonstration of a single mechanism of action in MG, although regulation of AChR antibody production or action seems likely (110). A moderate decrease in AChR antibody levels is often, but not always, seen after IVIg treatment (103,108–110). The reported frequency of adverse effects from IVIg is highly variable, ranging from 0% to 80% (103,107–109,112,113). When patients with neurological disease were surveyed, adverse effects were more common than in non-neurological patients (113). The most frequent adverse effects (Table 6) are mild, occur during or shortly after infusion, and can be minimized by reducing flow rates or managed with appropriate symptomatic therapy. Several factors increase the risk of more serious adverse effects, including a concurrent infection, high infusion rates or volumes in patients with preexisting cardiac or vascular disease, recipient IgA deficiency, immobility or hypercoagulability, preexisting renal failure, increased serum viscosity, and perhaps migraine. Although screening for IgA deficiency before IVIg use is often recommended, for fear that IgA-deficient recipients will have an allergic reaction to IgA contained in IVIg, there is little evidence for an increased risk of anaphylaxis in IgA-deficient individuals. Anaphylaxis may also occur because of reactions to non-IgA proteins in the IVIg preparation. Moreover, the use of IVIg is generally urgent enough that treatment must be started before the results of quantitative IgA levels are known. This issue is somewhat controversial (97,114).

Thus, IVIg appears to be as effective as plasma exchange in the treatment of acutely worsening MG. Their indications are similar, although IVIg may be better tolerated and is more accessible in many centers. Further studies are needed to clarify the relative roles of these two therapies in MG. Neither IVIg nor plasma exchange alter the long-term course of

Table 6.
Adverse Effects of Intravenous Immunoglobulin

Common, mild, early, reversible and infusion-rate related
Abdominal pain, arthralgia, backache, myalgia
Chest tightness, wheezing, dyspnea
Fever, chills
Headache
Nausea, vomiting
Presyncopal sensations
Rash, pruritis, skin flushing
Vasomotor/Cardiovascular—changes in blood pressure and heart rate
Rare, potentially more severe, delayed
Alopecia
Aseptic meningitis
Cerebral thrombosis/stroke, reversible cerebral vasospasm
Coagulopathy, deep vein thrombosis
Erythema multiforme
Hemolytic anemia (anti-blood group A or rhesus D contained in intravenous immunoglobulin)
Hypersensitivity/anaphylaxis (? more likely in IgA-deficient recipients)
Leukopenia, neutropenia (transient)
Renal failure, proteinuria
Transient increase in liver transaminases
Transmission of infection (hepatitis C)
Risk factors for adverse effects
Concurrent infection (antibody in intravenous immunoglobulin binding to infectious agent)
High infusion rates/volumes, especially with preexisting cardiac or vascular disease
Recipient IgA deficiency, ? increased risk of anaphylaxis
Immobility (? increased risk venous thrombosis)
Increased age
Increased serum viscosity—paraproteinemia, dehydration
Migraine (increased risk of headache and aseptic meningitis)
Renal failure (high solute load in IVIg or immune complex formation)

the disease. Increasingly, supplies of IVIg are limited and, as with plasma exchange, its expense is considerable.

Thymectomy

Although thymectomy is an accepted treatment for MG, its exact role remains controversial (115–117). Debates include who should have the procedure done, when it should be offered, and how the procedure should be done (51,116–118). Although widely practiced, there are no randomized controlled trials proving the efficacy of thymectomy in MG (116). There is considerable "expert opinion," and epidemiological evidence that the morbidity and mortality have been improved since the widespread practice of thymectomy in MG (5,46,119). The rationale for thymectomy is that the thymus is frequently pathologically involved in MG (24,120). In early-onset MG, thymic hyperplasia is found microscopically even when the thymus is radiologically normal. In late-onset MG, there is a 30% incidence of a thymoma (24,120). The most accepted indications for thymectomy are for seropositive early-onset MG patients with generalized disease, or for the removal of a thymoma (117). The removal of a thymoma may not improve the course of MG, whereas the removal of a hyperplastic thymus in early-onset MG appears to alter the course of the disease (119). Approximately 34% to 46% of individuals will be "in complete remission" within 2 to 5 years after thymectomy, seemingly higher than medically treated patients (116,121,122). Another 33% to 40% will be significantly improved (116,121,122).

The long latency until benefit after thymectomy means that there is no indication to rush into thymectomy in the management of an unstable MG patient. As such, thymectomy is an elective procedure and with rare exceptions should be delayed until the patient is improved with medical treatment. There is some evidence that early thymectomy is more likely to be beneficial. Although all studies to date are nonrandomized, most have suggested improvement from thymectomy (116). Comparisons of outcome in surgical and medical groups are confounded by differences in other baseline characteristics that might also affect prognosis (116). A recent analysis suggests an almost twofold improvement in outcome with thymectomy. Improvement may be more likely in females and in more severe disease, and less likely in males (116). However, multivariate analyses controlling for differences in baseline characteristics have not shown a consistent benefit from thymectomy (116). Limited analyses suggest that thymectomy may not be as effective for ocular MG, although given the high rate of subsequent generalization, the role of thymectomy in this subgroup remains to be proven (116).

Whether plasma exchange or IVIg should be offered routinely to all patients undergoing thymectomy, even when stable preoperatively, is controversial and should be the focus of future studies. In a patient who is significantly symptomatic, preoperative treatment with plasma exchange, or perhaps IVIg, should be given to reduce the chances of perioperative or postoperative complications. Although often suggested in the past, a reduction in AChEI dose after surgery may not be needed. Patients should be warned that improvement after surgery is likely the effect of plasma exchange or IVIg, and that they may revert to baseline within several weeks. Evidence of an invasive thymoma at the time of surgery should be followed by a radiation oncology referral for mediastinal radiotherapy, to reduce the risk of regrowth or of local or widespread metastases.

More controversial is whether thymectomy should be offered to late-onset MG patients (117,123). The most popular belief is that it is not effective in this group, with the

tissue removed generally consisting of either adipose tissue only or of a few scattered thymic remnants. Also controversial is the surgical approach (115,118). The cervical approach is less invasive, requires a shorter stay in hospital, and leaves a more cosmetically acceptable scar. The transsternal approach, preferred by most physicians managing MG, has the advantage of more completely removing the thymus and its many possible ectopic foci in the mediastinum, and appears to have a greater success rate (118). Which of the approaches has the best balance between benefit and risk remains to be proven (115). There is some evidence that higher remission rates are associated with a more aggressive surgical approach (118).

THE PATIENT WHO DOESN'T RESPOND

Despite highly effective treatments for MG, some patients do not respond. In a patient without detectable AChR antibodies, the possibility that they may not have myasthenia should be considered, and reinvestigation may be appropriate. Nevertheless, in both seronegative and seropositive MG patients, there are several possible reasons for not responding to treatment. Other processes unrelated to MG may be producing weakness. Because MG is an autoimmune disease, patients are more likely to have other autoimmune diseases including thyroid disease (9). Thus, increasing ocular symptoms may be a result of dysthyroid ophthalmopathy rather than myasthenia. Long-term corticosteroid use may produce a steroid myopathy. Despite sufficient treatment and objective evidence of improvement, some patients continue to be subjectively limited. This may reflect other social, financial, or occupational issues. Good clinical acumen, and occasionally electrophysiological investigations, are useful to differentiate the weakness of myasthenia gravis from nonspecific symptoms attributable to other causes. A common reason for lack of improvement is that insufficient time has elapsed since therapy was started. If the situation permits, simply waiting several more weeks or months is often enough for benefit to be seen. An occasional patient simply has severe disease and does not respond. Other immunosuppressive agents, including cyclosporine or occasionally cyclophosphamide, should be considered in this circumstance. The situation of very severe weakness not responding to initial treatment is perhaps more common in the postpartum period, when subsequent control can be difficult.

SPECIAL CIRCUMSTANCES

Children

For the most part, the treatment of children is the same as for adults. The first step in management is to rule out a nonimmune congenital myasthenic syndrome with the appropriate serological, electrophysiological, and genetic investigations (6). In children, immune-mediated MG is usually milder, often ocular, and perhaps more common in Orientals (3). The same medications can be used, although the potential effects of corticosteroids on growth must be considered. After the age of 1, there is little evidence that thymectomy results in any long-term immunodeficiency, and if the severity of the disease warrants it, thymectomy should be considered (51,124).

Ocular MG

Although the majority of individuals begin with ocular symptoms, 15% of MG patients are left with only ocular disease after the first 3 years (2,26,31). Thus, weakness confined to the ocular muscles beyond 3 years suggests a good prognosis, and a decreased likelihood of subsequent generalization. The diagnostic tests are less sensitive in ocular MG, and often the diagnosis relies on clinical observation, and occasionally on a therapeutic trial. AChEIs may be less, and corticosteroids more effective in the treatment of the ocular symptoms in MG (31). There is limited retrospective evidence that early therapy with corticosteroids may reduce the subsequent risk of generalization in patients beginning with ocular symptoms (58,73). Whether the presence of ocular symptoms only justifies aggressive treatment with immunosuppressives, or even thymectomy, remains controversial.

Seronegative MG

In 21% to 71% of patients with ocular myasthenia gravis, and 6% to 25% of patients with generalized MG, AChR antibodies are undetectable (8,9). However, the other diagnostic tests are just as useful in seronegative MG and the treatment the same. This includes evidence that plasma exchange and IVIg are effective in seronegative MG, also supporting the premise that seronegative MG nevertheless involves a humoral mechanism (8,125). Whether thymectomy is useful in seronegative MG is controversial, because the incidence of thymic hyperplasia may be less in this subgroup (126). In seronegative MG not responding to treatment, some suspicion in terms of the diagnosis is warranted and reinvestigation may be appropriate.

Pregnancy

The management of pregnancy in MG, and vice versa, may be complicated. It is equally likely that MG will remain stable, improve, or worsen during pregnancy. There is a higher risk of relapse in the postpartum period, when it may be particularly difficult to treat (127). In 1 of every 8 pregnancies in MG mothers, neonatal MG may occur (127). This is a result of the transplacental passage of AChR antibodies, and is generally manifest within hours of delivery by a weak cry or difficulties feeding. It is self-limited, although symptomatic treatment with AChEIs may occasionally be required. With the increased use of immunosuppression before or during pregnancy, neonatal MG seems to be less frequent. The absence of measurable AChR antibodies in a myasthenic mother does not preclude the occurrence of neonatal MG (128). Because of this risk, all MG mothers should have their

Table 7.
Drugs and Myasthenia Gravis

- Antibiotics
  - Aminoglycosides
    - Neomycin
    - Gentamicin
    - Streptomycin
    - Others
      - Kanamycin
      - Tobramycin (? Least toxic)
  - Macrolides—Erythromycin, clarithromycin, azithromycin
  - Fluoroquinolones (Norfloxacin, Ofloxacin, Pefloxacin, Ciprofloxacin)
  - Amikacin
  - Polymixin B, colistin
  - Tetracyclines, oxytetracyclines
  - Lincomycin and clindamycin
  - Ampicillin
- Cardiovascular Drugs
  - Beta blockers (including topical/ocular)
  - Quinidine
  - Procainamide
  - Verapamil, nimodipine and perhaps other calcium channel blockers
  - ? Clonidine
  - Bretylium (high doses)
  - Trimethaphan
  - ACE inhibitors (enalapril, captopril) if on azathioprine**
- CNS Active
  - Diphenylhydantoin/Phenytoin
  - Trimethadione
  - Lithium
  - Chlorpromazine, Promazine
  - Diazepam?
  - Barbiturates?
  - Trihexyphenidyl
  - Morphine??
  - Amantadine
- Anti-rheumatic
  - Chloroquine
  - D-penicillamine
  - Prednisone (high doses within first 2–3 weeks)
- Anesthetic agents
  - Non-depolarizing agents (Pancuronium, Vecuronium, Atracurium)—increased sensitivity in MG
  - Gallamine
  - Succinylcholine (decreased effect in MG, increased if on pyridostigmine)
- Other drugs
  - Allopurinol if on azathioprine**
  - Procaine and lidocaine (iv)
  - Magnesium
  - Bretylium
  - Topical ophthalmic drugs (timolol, beaxol, echothiophate)
  - Quinine??
  - Lactate
  - Iodinated contrast agents
  - Citrate anti-coagulant
  - Diphenhydramine
  - Aprotinin/Trasylol
  - Emetine
  - D,L-carnitine

*Those medications that are underlined appear to be most consistently associated with worsening in MG.
**Because of increased risk of bone marrow suppression.

pregnancies managed in a center in which neonatologists and anesthetists can attend at the time of delivery.

Most medications used to treat MG are safe during pregnancy. This includes AChEIs, prednisone, and azathioprine (48,52,85,127). As described above, there is little evidence that azathioprine is teratogenic above and beyond the baseline level of birth defects (85). Both plasma exchange and IVIg may also be used during pregnancy, although care must be taken with the former to avoid volume shifts that may place the mother or fetus at risk. If eclampsia occurs, the use of magnesium may interfere with neuromuscular transmission, worsening MG (127,129). A defect in neuromuscular transmission should not affect the normal progress of labor, although to the extent that voluntary muscular effort is required during delivery, early fatigue may occur. A cesarean section should not be routinely planned, but may be indicated in particularly severe disease if early fatigue ensues.

Other Drugs Interfering With Neuromuscular Transmission

A number of medications have the potential to impair neuromuscular transmission and worsen the situation in a myasthenic (Table 7) (130). Occasionally this can bring the diagnosis to light, but more commonly it raises management issues in a myasthenic who has other diseases requiring treatment. It is useful to disseminate a list of such medications to referring and family physicians. Care should be taken to make the point that none of the medications are absolutely contraindicated, but if one must be used the status of MG should be closely monitored. If possible, a medication not on the list should be used. If a potentially deleterious medication must be used and cannot be withdrawn, and if weakness does occur, the MG should be managed as usual.

CONCLUSION

The management of MG can be a very rewarding experience, with most patients responding well to treatment. It requires a thorough knowledge of the mechanisms of normal

and abnormal neuromuscular mechanism, and also of the specific agents used in the treatment of MG. The beneficial effects of treatment need to be balanced against the considerable risk of adverse effects, and treatment must be highly individualized.

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