Myasthenia Gravis
A Manual
for the Health Care Provider

James F. Howard, Jr., M.D., Editor

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FOUNDATION OF AMERICA, INC.

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Notice

Knowledge and best practice in the field of Myasthenia Gravis is constantly changing as new research and experience broadens the knowledge base. Changes in practice, treatment and therapy may be necessary or appropriate.

Readers are advised to check the most current information available. It is the responsibility of the health care provider, relying on their own knowledge and experience to make diagnoses, determine appropriate treatment, doses and schedules and overall best treatment plan for the pateint.

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Preface

The mission statement of the Myasthenia Gravis Foundation of America (MGFA) is to facilitate the timely diagnosis and optimal care of individuals affected by myasthenia gravis (MG) and closely related disorders and to improve their lives through programs of patient services, public information, medical research, professional education, advocacy and patient care. Since, at present, there is no cure, there must be a consistent, interdisciplinary effort by all allied health professionals to appropriately evaluate and treat patients with MG.

This handbook is written as an aide to all healthcare personnel who are involved in the care and management of patients with myasthenia gravis. Sections are included to assist the physician community in their evaluation, diagnosis and manage-

ment of MG. Every effort has been made to outline the varying opinion of the experts and it is recognized that more than one approach may be appropriate. The over riding principle that patients with MG are not in a vacuum and must be evaluated and treated based on their entire health care picture is necessary. The perspective of an anesthesiologist and dentist are also included because their interaction with the myasthenic patient is unique and special considerations are necessary.

Nursing plays a critical role in the day-to-day management of the hospitalized and community patient. A team approach to the patient will inevitably result in the optimal care of the myasthenic patient.

The patient with a chronic illness faces numerous obstacles in their every day life. The clinical social worker is invaluable to the patient (and the healthcare team) in navigating the bureaucracy and hurdles as it pertains to insurance, financial assistance and psychosocial well being.

The allied health evaluations should be objective and quantitative for each individual patient and should assist the physician in diagnosis, classification and effectiveness of medical treatment. These evaluations should enable the allied health professionals to determine a functional baseline and an appropriate exercise prescription. The patient will then be able to utilize a program of moderate-intensity exercise to improve his/her level of fitness, which will diminish the effect of exacerbations. Through the use of self-monitored exercise, each patient will have an improved sense of his/her own functional limitations and will be able to supply the physician with more detailed information about current treatment efficacy.

The pharmacist plays an important role in the safety and education of the myasthenic patient. Today's healthcare system often depends upon the specialist who has little knowledge of other disciplines. The ever growing list of drug-drug interactions that may be harmful to the patient places the pharmacist in a central position to be the watchdog and keep the patient out of harms way.

This coordinated, interdisciplinary approach will promote increased quality of life for those affected by myasthenia gravis.

The following guidelines are a culmination of over 35 years of clinical practice in university-based teaching hospitals. It is the authors' hope that these guidelines will challenge all allied health clinicians who work with patients diagnosed with myasthenia gravis to critically evaluate their current practice with respect to these patients. We submit that incorporation of these recommendations into the evaluation and treatment repertoire of allied health professionals will enhance the quality of care provided to people who have myasthenia gravis.

Historical Notes

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The unraveling of the molecular mechanisms of Myasthenia Gravis (MG) over the last three centuries has resulted in what we know today about the pathogenesis of MG and the rationale for its present and future treatments. The first descriptions of MG cases occurred more than 300 years ago, yet it was not until a series of discoveries in the early and mid 1970s that an understanding of and the general consensus that MG symptoms are due to an autoimmune response to the acetylcholine receptor (AChR) complex on the post-junctional membrane of the neuromuscular junction

The first two cases of a disease that was likely to be MG were described several centuries ago; one on the American continent and one in Europe. The latter is a clinical description of MG symptoms written in 1672 by the English clinician Sir Thomas Willis in his book on the nature of disease "De anima brutorum" where he describes an woman as follows (translated from Latin by Samuel Pordage (1683).

> *... nevertheless, those labouring with a want of Spirits, who will exercise local motions, as well as they can, in the morning are able to walk firmly, to fling about their Arms hither and thither, or to take up any heavy thing; before noon the stock of the Spirits being spent, which had flowed into the Muscles, they are scarcely able to move Hand or Foot. At this time I have under my charge a prudent and an honest woman, who for many years hath been obnoxious to this Tort of spurious Palsie, not only in her Members, but also in her tongue; she for .come time can speak freely and readily enough, but after she has spoke long, or hastily, or eagerly, she is not able to speak a word, but becomes as mute as a Fish, nor can she recover the use of her voice under an hour or two ...(Willis, 1672)*

Willis' description is generally considered to be the first description of MG. However, the first described case of MG may have occurred several decades earlier in North America (Marsteller, 1988). Opechankanough, a Native American Chief, in colonial Virginia was born in the middle of the 16th century and died in 1664. Marsteller concluded that Opechankanough developed MG late in life when he was between 70 and 90 years old based on the following description by Virginian chroniclers.

> *The excessive fatigue he encountered wrecked his constitution; his flesh became macerated; his sinews lost their tone and elasticity; and his eyelids were so heavy that he could not see unless they were lifted up by his attendants ... he was unable to walk; but his spirit rising above the ruins of his body directed from the litter on which he was carried by his Indians.*

It was not until the end of the 19th century that MG was recognized as a well-defined disease. In 1877 the English clinician, Wilks, described a patient suffering from generalized weakness that included the muscles of eye movement (ocular muscles), as well as bulbar symptoms, resulting in dysarthria (slurred speech) and dysphagia (difficulty swallowing). The patient died of respiratory failure shortly after the onset of her symptoms and her brain did not have identifiable lesions. Based on the description of the symptoms and the absence of brain lesions, this patient may well have had MG, although Wilks did not single her out as suffering from a distinct and defined syndrome (Wilks, 1877).

German, English, Polish and American clinicians described patients over the next 15 years who clearly suffered from MG. These patients had fluctuating weakness that involved both

limb and bulbar muscles, died of respiratory failure and autopsy findings did not detect brain lesions.

In 1879, Erb described three patients who had weakness of the limbs and the neck and bulbar symptoms that included ptosis (drooping of eyelids) and difficulties in chewing and swallowing. All symptoms tended to fluctuate and to show occasional spontaneous improvement. Erb proposed that the disease originated in the brain stem (Erb, 1879). Oppenheim, in 1887, described a woman who had intermittent weakness of limb muscles, later also involved bulbar muscles and who died of respiratory failure. With remarkable insight, Oppenheim noticed the similarities between the exercise-induced weakness of his patients and the symptoms of curare intoxication (Oppenheim, 1887).

In the next several years, physicians in Germany, England and the USA described patients with fluctuating weakness of the ocular or bulbar muscles. This weakness varied during the day and seemed to become more severe as the day progressed.

Samuel Goldflam around the same time described three patients suffering from muscle weakness that fluctuated in severity and sometimes improved spontaneously. He reviewed and summarized the unifying characteristics of similar cases described by other authors (Goldflam, 1893). His descriptions were so detailed that the symptoms he described became known as the Erb-Goldflam syndrome.

In 1895 Friederich Jolly described two young male patients suffering from a syndrome characterized by intermittent generalized weakness, ptosis and dysphagia, which he named pseudoparalysis myasthenica and later myasthenia gravis pseudoparalytica (Jolly, 1895a). He demonstrated that tetanizing electrical currents applied to the nerves of these patients resulted in an increasingly weaker muscle contraction, which then improved with rest (Jolly, 1895b).

This phenomenon was described by Mary Walker and became known as the Mary Walker phenomenon: after vigorous exercise of one muscle group, increasing weakness would develop in other non-exercised muscles, suggesting the presence of soluble toxic “factors,” released upon or generated by muscle exercise. Jolly suggested that physostigmine could be used to treat this disease, but he apparently did not try to use this drug (Walker, 1937).

The name myasthenia gravis was accepted at a meeting of the Berlin Society of Psychiatry and Neurology in 1899. In 1900, Campbell and Bramwell published an exhaustive review of the symptoms of MG compiled from the 60 cases reported in the literature up to that time (Campbell, 1900). Given the consistent absence of detectable abnormality at the autopsy of these patients, they proposed “that in myasthenia gravis, a toxin, probably of microbial origin, circulates in the blood and acts selectively upon the lower motor neuron, so as to modify its functional activity”.

Although MG cases with a mediastinal tumor had been reported earlier, a relationship between MG and an abnormal

thymus was first noted in 1901 by Weigert, in a patient who had MG and thymoma (Laquer, 1901).

In the 1930s, the unfolding of studies on chemical transmission at the neuromuscular junction and the observation of similarities between the symptoms of MG and curare poisoning, suggested an impairment of neuromuscular transmission as the functional defect in MG and led Mary Walker to treat MG patients with cholinesterase inhibitors (Walker, 1934, 1935).

> *At the time, she was a house officer at St. Alfege's hospital in London. Her patient was a 56-year-old myasthenic woman. According to Sir Geoffrey Keynes, the British thymectomy pioneer, One day she questioned the visiting neurologist, Dr Denny-Brown, about the mysteries of myasthenia. We may figure the scene as a hospital corridor with an eager and importunate junior pattering after the busy consultant. He is in a hurry and throws over his shoulder the remark, 'Yes, it's like curare poisoning'. Dr Walker, knowing from her textbook that the antidote to curare is physostigmine, thinks, 'Then why not try it on the patient?' The injection was given and there was striking temporary improvement. Walker's letter to The Lancet in 1934 documented the observation: In from half an hour to an hour after the injection the left eyelid 'goes up,' arm movements are much stronger and jaw drops rather less, swallowing is improved and the patient feels 'less heavy.' The effect wears off gradually in from two to three hours... On June 16, 1934, she injected neostigmine with dramatic results. She reported the results at the Royal Society of Medicine later that year. Walker's discovery of the therapeutic value of neostigmine was called The Miracle at St. Alfege's (Keynes, 1961, Viets, 1965)*

After a favorable report by Pritchard on the use of neostigmine for the treatment of MG, this drug became the standard management of MG. In the early 1950s neostigmine was substituted for physostigmine, due to the longer duration of its action and its less prominent muscarinic effects.

Dale had suggested in 1934 that an altered function of the motor end plate was likely responsible for myasthenic weakness because MG symptoms improved with the use of cholinesterase inhibitors (Dale, 1934). In 1935, Lindsley carried out electromyography in MG patients and showed that the motor unit potentials in these patients, while normal in rate and rhythm, had abnormal and variable amplitudes and concluded that the myasthenic muscle weakness resulted from a block of the neuromuscular transmission at the motor end plate (Lindsley, 1935). In 1941, Harvey and Masland demonstrated that repetitive nerve stimulation at low rates in MG patients produced a characteristic decremental response of the compound muscle action potential. This continues to be one of the standard diagnostic tests of MG (Harvey, 1941).

In the 1940s, thymectomy became an accepted treatment for MG. Blalock successfully removed a thymoma from a 20-year-old woman who had suffered from severe generalized MG during the previous four years in 1939 (Blalock, 1939). The patient's symptoms improved after the surgery and the improvement persisted for many years. Blalock started removing the thymus in MG patients who did not have thymoma. In 1944, he published 20 cases of MG patients, 32 only two of which had thymoma and in whom thymectomy resulted in long-lasting improvement of their symptoms (Blalock, 1944). His report led to the wide-spread use of thymectomy for the management of MG.

A very important step in the understanding of MG pathogenesis was the insight by Simpson in 1960 that MG could have an autoimmune origin (Simpson, 1960). He based his hypothesis on the association of MG with other autoimmune diseases, its chronic course and the fluctuations of its symptoms, with exacerbations followed by spontaneous improvements of the symptoms, on the frequent presence of abnormalities of the thymus, a central organ for the immune function and on the presence of transient neonatal MG, which suggested the presence of pathogenic antibodies produced by the mother and affecting the fetus via transplacental passage.

By the early 1970s it was recognized that MG involved a defect in neuromuscular transmission. However, based on electrophysiologic studies of MG muscles that revealed a reduced size of the miniature end plate potentials, a pre-synaptic abnormality in the synthesis, storage or release of acetylcholine was believed to cause myasthenic symptoms.

Crucial in the understanding of MG pathogenesis was the discovery by Patrick and Lindstrom that rabbits immunized with purified AChR developed muscular weakness similar to that of MG patients, suggesting that human MG might have a similar pathogenesis (Patrick, 1973).

Following their discovery, anti-acetylcholine antibodies were demonstrated in a large proportion of MG patients. Andrew Engel proved that auto-antibodies binding to the end-plate acetylcholine receptor were indeed involved in the pathogenesis of MG (Engel, 1971). He demonstrated that in MG patients the postsynaptic membrane of the neuromuscular junction had a highly simplified structure, with loss of the normal post-synaptic folds and immunoglobulin G (IgG) antibodies and complement were present in the inter-synaptic space.

In 1975 Toyka, Drachman and coworkers reported that MG symptoms could be transferred to mice by treatment with MG sera or with their IgG fraction, thus providing a direct demonstration that antibodies are the effectors of MG symptoms (Toyka, 1975). In 1976 Albuquerque and collaborators demonstrated that the neuromuscular junction of muscles from MG patients had a normal quantal content but reduced sensitivity to acetylcholine (ACh) and that the post-synaptic membrane believed to contain AChR were covered by particles with dimensions characteristic of antibodies. These observations led to the recognition that MG was due to a post-, not pre-

synaptic cause and ultimately the recognition of the autoimmune basis for the disease.

The last 30 years has seen the unraveling of the autoimmune mechanisms crucial in the pathogenesis of MG. This in turn has resulted in the continued emergence of newer therapies for MG with a focus on directed suppression of the immune abnormality. The future of MG is bright. The scientific advances that will continue to occur will inevitably lead to the improved quality of life of patients with this disorder.

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2

Physician Issues

James F. Howard, Jr.

Myasthenia gravis (MG) is the most common primary disorder of neuromuscular transmission. An acquired immunological abnormality is the usual cause, but some cases result from genetic abnormalities at the neuromuscular junction. Much has been learned about the pathophysiology and immunopathology of MG during the past 30 years. What was once a relatively obscure condition of interest primarily to neurologists is now the best characterized and understood autoimmune disease.

2.1 Epidemiology of MG

The current prevalence of MG in the US is estimated to be 20 per 100,000 population – between 53,000 and 60,000 cases (Phillips L, 2004). The true prevalence is probably higher because MG is frequently undiagnosed. Epidemiological studies have shown a trend for an increasing prevalence and a falling death rate for MG over the past 50 years. The primary factor for both appears to be an increased life span after diagnosis. Women are affected more often in the second and third decades and men, in the sixth. As the population ages, the average age at onset has increased correspondingly. More men are now affected than women and the majority of MG patients in the US are over age 50.

2.2 Pathophysiology of MG

2.2.1 Anatomy

The region of the neuromuscular junction is termed the *motor end-plate*. Motor neurons leaving the spinal cord course through their respective nerve roots, plexi and peripheral nerves to enter the belly of the muscle. There these axons divide intramuscularly to form a terminal arborization, branching to innervate 10 to 500 muscle fibers (Figure 2.1). In this region the myelin sheath is lost and the terminus is called the *nerve terminal*. This highly specialized region forms a small bulb (the synaptic bouton) within which are synaptic vesicles. Synthesis and packaging of the neurotransmitter,

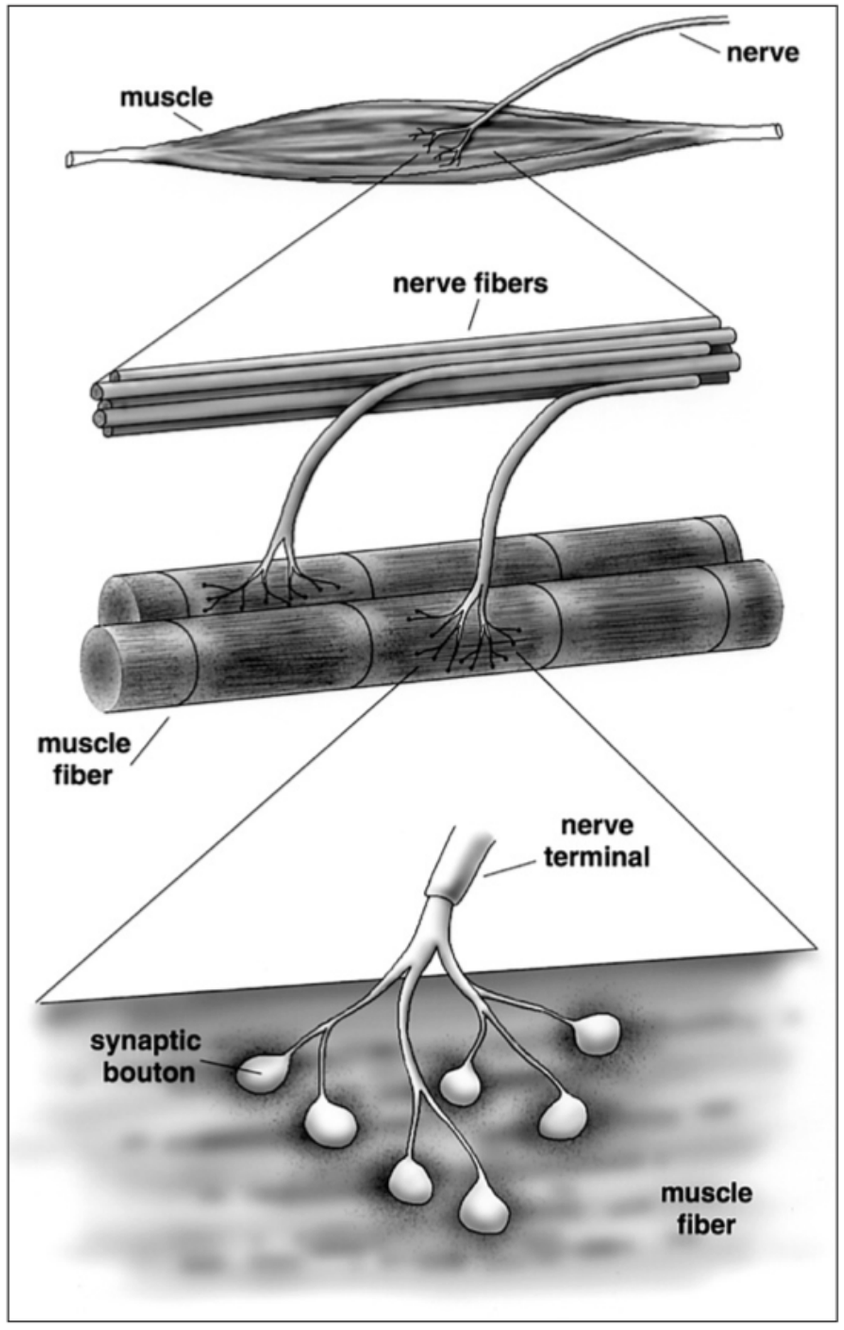

Figure 2.1*. Artist's rendition of the sequential magnification of the motor unit comprising the motor neuron (not shown), the peripheral nerve and its terminal arborization into the nerve terminal and synaptic bouton. The synaptic bouton overlies a single muscle fiber. (Reprinted with permission from Howard JF: Neuromuscular transmission. In Neuromuscular Function and Disease. Basic, Clinical and Electrodiagnostic Aspects. Volume 1, Chapter 21, edit., W Brown, C Bolton, M Aminoff, W.B. Saunders Co. Chapter 21, pp. 401-413, 2002).*

acetylcholine (ACh), occurs within the nerve terminal. Packaged transmitter (vesicles) aggregate in regions called *active release sites or active zones* (Figure 2.2a). Typically there is one end-plate region for one muscle fiber in most skeletal muscles.

The synaptic cleft is approximately 40 to 50 nm in width and separates the nerve terminal from the postjunctional region of the end-plate. The muscle membrane infolds to increase surface area and at the crests of these folds are sites of ACh receptors (AChR) (Figure 2.2b). Acetycholinesterase (AChE) is located deep in clefts of these folds.

2.2.2 Pharmacology

The neurotransmitter at peripheral neuromuscular junctions is acetylcholine. Synthesis occurs in the cytoplasm of the nerve terminal with processing of acetate + choline and with help of choline acetyltransferase. Most of the transmitter is stored in vesicles and there are three major stores of ACh. The first is the readily releasable store which is what is first released when nerve activation occurs. This store is about 1,000 quanta of ACh. It is flux in this transmitter store that serve as the basis for responses which are seen on electrodiagnostic testing. The second store is called the mobilization store. This is about 10,000 quanta of ACh. The third store is the main store where synthesis and packaging of neurotransmitter occur. It is a fairly stable store of about 100,000 quanta of ACh.

2.2.3 Physiology

Neuromuscular transmitter release is of two types. Spontaneous transmitter release is produced by interaction of a single quantum of ACh with the post-synaptic acetylcholine receptor (AChR). These small depolarizations, miniature end-plate potentials (MEPPs), are random and of variable frequency. A second form is evoked transmitter release. This results in a transient depolarization of the post-synaptic membrane in response to a synchronous release of many individual quanta of ACh called an endplate potential (EPP). If the EPP is of sufficient magnitude, the action potential (AP) threshold is exceeded, generating a propagated AP along the muscle membrane.

The pre-synaptic events of neuromuscular transmission include the nerve action potential (AP) depolarizing the axonal membrane of the nerve terminus producing a voltage dependent increase in calcium conductance. The entry of extracellular calcium into the axon terminal initiates ACh release. Exocytosis of synaptic vesicle contents occurs at highly specialized release zones and discharges the ACh into the synaptic cleft. There is prompt diffusion across synaptic cleft to the AChR complex.

The post-synaptic events of neuromuscular transmission include the binding of ACh molecules stereospecifically with post-synaptic AChR receptors. These ACh receptors are located primarily at the crests of post-synaptic folds. Binding produces a conformational change in the ACh AChR

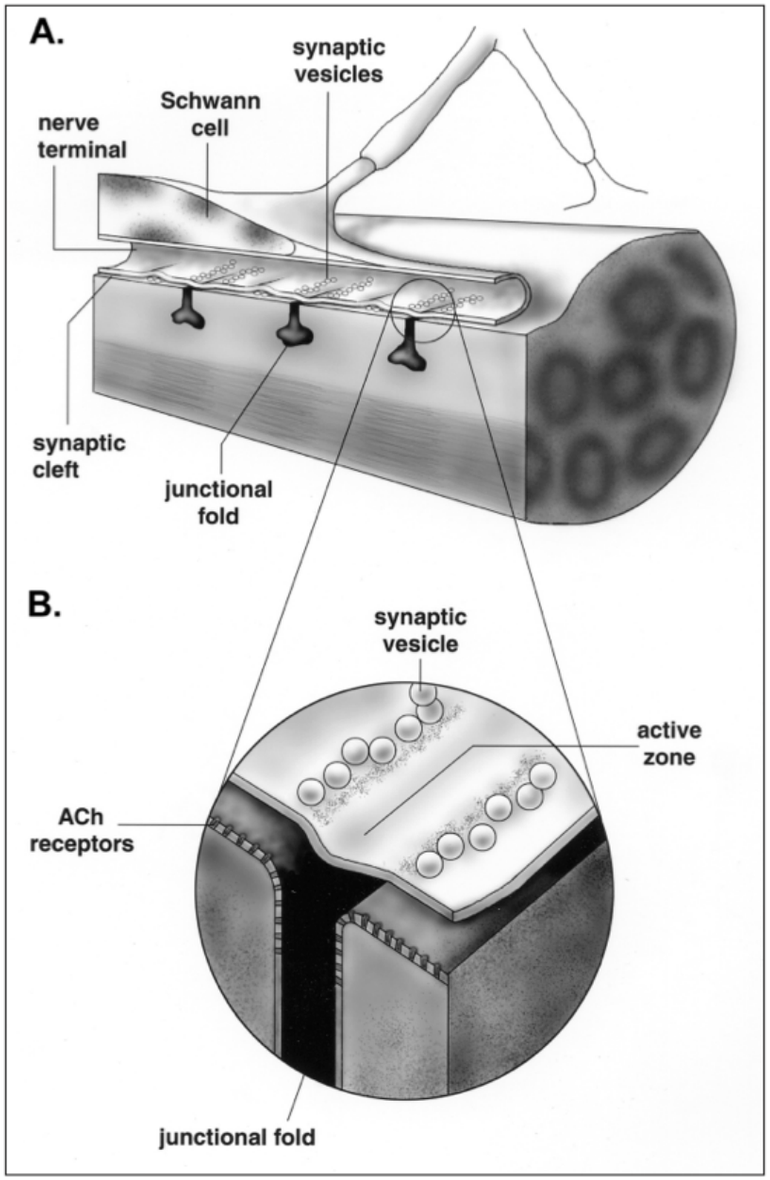

***Figure 2.2**. Artist's rendition of the morphological features of the neuromuscular junction. A. Note the terminal arborization of the peripheral nerve forming the synaptic bouton and pre-synaptic region containing synaptic vesicles. B. Synaptic vesicles are ordered in longitudinal arrays at "active zones" from which they are released to diffuse across the synaptic cleft and bind to acetylcholine receptors located on the tops of the post-junctional folds (Reprinted with permission from Howard JF: Neuromuscular transmission. In Neuromuscular Function and Disease. Basic, Clinical and Electrodiagnostic Aspects. Volume 1, Chapter 21, edit., W Brown, C Bolton, M Aminoff, W.B. Saunders Co. Chapter 21, pp. 401-413, 2002).*

complex with an increase permeability of sodium and potassium, the opening of about 1,500 individual ionic channels for about 1.0 millisecond resulting in the local depolarization of the end-plate zone which produces an action potential and muscle contraction.

Post-synaptic depolarization is terminated by passive diffusion of ACh out of the primary and secondary synaptic clefts and enzymatic hydrolysis of ACh into choline and acetate by AChE.

Acetylcholine is released from the motor nerve terminal in discrete packages, or quanta, and diffuses across the synaptic cleft where it binds to receptors located on the folded muscle endplate membrane in the normal neuromuscular junction. Many quanta of ACh are released, resulting in depolarization of the muscle endplate region and subsequently of the muscle membrane when the motor nerve is stimulated. This results in muscle contraction.

In acquired MG the post-synaptic muscle membrane is distorted and simplified, having lost its normal folded shape. The concentration of AChR on the muscle endplate membrane is reduced and antibodies are attached to this membrane. ACh is released normally, but its effect on the post-synaptic membrane is diminished because of these changes. The post-junctional membrane is less sensitive to applied ACh and there is a reduced probability that any nerve impulse will be followed by a muscle action potential (Figure 2.3).

The following observations indicate that MG is an autoimmune disease in which weakness results from an immunologic attack directed against the AChR complex:

1. Patients with MG frequently have other diseases that have a presumed or known immunological cause, such as thyroid disease, rheumatoid arthritis, vitamin B12 deficiency.

2. Neonatal passage of a transient form of disease is seen in autoimmune diseases, as in MG.

3. Certain tissue haplotypes are more common in patients with MG than in the general population. These tissue markers have been associated with other autoimmune diseases (see Section 2.6, *Genetics of MG*).

4. Treatment with corticosteroids and other immunosuppressive drugs produces improvement in most patients with MG.

5. The weakness in MG improves following removal of lymph by thoracic duct drainage and becomes worse following re-infusion of a high molecular weight protein fraction from the lymph, probably immunoglobulin G (IgG). Plasma exchange, which removes circulating antibodies, produces temporary improvement in most patients with MG.

6. An animal model of MG, experimental autoimmune myasthenia gravis (EAMG), can be produced by immunization with purified AChR protein.

7. Antibodies against human AChR are found in the serum of most patients with MG.

8. IgG and complement components are attached to the postsynaptic endplate membrane in myasthenic muscle.

9. Myasthenic serum or IgG produces a defect of neuromuscular transmission when injected into animals.

Because antibodies to AChR are found in the serum of most patients with MG, it is intuitively attractive to infer that they play a role in producing the physiologic abnormality of the disease. Serum AChR antibody levels vary considerably among patients with MG of similar severity, however, and up to 25% of patients with MG are seronegative for these antibodies. Even in patients without detectable serum antibodies, clinical improvement follows removal of circulating substances by plasma exchange, and it is possible to transfer the neuromuscular abnormality to animals by injection of serum from these patients. Thus, the antibodies responsible for the neuromuscular abnormality may not always be those that are measured in the serum, and the serum antibody level may not necessarily reflect the amount of antibody attached to the muscle endplate.

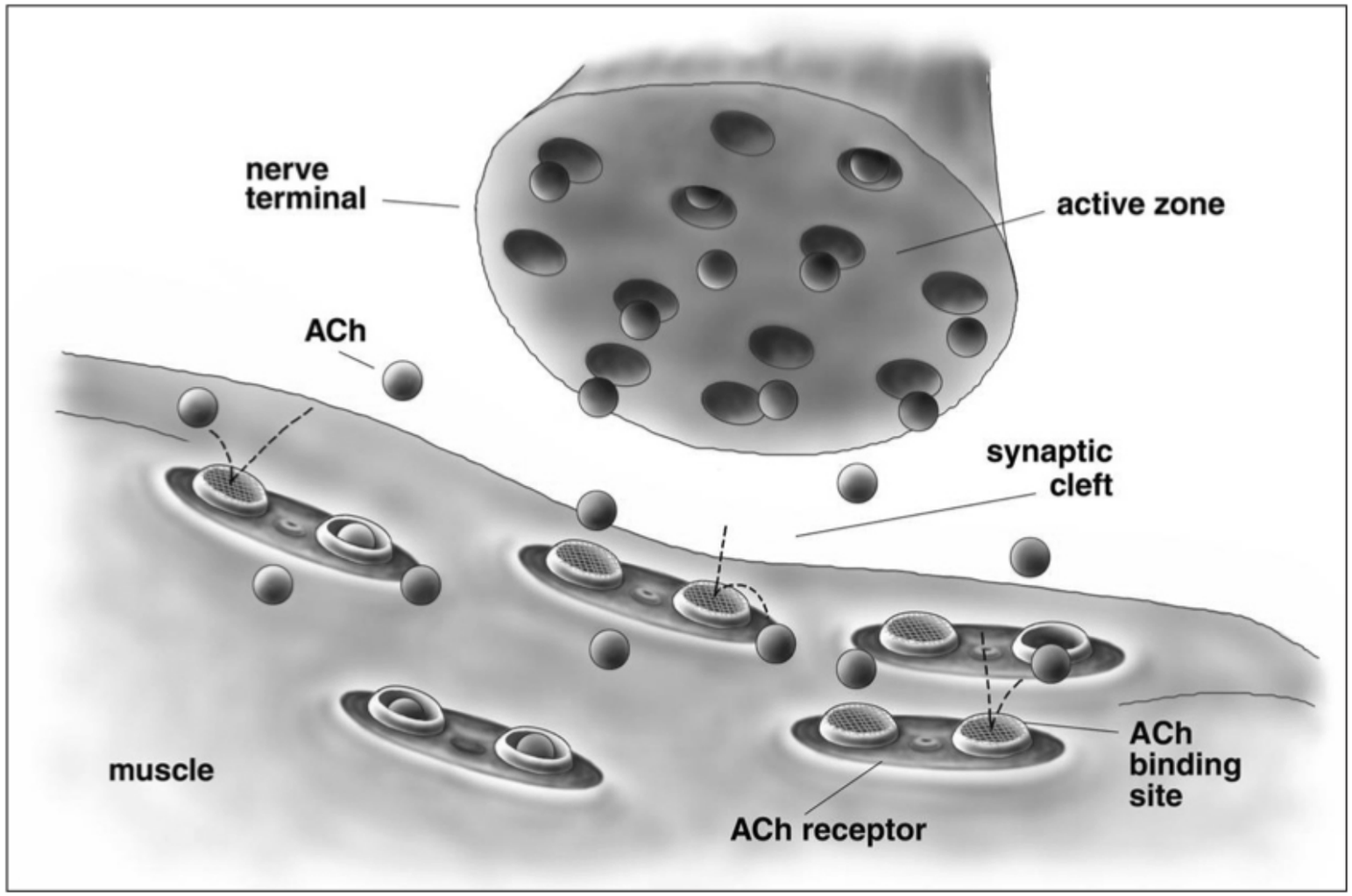

***Figure 2.3**. Artist's rendition of the myasthenic neuromuscular junction. The nerve terminal of a single synaptic bouton contains synaptic vesicles of acetylcholine (ACh). Copyright JF Howard, Jr.*

2.2.4 The Thymus Gland in MG

It has long been known that there is a relationship between the thymus gland and MG, although the precise nature of this relationship is still not clear. The thymus is abnormal in most patients with acquired MG: Ten percent have a thymic tumor and 70% have microscopic changes of hyperplasia that resemble the histology of active peripheral immune organs. These hyperplastic features include the presence of germinal centers, areas within lymphoid tissue where B-cells interact with helper T-cells to produce antibodies. Because the thymus is the central organ for immunological self-tolerance, it is reasonable to suspect that it plays a role in the breakdown in tolerance that leads to the autoimmune attack on AChR in MG. The thymus contains all the elements necessary for the pathogenesis of MG: myoid cells that express the AChR antigen, antigen presenting cells and immunocompetent T-cells. Thymus tissue from MG patients produces AChR antibodies when implanted into immunodeficient mice. However, it is still not clear if the role of the thymus is primary or secondary in the pathogenesis of MG.

2.2.5 Thymoma

Most thymic tumors in patients with MG are benign, well-differentiated and encapsulated and can be removed completely by surgery. It is unlikely that these tumors result from chronic thymic hyperactivity because MG may develop years after removal of a thymoma and the HLA haplotypes that predominate in MG patients with thymic hyperplasia differ from those in patients who develop a thymoma.

Patients with thymoma in general have more severe disease, higher levels of AChR antibodies, and more severe EMG abnormalities than patients without thymoma (Massey JM, Sanders DB, Howard JF – unpublished observation). Almost 20% of patients in whom MG began between the ages of 30 and 60 have a thymoma, whereas the frequency of thymoma is much less in those with onset MG after age 60.

2.3 Clinical Presentation of MG

Patients with MG seek medical attention for specific muscle weakness or dysfunction. While they may also have fatigue, it is not usually the major or presenting complaint. Ptosis or diplopia (double vision) is the initial symptom in two-thirds of patients. Almost all patients had both symptoms within 2 years. Difficulty chewing, swallowing, or talking is the initial symptom in 16% of patients and limb weakness in 10%. Rarely, the initial weakness is limited to single muscle groups, such as neck or finger extensors, hip flexors or ankle dorsiflexors.

Myasthenic weakness typically fluctuates during the day, usually being least in the morning and worse as the day progresses, especially after prolonged use of affected muscles. Ocular symptoms typically become worse while reading, watching television, or driving, especially in bright sunlight. Many patients find that dark glasses reduce diplopia and hide drooping eyelids. Jaw muscle weakness typically becomes worse during prolonged chewing, especially tough, fibrous or chewy foods.

Careful questioning often reveals evidence of earlier, unrecognized myasthenic manifestations, such as frequent purchases of new eyeglasses to correct blurred vision, avoidance of foods that became difficult to chew or swallow, or cessation of activities that require prolonged use of specific muscles, such as singing. Friends and colleagues may note a sleepy or sad facial appearance caused by ptosis or facial weakness.

The course of disease is variable but usually progressive in the untreated state. Weakness remains restricted to the ocular muscles in approximately 10% of cases, although some reports note lack of spread in over 40% of cases. In the remainder, weakness progresses during the first two years and ultimately involves oropharyngeal and limb muscles. Maximum weakness occurs during the first year in 66% of patients. Before immunotherapy, approximately one-third of patients improved spontaneously, one-third became worse and one-third died of the disease. Improvement, even remission, may occur early on but is rarely permanent or long-lasting. Symptoms typically fluctuate over a relatively short period and then become more

severe (active stage). Left untreated, the active stage is followed by an inactive stage, in which fluctuations in strength still occur but are attributable to fatigue, intercurrent illness, or other identifiable factors. After 15 to 20 years, untreated weakness becomes fixed and the most severely involved muscles are frequently atrophic (burned-out stage).

Factors that worsen myasthenic symptoms are emotional upset, systemic illness (especially viral respiratory infections), hypothyroidism or hyperthyroidism, pregnancy, the menstrual cycle, drugs affecting neuromuscular transmission (see Drugs That Adversely Affect Myasthenia Gravis, later in this section and Section 11) and fever.

2.4 Physical Findings in MG

It is critical that the examination be performed in a manner that will detect variable weakness in specific muscle groups. Strength should be assessed repetitively during maximum effort and again after rest. Performance on such tests fluctuates in diseases other than MG, especially if testing causes pain. The strength fluctuations of MG are best shown in ocular and oropharyngeal muscles, which are less likely to be affected by effort, pain and other factors. The symptoms of MG, however, do not always vary, thus making the diagnosis difficult.

Most patients with MG have weakness of ocular muscles. Asymmetrical weakness of several muscles in both eyes is typical. The pattern of weakness is not characteristic of lesions of one or more nerves and the pupillary responses are normal. Weakness is most frequent and is usually most severe in the medial rectus muscles. Inferior gaze is often preserved. Ptosis is usually asymmetrical and varies during sustained activity (Figure 2.4). The frontalis muscle may be chronically contracted to compensate for ptosis, producing a worried or surprised look. Unilateral frontalis muscle contraction is a clue that the lid elevators are weak on that side. This may be the only visible evidence of facial weakness. Eyelid closure is almost always weak in MG, even when strength is normal in all other facial muscles and may be the only residual weakness in those with otherwise complete clinical remission. This is usually asymptomatic unless it is severe enough to allow soap or water in the eyes during bathing. With moderate weakness of these muscles, the patient does not “bury” the eyelashes during forced eye closure. Fatigue in these muscles may result in slight involuntary opening of the eyes as the patient tries to keep the eyes closed, the “peek” sign.

Oropharyngeal muscle weakness causes changes in the voice, difficulty chewing and swallowing, inadequate maintenance of the upper airway and altered facial appearance. The voice may be nasal, especially after prolonged talking and liquids may escape through the nose when swallowing because of palatal muscle weakness.

Weakness of the laryngeal muscles causes hoarseness. This can also be shown by asking the patient to make a high-pitched /*eeeee*/ sound. Difficulty swallowing is detected from a history of frequent choking or clearing of the throat or cough-

ing after eating. Respiratory dysfunction is rarely the first symptom of MG with the exception of some patients with anti-MuSK-antibody positive MG. Isolated dysphagia is rarely the initial symptom of MG.

Myasthenic patients often have a characteristic facial appearance, the myasthenic snarl. At rest, the corners of the mouth often droop downward, giving a depressed appearance. Attempts to smile often produce contraction of the medial portion of the upper lip and a horizontal contraction of the corners of the mouth without the natural upward curling, which gives the appearance of a snarl (Figure 2.5).

Jaw weakness can be demonstrated by manually opening the jaw against resistance, which is not possible in normal people. The patient may support a weak jaw with the thumb under the chin, the middle finger curled under the nose or lower lip and the index finger extended up the cheek, producing a studious or attentive appearance.

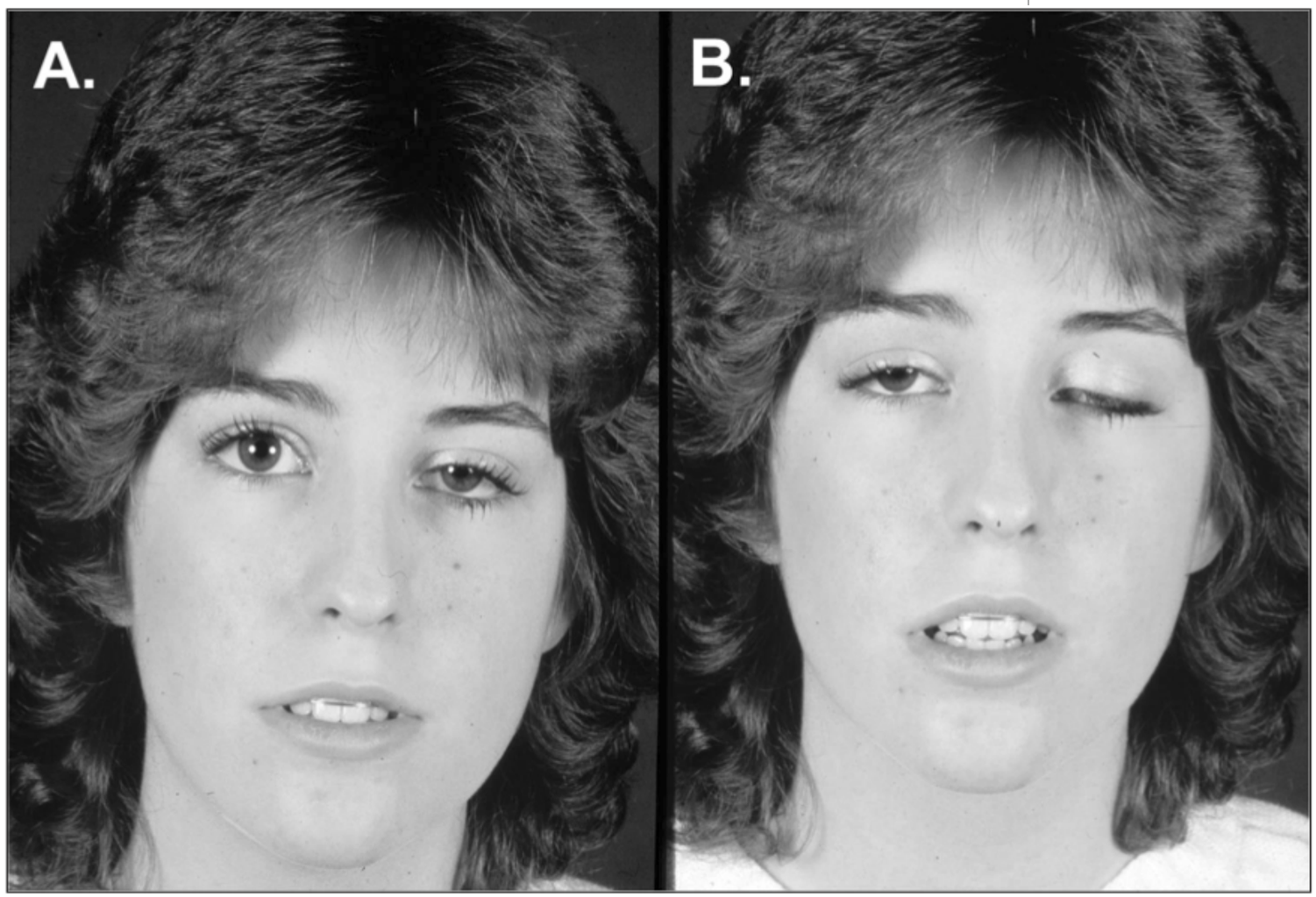

Figure 2.4. *A. Myasthenic ptosis at rest in a young woman with generalized myasthenia gravis. Note the asymmetrical eyelid, the left lower than the right. B. The demonstration of fatigable ptosis after 30 seconds of fixed gaze, with worsening ptosis of the left eyelid and the development of ptosis in the right eyelid. Copyright JF Howard, Jr.*

Weakness begins in limb or axial muscles in about 20% of MG patients (Kuks JBM, 2004). Any trunk or limb muscle may be weak but some are more often affected than others. Neck flexors are usually weaker than neck extensors and the deltoids, triceps and extensors of the wrist and fingers and ankle dorsiflexors are frequently weaker than other limb muscles.

2.5 Classification of MG

The Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America published a series of recommendations for clinical research standards in MG in 2000 (Task Force.., 2000). This classification (Table 2.1) is designed to identify subgroups of patients with MG who share distinct clinical features or severity of disease that may indicate different prognoses or responses to therapy. The authors state it should not be used to measure clinical outcome. Rather, it defers quantitative assessment of muscle weakness to the more precise Quantitative MG Score (QMG) for Disease Severity (Appendix 2.1), defers response to therapy to the MGFA Post-intervention Status Severity and the Quantitative MG Score and defers the status of medication to the Therapy Status classification. The Post-intervention Status (Appendix 2.2) is designed to assess the clinical state of MG patients at any time after institution of treatment for their MG. The MGFA Therapy Status (Appendix 2.3) defines the treatment regimen of the patient at a given time and is most useful when used with the MGFA Post-intervention Status. The reader is urged to refer to the cited source for more details.

The fluctuating extent and severity of MG and the variable predominance of the muscle groups involved, makes it extremely difficult to classify these patients. Most existing classifications are modifications of Osserman's original scheme that separated patients with purely ocular involvement from those with generalized weakness and further separated those with mild, moderate, or severe generalized weakness. These classification schemes are limited by their subjective assessment and the variability in the definitions of mild, moderate and severe weakness. The Task Force also recommended that the most severely affected muscles be employed to define the patient's Class and that the "maximum severity" designation be used to identify the most severe pretreatment clinical classification status. The "maximum severity" designation may be made historically and is employed as a point of reference. The maximum severity remains the point of reference thereafter, with any worsening of the MG being reflected in the post-intervention status determination.

TABLE 2.1: MGFA CLINICAL CLASSIFICATION

CLASS I:	Any ocular 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 oropharngeal weakness
IIb:	Predominantly affecting oropharngeal 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 oropharngeal muscles
IIIb:	Predominantly affecting oropharngeal, 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
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

2.6 Genetics of MG

Autoimmune MG is not transmitted by mendelian inheritance, but family members of patients are approximately 1,000 times more likely to develop the disease than is the general population. Increased neruomuscular jitter with single fiber EMG has been demonstrated in 33 to 45% of asymptomatic first degree family members and acetylcholine receptor antibodies are slightly elevated in up to 50%. These observations suggest that there is a genetically determined predisposition to develop MG although the exact mechanism remains unknown.

The human leukocyte antigen (HLA) complex occupies a large region of chromosome 6p21 and is divided into three regions, or classes: classes I and II contain genes that encode membrane-bound molecules that present antigenic epitopes to lymphoid cells. The HLA-A1 and HLA-B8 genes from Class I and DRB3 from Class II are closely associated and form the most highly conserved HLA haplotype in Caucasians. This combination of genes has been associated with a large number of autoimmune and immune-related diseases. Certain HLA types (-DR2, -DR3, -B8, -DR1) predispose to MG whereas others may offer resistance to disease. HLA-B8,-DR2 and -DR3 types occur more commonly in patients with early onset disease, HLA-B7 and -DR2 in late onset disease and HLADR1 in ocular myasthenia. Anti-MuSK-antibody positive MG is associated with HLA-DR14-DQ5.

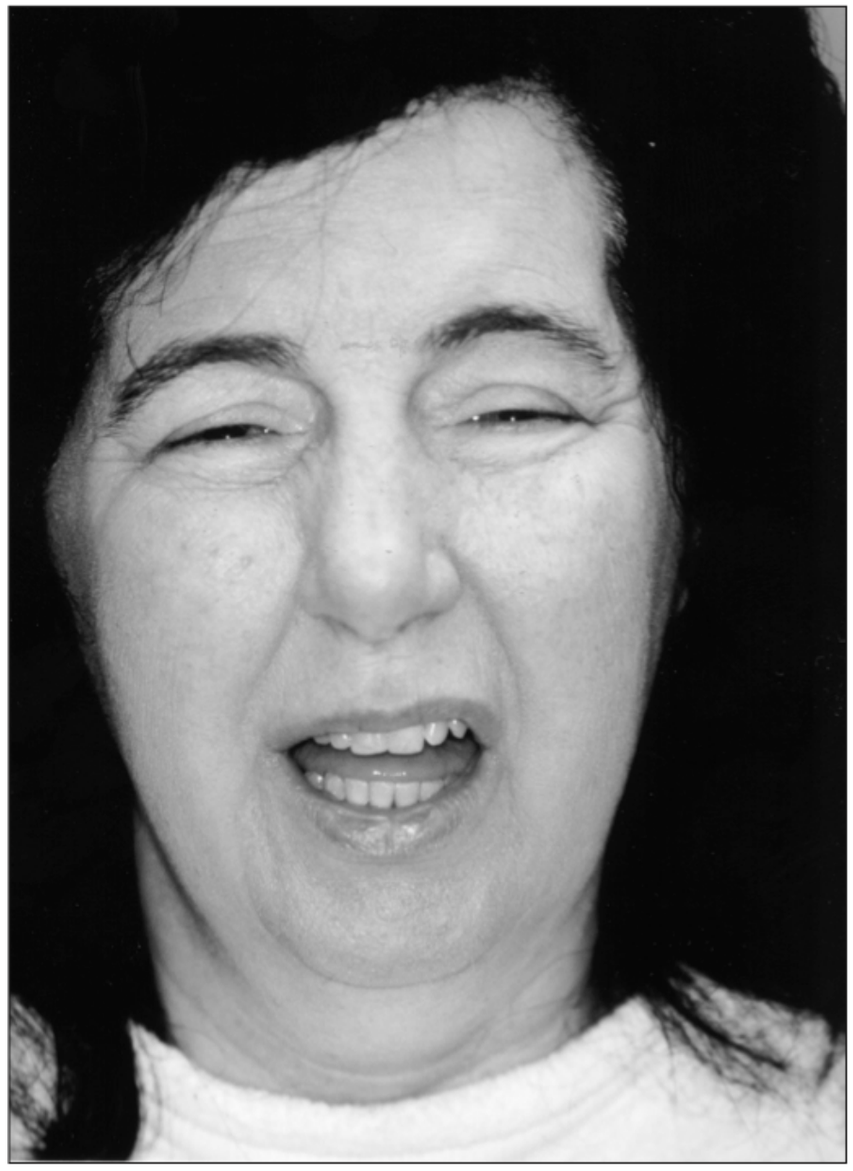

Figure 2.5. *The characteristic smile (myasthenic snarl) of a woman with moderately severe myasthenia gravis that results from the horizontal contraction of the corners of the mouth with elevation of the medial portion of the upper lip rather than the normal upward turn of the corners of the mouth. This gives the patient an angry appearance and may be seen even with laughter. (Reprinted with permission from Howard JF: The myasthenic facies and snarl. Journal of Clinical Neuromuscular Disease 1:214-215, 2000).*

2.7 Diagnostic Procedures in MG

The diagnosis is frequently delayed months or even years. The unusual distribution and fluctuating symptoms often suggests psychiatric disease. Conversely, ptosis, diplopia and oropharyngeal symptoms suggest intracranial pathology and often lead to unnecessary imaging studies or arteriography. Patients with anti-MuSK-antibody positive MG may have focal or regional weakness and muscle atrophy that are more suggestive of motor neuron disease or myopathy.

2.7.1 Edrophonium Chloride Test

Edrophonium and other cholinesterase inhibitors slow the breakdown of ACh by inhibiting the action of AChE, thus allowing ACh to diffuse more widely throughout the synaptic cleft and to have a more prolonged interaction with ACh receptors (AChR) on the post-synaptic muscle membrane. This facilitates repeated interaction of ACh with the reduced number of AChRs and results in greater endplate depolarization. Weakness from abnormal neuromuscular transmission characteristically improves after administration of cholinesterase inhibitors and this is the basis of the diagnostic edrophonium test.

Assessing the effect of edrophonium on most muscles depends on the patient exerting maximum effort before and after drug administration. The edrophonium test is most reliable when it produces dramatic improvement in eyelid ptosis, ocular muscle weakness or dysarthria because observed function in these muscles is largely independent of voluntary effort. Changes in strength of other muscles must be interpreted cautiously, especially in a suggestible patient. Testing of selected muscles with a hand-held dynamometer may improve the reliability of assessing limb muscle strength.

The edrophonium test is reportedly positive in 60% to 95% of patients with ocular myasthenia and in 72% to 95% with generalized MG (Pascuzzi RM, 2003). Some improvement after edrophonium is not unique to MG, however and may also be seen in congenital myasthenic syndromes, the Lambert-Eaton syndrome, intracranial aneurysms, brainstem lesions, cavernous sinus tumors, end-stage renal disease and in muscle disease affecting the ocular muscles. However, the Lazarus effect, profound improvement, after edrophonium administration is more likely seen in MG.

The optimal dose of edrophonium varies among patients and cannot be predetermined. In a study of ocular myasthenia, the mean dose of edrophonium that gave a positive response was 3.3 mg for ptosis and 2.6 mg for ocular motor dysfunction (Kupersmith M, 2003). The lowest effective dose can be determined by injecting small incremental doses up to a maximum total of ten mg. Most commonly, a test dose of two milligrams is injected initially and the response is monitored for 60 seconds. Subsequent injections of three and five mg may then be given, but if clear improvement is seen within 60 seconds after any dose, the test is positive and no further injections are necessary (Appendix 2.4). Weakness that develops or worsens after injection of ten mg or less also indicates a defect of neuro-

muscular transmission, as this dose will not weaken normal muscle.

Some patients who do not respond to intravenous edrophonium may improve after injection of parenteral neostigmine methylsulfate, 0.5 mg intramuscularly (I.M.) or subcutaneously (S.C.), which has a longer duration of action. Onset of action after I.M. injection is 5 to 15 minutes. The longer duration of action compared to edrophonium is particularly useful in infants and children. A therapeutic trial of oral pyridostigmine or neostigmine for several days may produce improvement that can not be appreciated after a single dose of edrophonium or neostigmine. Results should be interpreted with caution if the patient's subjective reports are the main measure of response.

Common side effects of edrophonium are nausea, stomach cramps, increased salivation and sweating and fasciculations. Serious complications (bradycardia or syncope) have been reported in only 0.16% of edrophonium tests (Ing EB, 2005). These symptoms generally resolve with rest in the supine position. Atropine (0.4 mg to 2 mg) should be available for I.V. injection in the event that bradycardia is severe. The risk of these rare complications must be weighed against the potential diagnostic information that the edrophonium test may uniquely provide.

Many patients with MuSK antibody-positive MG do not improve and may even become worse with edrophonium or pyridostigmine, which often produce profuse fasciculations in these patients (Hatanaka Y, 2005).

Techniques that show a more objective effect of cholinesterase inhibitors on ocular muscles include EMG of the ocular muscles, tonometry, oculography and Lancaster red-green tests of ocular motility. These tests increase sensitivity but are nonspecific and may yield false-positive results.

2.7.2 Auto-Antibodies in MG

2.7.2.1 Anti-striational muscle antibodies

These antibodies, which react with contractile elements of skeletal muscle, are not pathogenic for MG. They are found in more than 90% of MG patients with thymoma and in one-third of patients with thymoma who do not have MG. One-third of MG patients without thymoma also have these antibodies and they are more frequent in older patients and in those with more severe disease. Striational muscle antibodies are also elevated in autoimmune liver disease and infrequently in Lambert-Eaton syndrome and in primary lung cancer. There antibodies are rarely, if ever, elevated in MG in the absence of acetylcholine receptor antibodies and are therefore of limited use in confirming the diagnosis. The main clinical value of striatinal antibody is in predicting thymoma: 60% of patients with MG with onset before age 50 who have elevated antibody have thymoma.

2.7.2.2 Acetylcholine receptor antibodies (AChR-ab)

Assay for AChR-abs is an essential diagnostic test for MG. The most commonly performed assay measures binding to purified AChR from human skeletal muscle that is labeled with radioiodinated -bungarotoxin. The reported sensitivity of this binding assay ranges from 70% to 95% for generalized MG and 50% to 75% for ocular myasthenia. In a comparison of diagnostic tests performed in 550 untreated MG patients, elevated binding antibodies were found in 80% of patients with generalized MG and in 55% of those with purely ocular weakness (Sanders DB, 2008).

Another assay for AChR antibodies measures inhibition of binding of radiolabeled -bungarotoxin to the AChR. The blocking antibodies measured by this technique are directed against the ACh binding site on the sub-unit of the AChR. In most patients, relatively few of the circulating antibodies recognize this site, resulting in a lower sensitivity for this assay. These blocking antibodies are found in less than 1% of MG patients who do not have measurable binding antibodies and thus have limited diagnostic value.

AChR antibodies cross link the AChR in the membrane and increase their rate of degradation. The AChR modulating antibody assay measures the rate of loss of labeled AChR from cultured human myotubes. AChR modulating antibodies are found in about 10% of MG patients who do not have elevated binding antibodies.

Finding elevated AChR antibodies in a patient with compatible clinical features essentially confirms the diagnosis of MG but normal antibody measurements do not exclude the disease. Assay for AChR antibodies may be normal at symptom onset and become abnormal later in the disease; thus, repeat testing is appropriate when values obtained within 6 to 12 months of symptom onset are normal.

Virtually all patients with MG and thymoma have elevated AChR-binding antibodies and many have high concentrations of AChR-modulating, AChR-blocking and striational muscle as well.

False positive AChR antibody tests are rare, but have been reported in autoimmune liver disease, systemic lupus, inflammatory neuropathies, amyotrophic lateral sclerosis, patients with rheumatoid arthritis receiving penicillamine, patients with thymoma without MG and in first degree relatives of patients with acquired autoimmune MG.

AChR antibody levels tend to be lower in patients with ocular or mild generalized MG but the serum antibody concentration varies widely among patients with similar degrees of weakness and thus does not predict the severity of disease in individual patients. Antibody levels fall in most MG patients after immunosuppressive treatment and may become normal in some. However, the AChR antibody level may actually rise in some patients as their symptoms improve and thus is not a reliable marker of response to therapy.

2.7.2.3 Anti-MuSK antibodies

Antibodies to muscle-specific receptor tyrosine kinase (MuSK), a surface membrane component essential in the development of the neuromuscular junction, are found in 35% to 50% of MG patients who are seronegative for AChR antibodies (Evoli A, 2003).

2.7.2.5 Other auto-antibodies

Auto-antibodies directed against several muscle antigens other than the AChR are found in the serum of many MG patients, primarily those with thymoma or late-onset MG. These antibodies are not pathogenic but are found more often in patients with more severe disease, suggesting that disease severity is related to a more vigorous humoral response against many antigens.

Anti-titin antibodies are found in patients with late-onset disease or thymoma and thus are a marker for thymoma in young MG patients. Anti-RyR antibodies are found in 75% of MG patients with thymoma and in approximately 10 to 20% of late-onset MG without thymoma. RyR antibody testing has been reported to have 70% sensitivity and specificity for thymoma in patients with MG.

2.7.3 Electrodiagnostic Testing in MG

2.7.3.1 Repetitive Nerve Stimulation

The following are Practice Recommendations of the American Association of Neuromuscular and Electrodiagnostic Medicine regarding the use of electrodiagnosis in MG (AAEM Quality Assurance Committee et al., 2001):

> *Repetitive nerve stimulation (RNS) of a nerve supplying a symptomatic muscle should be performed. Abnormality in MG is considered to be a reproducible 10% decrement in amplitude when comparing the first stimulus to the fourth or fifth, which is found in at least one muscle. Anticholinesterase medications should be withheld 12 hours prior to testing, if this can be done safely.*
> *If RNS is normal and there is a high suspicion for a neuromuscular junction (NMJ) disorder, single fiber EMG (SFEMG) of at least one symptomatic muscle should be performed. If SFEMG of one muscle is normal and clinical suspicion for a NMJ disorder is high, a seocnd muscle should be studied. Option. If the patient has very mild or solely ocular symptoms and it is believed the RNS will be normal, or if the discomfort associated with RNS prevents completion of RNS, SFEMG testing may be performed in place of RNS as the initial NMJ test. In laboratories with SFEMG capability, SFEMG may be performed as the initial test for*

disorders of neuromuscular transmission as it is more sensitive than RNS. Routine needle EMG and nerve conduction studies may be necessary to exclude disorders other than MG or Lambert-Eaton syndrome.

The decrementing response to RNS is seen more often in proximal muscles, such as the facial muscles, biceps, deltoid and trapezius, than in the distal ADQ and APB muscles of the hand. One must pay attention to the quality control issues of temperature control, immobilization and stimulation rates to insure the study is not confounded by artifact (Howard JF, 1994).

2.7.3.2 Single Fiber EMG

SFEMG is the most sensitive clinical test of neuromuscular transmission and shows increased jitter in some muscles in almost all patients with MG. Jitter is greatest in weak muscles but is usually abnormal even in muscles with normal strength.

In ocular myasthenia, jitter is abnormal in a limb muscle in 60% of patients, but this does not predict the subsequent development of generalized myasthenia.

When there is any degree of non-ocular muscle weakness, jitter is increased in the forearm extensor digitorum communis in almost 90% of patients. In the rare patient who has weakness only in a few limb muscles, abnormal jitter may be demonstrated only if a weak muscle is examined. This is particularly true in some patients with MuSK antibody-positive MG.

Increased jitter is a nonspecific sign of abnormal neuromuscular transmission and can occur in other motor unit diseases. Therefore, when jitter is increased, EMG should be performed to exclude neuronopathy, neuropathy, or myopathy. Normal jitter in a clinically weak muscle excludes abnormal neuromuscular transmission as the cause of weakness.

2.7.4 Ocular Cooling

Myasthenic weakness typically improves with muscle cooling. This is the basis of the “ice-pack” test, in which cooling of a ptotic eyelid improves lid elevation. An ice pack is placed over the ptotic eyelid, usually for two minutes and improvement in ptosis is assessed. Positive responses have been reported even when edrophonium tests are negative. A meta analysis of six studies showed this test to have a sensitivity of 89% and a high specificity in MG, suggesting that it may be useful in patients with lid ptosis, particularly if the edrophonium test is negative or contraindicated (Larner AJ, 2004).

The edrophonium test is often diagnostic in patients with ptosis or ophthalmoparesis but is less useful in assessing other muscles. The presence of serum AChR or anti-MuSK antibodies virtually assures the diagnosis of MG but their absence does not exclude it. RNS confirms impaired neuromuscular transmission but is frequently normal in mild or purely ocular disease. SFEMG demonstrates increased jitter in almost all patients with MG and normal jitter in a weak muscle excludes

MG as the cause of the weakness. Neither electrodiagnostic test is specific for MG because increased jitter, even abnormal RNS, may also be seen when other motor unit disorders impair neuromuscular transmission.

2.7.5 Other Studies

Patients diagnosed with MG should have thyroid function and serum B12 tests and a chest imaging study (CT or MRI) to assess possible thymoma. A TB skin test should be done if the use of immunosuppression is contemplated.

2.8 Treatment of MG

Controlled clinical trials for any treatment of MG are rare. All recommended regimens are empirical and experts disagree on treatments of choice. Treatment decisions must be based on knowledge of the predicted course of disease in each patient and the predicted response to a specific treatment. Treatment goals must be individualized, taking into account the severity of disease, the patient's age and the degree of functional impairment, resources of the patient and their compliance with therapy. Successful treatment of MG requires close medical supervision and long-term follow-up. Return of weakness after a period of improvement should be considered a herald of further progression that requires reassessment of current treatment and evaluation for underlying systemic disease or thymoma.

2.8.1 Cholinesterase Inhibitors

Cholinesterase inhibitors slow the enzymatic hydrolysis of ACh at cholinergic synapses so that ACh accumulates at the neuromuscular junction with prolonged effect. Cholinesterase inhibitors cause considerable improvement in some patients and little to none in others. They have a major role as a diagnostic test and as early, symptomatic treatment in most patients and are used as adjunctive therapy in most patients undergoing more definitive treatment. Cholinesterase inhibitors alone may provide adequate chronic treatment in some patients but the response frequently becomes less with chronic use.

Pyridostigmine bromide and neostigmine bromide are the most commonly used cholinesterase inhibitors. Pyridostigmine is generally preferred because it has a lower frequency of gastrointestinal side effects and longer duration of action. The initial oral dose in adults is 30–60mg every 4–8 hours. The equivalent dose of neostigmine is 7.5–15 mg. In infants and children, the initial oral dose of pyridostigmine is 1 mg/kg and of neostigmine is 0.3 mg/kg (Table 2.2.) Pyridostigmine is available as syrup (60 mg/5 ml) for children or for nasogastric tube administration in patients with impaired swallowing. A timed-release tablet of pyridostigmine is useful as a bedtime dose for patients who are too weak to swallow in the morning. However, its absorption is erratic, leading to possible overdosage and underdosage and it should not be used during waking hours. Even at night, it is sometimes preferable for the patient to awaken at the appropriate dosing interval and take the regu-

lar tablet. Neostigmine and pyridostigmine can be administered by nasal spray or nebulizer to patients who cannot tolerate or swallow oral medications.

No fixed dosage schedule suits all patients. The need for cholinesterase inhibitors varies from day to day and during the same day. Different muscles respond differently—with any dose, some muscles get stronger, others do not change and still others become weaker. The drug schedule should be titrated to produce an optimal response in muscles causing the greatest disability. Patients with oropharyngeal weakness need doses timed to provide optimal strength during meals. Ideally, the effect of each dose should last until time for the next, without significant underdosing or overdosing at any time. In practice, this is frequently not possible. Attempts to eliminate all weakness by increasing the dose or shortening the interval may cause overdose at the time of peak effect.

TABLE 2.2 EQUIVALENT DOSES OF CHOLINESTERASE INHIBITOR DRUGS

	Route and dose (mg)			
	Oral	Intramuscular	Intravenous	Syrup
Neostigmine bromide (Prostigmin Bromide®)	15			
Neostigmine methylsulfate (Prostigmin Methylsulfate®)		1.5	0.5	
Pyridostigmine bromide (Mestinon Bromide®, Regonol)	60	2.0	0.7	60 mg/ 5 ml
Pyridostigmine bromide [longacting] (Mestinon Timespan®)	90 to 180			
Ambenonium chloride (Mytelase Chloride®)	5			

We aim for a dose that provides definite improvement in the most important muscle groups within 30–45 minutes and which wears off before the next dose. This minimizes the possibility that the dose will be increased to the point of causing cholinergic weakness. Giving edrophonium at the time when pyridostigmine has its maximal effect, to determine if the patient will respond to greater dosages of cholinesterase inhibitors, is not without danger. Acute overdosage may cause cholinergic weakness of respiratory muscles and apnea.

Adverse effects of cholinesterase inhibitors result from ACh accumulation at muscarinic receptors on smooth muscle and autonomic glands and at nicotinic receptors of skeletal muscle. Central nervous system side effects are rarely seen with the doses used to treat MG. Gastrointestinal complaints are common: queasiness, nausea, vomiting, abdominal cramps, loose stools and diarrhea. Increased bronchial and oral secretions may be a serious problem in patients with swallowing or respiratory insufficiency. These symptoms of muscarinic overdosage may indicate that nicotinic overdose (weakness) is also occurring. Gastrointestinal side effects can be suppressed with loperamide hydrochloride, propantheline bromide, glycopyrrolate and diphenoxylate hydrochloride with atropine. Some of these drugs themselves produce weakness at high dosages.

Bromism, presenting as acute psychosis, is a rare complication of large amounts of pyridostigmine bromide. The diagnosis can be confirmed by measuring the serum bromide level. Some patients are allergic to bromide and develop a rash even at modest doses.

2.8.2 Thymectomy

Although thymectomy is widely used as treatment for autoimmune MG, it has never been demonstrated to be effective in a prospective, controlled study. Based on review of existing studies, the Quality Standards Subcommittee of the American Academy of Neurology concluded that MG patients undergoing thymectomy are twice as likely to attain medication-free remission, 1.6 times as likely to become asymptomatic and 1.7 times as likely to improve (Gronseth GS, 2000). The following practice recommendations were made:

For patients with non-thymomatous autoimmune MG, thymectomy is recommended as an option to increase the probability of remission or improvement.

Thymectomy is recommended for most patients with MG whose symptoms begin before age 60. The response to thymectomy is unpredictable and significant impairment may continue for months or years after surgery, even in patients who do ultimately improve. The best responses to thymectomy have been seen in young people, especially women, early in the disease, but improvement can occur even after many years of symptoms. Many believe that patients with disease onset after the age of 60 rarely show substantial improvement from thymectomy; others, however, have reported improvement after thymectomy even in older patients. Patients with a thymoma do not respond to thymectomy as well as those without thymoma, but others have reported good responses after re-

moval of the tumor along with the thymus (Schrager JB, 2002). Although thymectomy is not generally recommended for patients with purely ocular myasthenia, these patients also may respond well after thymectomy (Schrager JB, 2002) and it is recommended it in certain circumstances, particularly in young patients with relatively recent onset of myasthenia. The major advantage of thymectomy is the potential to induce a sustained, drug-free remission. Another is to exclude or remove a thymoma.

Surgical approaches will differ among surgeons. For many, the preferred surgical approach is transthoracic; the sternum is split, which allows wide exploration of the anterior mediastinum. Transcervical and endoscopic approaches have less postoperative morbidity but do not allow sufficient exposure for total thymic removal and are not recommended when there is a thymoma. However, it has not been demonstrated that the extent of thymic removal determines outcome and until there has been a prospective study comparing different thymectomy techniques, the value of different surgical approaches will not be clear. In our experience, the operative morbidity from transthoracic thymectomy is very low when patients are optimally prepared with plasma exchange (PLEX) or immunosuppression and skilled postoperative management is provided. Extubation is usually accomplished within hours after surgery and most patients are discharged home as early as the second or third postoperative day.

Repeat thymectomy has been reported to provide significant improvement in some patients. We consider repeat thymectomy when there is concern that all thymic tissue was not removed at prior surgery and when a good response to the original surgery is followed by later relapse. MR imaging with appropriate cardiac gating may be useful in identifying residual thymus tissue.

Even seronegative patients may improve after thymectomy, some to the point of remission. Thus, we do not base the decision to perform thymectomy on the presence or level of AChR antibodies. The role of thymectomy in MuSK-antibody positive MG has not yet been determined.

2.8.3 Corticosteroids

Prednisone produces marked improvement or complete relief of symptoms in more than 75% of MG patients and some improvement occurs in most of the rest. Much of the improvement occurs in the first 6 to 8 weeks but strength may increase to total remission in the following months. The best responses occur in patients with recent onset of symptoms but those with chronic disease also may respond. The severity of disease does not predict the ultimate improvement. Patients with thymoma usually respond well to prednisone, before or after removal of the tumor.

The most predictable response to prednisone occurs when treatment begins with a dose of 1.5 to 2 mg/kg per day. This dose is given until sustained improvement occurs, which is usually within 2 weeks. The dose is then decreased over many months to the smallest amount necessary to maintain improvement, which is ideally less than 20 mg every other day.

The rate of decrease should be individualized—patients who have a rapid initial response can reduce the dose on alternate days by 20 mg each month to 60 mg every other day. In those with a less dramatic initial response it may be preferable to change to an alternate day dose of 100 to 120 mg and taper this by 20 mg each month to 60 mg every other day. The dose is then tapered more slowly to a target dose of 10 mg every other day as long as improvement persists. If any weakness returns during dose reduction, the dose should be increased, another immunosuppressant should be added, or both, to prevent further worsening. Weakness invariably returns if the drug is stopped, but a very low dose (5 to 10 mg every other day) may be sufficient to maintain good improvement in many patients. For this reason, the dose is not reduced further than this unless another immunosuppressant is also being given.

Approximately one-third of patients have a temporary exacerbation after starting prednisone; this usually begins within the first 7 to 10 days with high prednisone doses and lasts for several days. In mild cases this worsening can usually be managed with cholinesterase inhibitors. In patients with oropharyngeal or respiratory involvement, we perform plasma exchange before beginning prednisone to prevent or reduce the severity of corticosteroid induced exacerbations and to produce a more rapid response. Once improvement begins, subsequent corticosteroid-induced exacerbations are unusual.

An alternative approach favored by some is to begin prednisone with 20 mg/day and increase the dose by 10 mg every 1 to 2 weeks until improvement begins. The dose is maintained until improvement is maximum and then tapered as above. Exacerbations still may occur with this protocol but the onset of such worsening and the therapeutic response are less predictable. A similar dose schedule is frequently used in purely ocular myasthenia. Most patients with ocular myasthenia achieve complete resolution of ocular symptoms after treatment with prednisone, which also may prevent development of generalized MG (Kupersmith M, 2004).

The major disadvantages of chronic corticosteroid therapy are the side effects. Hypercorticism occurs in approximately one-half the patients treated with high doses. The severity and frequency of side effects increase when high doses are continued for more than one month. Fortunately, this is rarely necessary, especially if plasma exchange is begun at the same time as prednisone. Most side effects improve as the dose is reduced and become minimal at less than 20 mg every other day. Side effects can be minimized by a low-fat, low-sodium diet and supplemental calcium. Postmenopausal women should also take supplementary vitamin D or a bisphosphonate. Patients with peptic ulcer disease or symptoms of gastritis need H2 antagonists. Prednisone should not be used in untreated tuberculosis.

Prednisone given with azathioprine, cyclosporine, mycophenolate or other immunosuppressant drugs may produce more benefit than either drug alone (see next section, Immunomodulatory Drugs).

Patients may improve on prednisolone when equivalent doses of prednisone did not produce improvement or side effects.

2.8.4 Immunomodulatory Drugs

Several immunosuppressant drugs are reportedly effective in MG (Table 2.3). Azathioprine is the most frequently used. It improves weakness in most patients but benefit may not be apparent for 4 to 8 months. The initial dose
is 50 mg/day, which is increased 50 mg/day every 7 days to a total of 150 to 200 mg/day. Improvement persists as long as the drug is given but symptoms almost always recur if it is discontinued or the dose is reduced below the minimal effective dose. Patients may respond better and more rapidly if prednisone is started at the same time. The prednisone is tapered as above and may be discontinued after azathioprine becomes effective.

A prospective randomized study showed that the addition of azathioprine to prednisolone significantly reduced the dose of prednisolone required to maintain remission and reduced the number of treatment failures (Palace J, 1998). An idiosyncratic reaction, with "flu-like" symptoms occurs within 10 to 14 days after starting azathioprine in 15% to 20% of patients; this reaction requires that the drug be stopped. Gastrointestinal irritation can be minimized by using divided doses after meals or by dose reduction. Leukopenia and even pancytopenia can occur at any time during treatment, but are not common. To guard against this, the blood count should be monitored every week during the first month, every one to

TABLE 2.3 IMMUNOSUPPRESSANT DRUGS USED FOR MG

	Onset Action	Side Effects
Azathioprine	4 to 8 months	Common: allergic reaction ("flu-like syndrome). Less common: hepatic toxicity, leukopenia
Cyclosporine A	2 to 3 months	Common: renal toxicity hypertension, multiple potential drug interactions
Cyclophosphmide	variable	Common: leukopenia, hair loss, cystitis
Mycophenolate mofetil	2 to 4 months (?)	Common: diarrhea, mild leukopenia

three months for a year and every 3 to 6 months thereafter. If the peripheral white blood cell (WBC) count falls below 3,500 cells/mm3, the dose should be temporarily reduced and then gradually increased after the WBC count rises. The drug should be discontinued temporarily if counts fall below 1,000 WBC/mm3. To prevent liver toxicity treatment should be discontinued if transaminase concentrations exceed twice the upper limit of normal and restart the drug at lower doses after values become normal. Rare cases of azathioprine-induced

pancreatitis are reported but the cost-effectiveness of monitoring serum amylase concentrations is not established. The safety of azathioprine during pregnancy has not been established.

Cyclosporine (CYA) is a potent immunosuppressant that binds to the cytosolic protein cyclophilin (immunophilin) of immunocompetent lymphocytes, especially T-lymphocytes. This complex of cyclosporine and cyclophilin inhibits calcineurin, which activates transcription of interleukin-2. It also inhibits lymphokine production and interleukin release and leads to reduced function of effector T-cells. Retrospective analyses have reported improvement in most MG patients taking CYA, with or without corticosteroids. Renal toxicity and hypertension are the important adverse reactions of CYA. Many medications interact with CYA and must be avoided or used with caution.

CYA is typically started at a daily dose of 5 to 6 mg/kg, given in two divided doses 12 hours apart. Trough serum levels of CYA should be measured after one month when tissues have become saturated. The dose is then adjusted to produce a trough serum CYA concentration of 75 ng/ ml to 150 ng/ml. Serum creatinine should be measured monthly and the dose adjusted to keep the creatinine below 150% of pretreatment values. Thereafter, serum creatinine should be measured at least every 2 to 3 months and more frequently after any new medications are begun. Blood pressure should also be monitored at least monthly until the maintenance CYA dose has been determined.

Improvement begins within 2 to 3 months in most patients and maximum improvement is achieved after 6 months or longer. As with azathioprine, prednisone may be started at the same time and the dose tapered or discontinued altogether after CYA has become effective. After achieving the maximal response, the CYA dose is gradually reduced to the minimum effective dose, which may be as little as 50 mg/day in some patients.

Cyclophosphamide (CP) given intraveously in monthly pulsed doses has been used in severe, generalized MG that is refractory to other therapy (Drachman DB, 2002). CP can also be given orally, 150 to 200 mg per day, to a total of 5 to 10 g, as required to relieve symptoms. Alopecia is the major side-effect with this regimen. Cystitis, leukopenia, nausea, vomiting, anorexia and discoloration of the nails and skin occur less frequently and bladder cancer is a major concern.

Mycophenolate mofetil (MMF) selectively inhibits the proliferation of activated B and T lymphocytes. It also suppresses the formation of antibodies active in complement-dependent lysis and antibody-dependent, cell-mediated cytotoxicity. Case reports, pilot studies and retrospective series have demonstrated a potential role for MMF as a corticosteroid-sparing agent and as adjunctive or primary therapy in refractory MG (Meriggioli MN, 2003). The dose usually used is 2 grams/day, in divided doses taken 12 hours apart. Improvement is usually seen within 2 to 6 months in responding patients. The most common side effect is diarrhea, which can usually be managed by altering the dose schedule. The risk of leukopenia requires

periodic blood counts, especially after beginning therapy. Two controlled trials did not establish superior efficacy over prednisone in MG. Many clinicians are using MMF in refractory MG, as a corticosteroid-sparing agent when azathioprine has produced intolerable side effects or has not been effective, or when a more rapid response is needed than can be expected with azathioprine.

Effective use of immunosuppressants in MG requires a long-term commitment few patients maintain improvement unless they are continued at effective doses. The long-term risk of malignancy is not established, but there are no reports of an increased incidence of malignancy in patients with MG receiving immunosuppression.

2.8.5 Plasma Exchange (PLEX)

Therapeutic apheresis (PLEX) temporarily improves myasthenic weakness in nearly all patients (Gajdos P, 2002). It is used as a short-term intervention for patients with sudden worsening of myasthenic symptoms for any reason, to rapidly improve strength before surgery, to prevent exacerbations induced by corticosteroids and as a chronic intermittent treatment for patients who are refractory to all other treatments. The need for PLEX and its frequency of use are determined by the goals and clinical response in the individual patient.

In a typical PLEX protocol, 2 to 3 liters of plasma are removed 3 times a week until improvement plateaus, usually after 5 to 6 exchanges. Improvement usually begins within the first week. Improvement induced by PLEX lasts for up to 3 months in most patients and then the effect is lost unless the exchange is followed by thymectomy or immunosuppressive therapy. Most patients who respond to the first course respond again to subsequent courses. Repeated exchanges do not have a cumulative benefit and should not be used as chronic maintenance therapy unless other treatments have failed or are contraindicated.

Adverse reactions to PLEX include transitory cardiac arrhythmias, nausea, lightheadedness, chills, obscured vision and pedal edema. The major complications are related to the route of access and peripheral venipuncture should be used whenever possible. Thromboses, thrombophlebitis and subacute bacterial endocarditis, as well as pneumothorax and brachial plexus injury are risks when subclavian lines, arteriovenous shunts or grafts are placed for vascular access.

2.8.6 Intravenous Immunoglobulin (IGIv)

Improvement in MG has been reported in 50 to 100% of MG patients after infusion of high-dose IGIv, typically 2gm/kg given over 2 to 4 days. Improvement usually begins within 1 week and lasts for several weeks or months. The minimum dose has not been established and no prospective controlled trial has yet been reported. A single dose of 1 gm/kg has been reported to be as effective as 2 gm/kg in treating myasthenic crisis (Gajdos P, 2006).

The precise mechanism(s) of action in MG are not known but IGIv appears to modulate the inhibitory pathways with a re-

duction in AChR-specific cellular and humoral immune reactivity.

Common adverse effects of IGIv are related to the rate of infusion and include headaches, chills and fever. These reactions can be reduced by giving acetaminophen or aspirin with diphenhydramine before each infusion. Vascular-type headaches may be sufficiently severe to limit the use of IGIv. These headaches can be managed with oral acetaminophen 1g and ibuprofen 600mg, or intravenous dihydroergotamine before and immediately after the IGIv infusion.

Severe reactions to IGIv are uncommon. Renal failure has been reported in patients with impaired renal function. Cerebrovascular and myocardial infarction have been reported but the mechanism for these is not known and it is unclear if they are related to the infusion rate, the immunoglobulin concentration, bystander products or the osmolality of the preparation. Pre-existing arteriosclerosis appears to be a prerequisite for the occurrence of strokes or heart attacks. Other less severe adverse events such as alopecia, aseptic meningitis, leukopenia and retinal necrosis have also been reported.

Patients with selective IgA deficiency may develop anaphylaxis to the IgA in IGIv preparations, thus IgA levels should be measured in all patients before the initial IGIv infusion to detect this condition. Human immunodeficiency virus (HIV) is not known to be transmitted by IGIv but the transmission of non-A, non-B hepatitis has been reported. IGIv preparations are now prepared from donors shown to be without these viral infections and the preparations are pasteurized. Although contamination of human blood products by donors having Creutzfeldt-Jakob disease has been reported, there is no reported case of transmission of this disease by blood products.

The indications for IGIv are similar to those for PLEX. Intravenous immunoglobulin is an alternative to PLEX, especially in children, patients with poor vascular access or when PLEX is not readily available. As with PLEX, IGIv should not be used as chronic therapy unless other treatments are contraindicated or have been ineffective.

2.8.7 Miscellaneous Treatments

Ephedrine has been used in patients with congenital myasthenia and in patients with acquired myasthenia in whom cholinesterase inhibitors alone are not effective, but it may not be currently available in the United States. Terbutaline, a ß-adrenergic agonist, has also been used in this fashion. These agents carry a significant risk of arrhythmia, hypotension and pulmonary edema and should be used with great caution.

Numerus case reports or small uncontrolled studies indicate that MG patients may improve after treatment with a number of immune modifying agents. Among them are rituximab, a chimeric monoclonal antibody, that reacts to the CD20 antigen. Its mechanism(s) of action in MG are unknown. Tacrolimus, a macrolide antibiotic that inhibits calcineurin, thus inhibiting T-cell signal transduction and IL-2 transcription, has been reported to improve myasthenic weakness in doses of 2-8 mg/day. While similar to CYA, with similar adverse effects,

it is more potent at equivalent dosages. Case reports and retrospective reviews suggest its potential value in MG.

2.9 Association of MG with Other Diseases

MG is often associated with other immune-mediated diseases, especially hyperthyroidism and rheumatoid arthritis. Seizures have been reported to occur with increased frequency in children with MG. One-fifth of our MG patients have another disease: 7% had diabetes mellitus before corticosteroid treatment, 6% have thyroid disease, 3% have an extrathymic neoplasm and less than 2% have rheumatoid arthritis. Cases of MG related to human immunodeficiency virus and after allogeneic bone marrow transplantation suggest a more than coincidental relationship. Extrathymic malignancies have been reported to be common in MG patients, especially in the older age group, possibly due to a common background of immune dysregulation (Levin N, 2005).

2.9.1 Treatment of Associated Diseases

It is important to recognize the effect of concomitant diseases and their treatment on myasthenic symptoms. Thyroid disease should be vigorously treated both hypo and hyperthyroidism adversely affect myasthenic weakness. Intercurrent infections require immediate attention because they exacerbate MG and can be life threatening in patients who are immunosuppressed.

Drugs that cause neuromuscular blockade must be used with caution (see Drugs That Adversely Affect MG later in this chapter and Section 11). Many antibiotics fall into this category. Ophthalmic preparations of beta blockers and aminoglycoside antibiotics may cause worsening of ocular symptoms. d-Penicillamine should not be used because it can induce or exacerbate MG. If corticosteroids are needed to treat concomitant illness, the potential adverse and beneficial effects on MG must be anticipated and explained to the patient.

MG has been reported to develop in patients during interferon alpha-2b treatment for malignancy and chronic active hepatitis C; in some cases the presentation of MG has been fulminant with myasthenic crisis. The mechanism is not well understood but it has been shown that the expression of interferon gamma at motor endplates of transgenic mice results in weakness and abnormal NMJ function that improve with cholinesterase inhibitors. This suggests an autoimmune humoral response, similar to what occurs in human MG.

Patients with neuromuscular disease, such as MG, are at risk of systemic side-effects, including dysphagia and respiratory compromise, from botulinum toxin injections, which should be administered with great caution.

Annual vaccination against influenza is generally recommended for patients with MG. Vaccination against pneumococcus is recommended in at-risk patients before starting prednisone or other immunosuppressive drugs. However, because immunizations can induce exacerbations in MG, this risk

must be weighed against that of the infection for each MG patient. Inactivated or recombinant vaccines (e.g. polio), rather than attenuated live (e.g. oral polio, herpes zoster) vaccine should be used in immunocompromised patients or in children who have household contacts with immunocompromised individuals. The Centers for Disease Control and Prevention reports that those taking less than 2 mg/kg per day of prednisone or everyother-day prednisone are not at risk. Patients with prior thymectomy should not receive the yellow fever vaccine.

2.10 Treatment Plan for MG

It is not the purpose of this manual to propose any one methodology of treatment but that offered below is an example of a management strategy. There is no standard cookbook approach and the decisions of management approach must be based upon the unique features of the patient; their degree of weakness, pattern of weakness, reliability, resources available, etc.

2.10.1 Ocular Myasthenia

Most patients are started on cholinesterase inhibitors. If the response is unsatisfactory, prednisone is added, either in incrementing or high daily doses. Thymectomy may be considered in young patients when ocular weakness persists despite cholinesterase inhibitors. The development of weakness in muscles other than the ocular or periocular muscles moves patients with ocular myasthenia to the generalized myasthenia protocol.

2.10.2 Generalized Myasthenia, Onset before Age 60

Thymectomy is recommended for all patients. Immunosuppression with prednisone or other drugs, PLEX, or both, are used preoperatively in patients with oropharyngeal or respiratory involvement to minimize the risks of surgery. Immunosuppression is recommended if disabling weakness recurs or persists after thymectomy, or if there is not continual improvement 12 months after surgery (see Corticosteroids and Immunosuppressant Drugs, earlier in this chapter).

2.10.3 Generalized Myasthenia, Onset after Age 60

Life expectancy and concurrent illness are important considerations in developing a treatment plan in this age group. Cholinesterase inhibitors are used initially. If the response is unsatisfactory, we add azathioprine in patients who can tolerate the expected delay before responding.

If treatment with azathioprine is unsatisfactory, prednisone is added or mycophenolate mofetil is substituted for azathioprine. If a rapid response is needed, we use prednisone as the first drug, with or without PLEX or IGIv.

Azathioprine or mycophenolate mofetil may be started at the same time and the prednisone dose reduced or even discontinued after the maximum response has been obtained.

2.10.4 Thymoma

Thymectomy is indicated in virtually all patients with thymoma; all identifiable thymic tissue is removed at the same time. Patients are pretreated with immunosuppression, with or without PLEX, until maximal improvement is attained. Postoperative radiation and chemotherapy are used if tumor resection is incomplete or if the tumor has spread beyond the thymic capsule. Medical treatment is then the same as for patients without thymoma. Elderly patients with small tumors who have a major risk for surgery may be managed medically while tumor size is monitored radiologically.

2.10.5 Juvenile MG

The onset of immune-mediated MG before age 20 is referred to as juvenile MG (Andrews PI, 2002). The pathophysiology is the same as in adults. Twenty percent of children with juvenile MG and almost 50% of those with onset before puberty are seronegative (see Seronegative Myasthenia Gravis, later in this chapter). Many children who are initially seronegative later develop AChR-antibodies (Anlar B, 2005). The female:male ratio in children is 3:1, compared to almost 1:1 in adult-onset MG. Thymomas are rare in this age group, but the few that we have seen were malignant.

When myasthenia begins in childhood, it is important to determine if the patient has acquired autoimmune MG or a genetic form that does not respond to immunotherapy (see Congenital Myasthenic Syndromes, later in this chapter). Because the absence of AChR or antiMuSK antibodies does not distinguish these conditions, a therapeutic trial of PLEX or IGIv may be indicated those who definitely improve are candidates for thymectomy or immunotherapy, although failure to respond does not exclude autoimmune MG.

Treatment decisions in children with autoimmune MG are made more difficult because the rate of spontaneous remission is high. Cholinesterase inhibitors alone are recommended in prepubertal children who are not disabled by weakness. If disability persists or weakness progresses, most would recommend thymectomy.

Children with postpubertal onset are treated the same as adults.

2.10.6 MG in the Elderly

Some reports have suggested that patients with late-onset MG have more severe disease and are more likely to have thymoma or to be seronegative, but this has not been our experience. One study found a high prevalence of previously unrecognized positive AChR antibodies in randomly selected subjects over 75 years old, suggesting that MG may be substantially underdiagnosed in older people (Vincent A., 2003). In this age group particularly the symptoms of MG may be initially attributed to cerebrovascular or neurodegenerative diseases. As the population continues to age, one can expect to see even more patients with MG, who will live longer with their disease, be progressively older and require treatment for longer periods.

2.11 Seronegative MG (SN-MG)

Ten percent of patients with acquired, presumably immune-mediated MG do not have detectable serum antibodies to AChR or MuSK (Chan KH, 2006; Sanders DB, 1997). In these seronegative patients, the diagnosis is based on the clinical presentation, the response to cholinesterase inhibitors and EMG findings. Genetic myasthenia must be considered in all childhood-onset SN-MG. Otherwise, treatment of these patients is the same as for those with AChR antibodies.

2.12 Anti-MuSK-Antibody Positive MG (MMG)

Antibodies to muscle specific tyrosine kinase (MuSK) have been reported in 40% to 50% of patients with generalized MG who lack antibodies to AChR (Evoli A, 2003; McConville J, 2004; Sanders DB, 2003; Vincent A, 2004). More recently, these antibodies have been reported in ocular myasthenia as well. MMG predominantly affects females and begins from childhood through middle age. The clinical findings may be indistinguishable from MuSK-negative MG, with fluctuating ocular, bulbar and limb weakness. However, many patients have predominant weakness in cranial and bulbar muscles, frequently with marked atrophy of these muscles (Evoli A, 2003; Farrugia, ME, 2006). Others have prominent neck, shoulder and respiratory weakness, with little or no involvement of ocular or bulbar muscles.

Many MMG patients do not improve with cholinesterase inhibitors—some actually become worse and many have profuse fasciculations with these medications. Most improve dramatically with PLEX or corticosteroids, but the response to other immunosuppressive agents varies (Sanders DB, 2003). Thymic changes are absent or minimal and the role of thymectomy in MMG is not yet clear.

Electrodiagnostic abnormalities may not be as diffuse as in other forms of MG and it may be necessary to examine different muscles to demonstrate abnormal neuromuscular transmission (Stickler DE, 2005). The potentially more limited distribution of physiologic abnormalities also may limit the interpretation of microphysiologic and histologic studies in MMG, inasmuch as abnormalities might not be seen in the muscles that are usually biopsied for these studies.

The diagnosis of MMG may be elusive when the clinical features, electrodiagnostic findings and response to cholinesterase inhibitors differ from typical MG.

2.13 Special Situations

2.13.1 Myasthenic or Cholinergic Crisis

Myasthenic crisis is respiratory failure from myasthenic weakness. A precipitating event, such as infection, aspiration, surgery, or medication changes, can be identified in most episodes of crisis. Cholinergic crisis is respiratory failure from overdose of cholinesterase inhibitors and was more common

before the introduction of immunosuppressive therapy, when very large dosages of cholinesterase inhibitors were used.

In MG patients with progressive respiratory symptoms, no single factor determines the need for ventilatory support. The safest approach is to admit the patient to an intensive care unit and observe closely for impending respiratory insufficiency. Serial measurements of negative inspiratory force (NIF) provide the best measure of deteriorating respiratory function in MG. Respiratory assistance is needed when the NIF is less than –20 cm H2O, when tidal volume is less than 4 to 5 cc/kg body weight and maximum breathing capacity is less than three times the tidal volume, or when the forced vital capacity is less than 15 cc/kg body weight. A mask and breathing bag can be used acutely but tracheal intubation should quickly be done with a low-pressure, high-compliance cuffed endotracheal tube. A volume-controlled respirator set to provide tidal volumes of 400 to 500 cc and automatic sighing every 10 to 15 minutes is preferred. The pressure of the tube cuff should be checked frequently and the tube position verified daily by chest radiographs. Assisted respiration is used when the patient's own respiratory efforts can trigger the respirator. An oxygen-enriched atmosphere is used only when arterial blood oxygen values fall below 70 mm Hg. The inspired gas must be humidified to at least 80% at 37°C to prevent drying of the tracheobronchial tree. Tracheal secretions should be removed periodically using aseptic aspiration techniques. Lowpressure, high-compliance endotracheal tubes may be tolerated for long periods and usually obviate the need for tracheostomy.

Many case series report short-term benefit from PLEX and IGIv in myasthenic crisis. Retrospective studies indicate that both are equally effective in disease stabilization (Murthy JMK, 2005). Others suggest PLEX is superior, producing more rapid respiratory improvement (Qureshi AI, 1999). Further research is needed to compare PLEX with alternative short-term treatments for myasthenic crisis, such as IGIv (Gajdos P, 2002).

Cholinesterase inhibitors can safely be discontinued once the patient is being ventilated this eliminates the possibility of cholinergic overdose and permits determination of disease severity. These medications can be added in low doses and titrated to the optimal dose after the crisis precipitating factors have been addressed.

When respiratory strength improves, weaning from the respirator should be started for 2 or 3 minutes at a time and increased as tolerated. Extubation can be considered when the patient has a NIF greater than –20 cm H2O and an expiratory pressure greater than 35 to 40 cm H2O. The tidal volume should exceed 5 cc/kg, which usually corresponds to a vital capacity of at least 1,000 cc. If the patient complains of fatigue or shortness of breath, extubation should be deferred even if these values and blood gas measurements are normal.

Prevention and aggressive treatment of medical complications offer the best opportunity to improve the outcome of myasthenic crisis.

2.13.2 Anesthetic Management in MG

The stress of surgery and some drugs used perioperatively may worsen myasthenic weakness. As a rule, local or spinal anesthesia is preferred over inhalation anesthesia. Neuromuscular blocking agents should be avoided or used sparingly. Adequate muscle relaxation usually can be produced by inhalation anesthetic agents alone. The required dose of depolarizing blocking agents may be greater than that needed in nonmyasthenic patients but low doses of nondepolarizing agents cause pronounced and long-lasting blockade that require prolonged postoperative assisted respiration. See Section 4 on Guidelines for the Anesthesiologist.

2.13.3 Pregnancy

Myasthenia may improve, worsen, or remain unchanged during pregnancy and it is not uncommon for the first symptoms of MG to begin during pregnancy or postpartum. First trimester worsening is more common in first pregnancies, whereas third-trimester worsening and postpartum exacerbations are more common in subsequent pregnancies. Complete remission may occur late in pregnancy. The clinical status at onset of pregnancy does not reliably predict the course during pregnancy. Pregnancy is more difficult to manage at the beginning of MG and it is recommended that women affected with MG begin a pregnancy after the disease is stable.

Therapeutic abortion is rarely, if ever, needed because of MG and the frequency of spontaneous abortion is not increased. Oral cholinesterase inhibitors are the first-line treatment during pregnancy. Intravenous cholinesterase inhibitors are contraindicated because they may produce uterine contractions. Prednisone is the immunosuppressive agent of choice. Studies are lacking for other immunosuppressive agents and animal studies have shown a risk to the fetus, or are lacking as well. We do not use immunosuppressive drugs during pregnancy because of theoretical potential mutagenic effects. However, others feel that azathioprine and even cyclosporine can be used safely during pregnancy (Ferrero S, 2005). Until information is available regarding safety, mycophenolate mofetil should not be used during pregnancy. Plasmapheresis or IGIv have been used when an immediate, albeit temporary improvement is needed during pregnancy. Increased risk of fetal malformation has been reported when men used azathioprine prior to conception (Norgard B, 2004).

Magnesium sulfate should not be used to manage preeclampsia because of its neuromuscular blocking effects. Barbiturates usually provide adequate treatment. Labor and delivery are usually normal. Cesarean section is needed only for obstetrical indications. Regional anesthesia is preferred for delivery or cesarean section. MG does not affect uterine smooth muscle and therefore the first stage of labor is not compromised. In the second stage of labor, striated muscles are at risk for easy fatigue and therefore outlet forceps or vacuum extraction may be needed.

Weakness due to transplacental passage of maternal pathogenic auto-antibodies may be manifest by the fetus in utero as arthrogryposis, weak fetal movements, polyhydramnios due to poor fetal swallowing, pulmonary hypoplasia due to reduced

fetal respiratory movements, hydrops fetalis and stillbirth. Lack of fetal movements is probably the factor responsible for this complex phenotype, also known as the fetal akinesia deformation sequence. It probably results when antibodies specific for the fetal isoform of AChR cross the placenta and paralyze the fetus in utero. There is no evident correlation between maternal disease severity and this fetal condition. Decreased fetal movement is considered an indication for plasmapheresis or IGIv. Birth of a child with arthrogryposis should prompt a search for MG in the mother.

Complications of pregnancy in MG may also result from coincidental autoimmune disease or underlying immunological dysfunction.

Breast-feeding does not appear to be a problem for myasthenic mothers, despite the theoretical risk of passing maternal AChR antibodies to the newborn.

2.13.4 Transient Neonatal MG (TNMG)

A temporary form of MG affects 10 to 20% of newborns whose mothers have immune-mediated MG. The severity of symptoms in the newborn does not correlate with the severity of symptoms in the mother. The maternal antibody level correlates with the frequency and severity of TNMG and TNMG occurs only rarely in infants of seronegative mothers. An affected mother who delivers an infant with TNMG is likely to have similarly-affected, subsequent infants. Affected newborns are hypotonic and feed poorly during the first 3 days. In some newborns, symptoms may be delayed for 1-2 days. Symptoms usually last less than 2 weeks but may continue for as long as 12 weeks, which correlates with the half-life of neonatal antibodies. It is not clear why some newborns develop weakness and others, with equally high antibody concentrations do not. Some mothers with antibodies directed specifically against fetal AChR may themselves be asymptomatic, which makes diagnosis of TNMG more difficult.

All infants born of myasthenic mothers should be examined carefully at birth. Detection of AChR antibodies in the child provides strong evidence for the diagnosis although seronegative mothers have delivered affected seronegative infants. Improvement following injection of 0.1mg/Kg of edrophonium supports the diagnosis of TNMG but it may be hard to assess the response to edrophonium in an intubated and ventilated neonate. Improvement after edrophonium does not distinguish TNMG from some congenital myasthenic syndromes. A decremental response to RNS confirms abnormal neuromuscular transmission, but also does not distinguish TNMG from many congenital myasthenic syndromes.

Affected newborns require symptomatic treatment with cholinesterase inhibitors if swallowing or breathing is impaired. Exchange transfusion should be considered in the rare newborn with respiratory weakness.

2.13.5 d-Penicillamine-Induced MG

d-Penicillamine is used to treat rheumatoid arthritis, Wilson disease and cystinuria. Rarely, patients treated with d-penicillamine for several months develop a myasthenic syn-

drome that disappears when the drug is stopped. d-Penicillamine-induced myasthenia is usually mild and often restricted to the ocular muscles. The diagnosis is often difficult because weakness may not be recognized when there is severe arthritis. The diagnosis is established by the response to cholinesterase inhibitors, characteristic EMG abnormalities and serum AChR antibodies. It is likely that d-penicillamine stimulates or enhances an immunological reaction against the neuromuscular junction. Cholinesterase inhibitors usually relieve the symptoms. The myasthenic response induced by d-penicillamine usually remits within a year after the drug is stopped. If myasthenic symptoms persist thereafter, the patient should be treated for acquired MG.

2.14 Congenital Myasthenic Syndromes (CMS)

Congenital forms of myasthenia comprise a heterogeneous group of genetically-determined, non immunemediated disorders caused by several abnormalities of neuromuscular transmission (Engel AG, 2007). This area is a hotbed of research and our knowledge base and understanding of these disorders is expanding rapidly.

Individually and collectively they are rare; some forms have only been described in one or two families. Symptoms are present at birth in most forms, but in others, symptoms may not begin until early childhood or even young adult life. Except for TNMG, all myasthenia that begins at birth is genetic. Myasthenia that begins in infancy or childhood may be genetic or acquired.

All genetic forms of myasthenia are known or presumed to be transmitted by autosomal recessive inheritance except the slow-channel syndrome, which has autosomal dominant inheritance. Some have characteristic clinical or electrodiagnostic features, but in many, the specific form can only be determined by genetic studies or specialized morphologic and electrophysiologic studies on muscle biopsy.

Overall, there is a 2:1 male predominance. Ophthalmoparesis and ptosis are present during infancy; mild facial paresis may be present as well. Ophthalmoplegia is often incomplete at onset but progresses to complete paralysis during infancy or childhood. Some children develop generalized fatigue and weakness but limb weakness is usually mild compared to ophthalmoplegia. Respiratory distress is unusual.

Congenital myasthenia should be suspected in any newborn or infant with ptosis or ophthalmoparesis.

Weakness that varies from time to time should always raise the question of myasthenia. In older children, a careful history will usually reveal symptoms in infancy or early childhood and possible involvement of other family members.

Subcutaneous injection of edrophonium usually produces a transitory improvement in ocular motility. A decremental response to RNS is found in some limb muscles but it may be necessary to test proximal or facial muscles if hand muscles show a normal response. SFEMG shows increased jitter. The combination of clinical examination, response to cholinesterase inhibitors and EMG findings is often sufficient to make a

definitive diagnosis of congenital myasthenia and in some cases, to characterize the subtype.

Cholinesterase inhibitors improve limb muscle weakness in many forms of CMS and may be effective even when edrophonium is not. Ocular muscle weakness is less responsive to cholinesterase inhibitors. The weakness in some children responds to 3,4-diaminopyridine (Harper CM, 2000). Thymectomy and immunosuppression are not effective.

2.14.1 Congenital AChR Deficiency

Most patients with congenital myasthenia have a primary deficiency of the AChR. This is a genetically heterogeneous group— over 50 mutations with an autosomal recessive or sporadic inheritance pattern have been described (Engel AG, 2007). The age of symptom onset ranges from infancy to adulthood. Clinical manifestations include hypotonia, respiratory insufficiency, weakness of ocular and bulbar muscles and skeletal deformities. The findings on electrodiagnostic studies are indistinguishable from autoimmune MG.

2.14.2 Choline acetyl transferase (ChAT) Deficiency

This condition, previously called congenital myasthenic syndrome with episodic apnea or familial infantile myasthenia, has characteristic clinical and electrophysiological features that differ from other congenital myasthenic syndromes. Generalized hypotonia is present at birth and the neonatal course is complicated by repeated episodes of life-threatening apnea and feeding difficulty. Arthrogryposis may be present. Ocular muscle function is usually normal. Within weeks after birth, the child becomes stronger and ultimately breathes unassisted. However, episodes of life-threatening apnea occur repeatedly throughout infancy and childhood, even into adult life. There is often a history of sudden infant death syndrome in siblings and the correct diagnosis may not be suspected until a second affected child is born.

Edrophonium usually improves both weakness and respiratory distress. A decremental response to RNS is usually present in weak muscles but may be demonstrated in strong muscles only after exhausting the muscle by several minutes of RNS or voluntary contraction. Abnormal resynthesis and repackaging of ACh in the motor nerve has been shown in some patients.

Cholinesterase inhibitors improve strength in most children with ChAT deficiency. As the patients get older, weakness improves, attacks of respiratory distress become less frequent and the need for medication decreases.

We have seen sustained symptomatic improvement in children from several families with this syndrome when 3,4-diaminopyridine is given with pyridostigmine.

2.14.3 Slow-Channel Congenital Myasthenic Syndrome (SCCMS)

This syndrome may be difficult to distinguish from acquired MG because the onset of symptoms may be delayed until adult life. The disease is transmitted by autosomal dominant inheritance and a family history of similar illness often is obtained.

SCCMS is rare. Onset of symptoms is always after infancy and may be as late as the third decade. Slowly progressive weakness selectively involves the arm, leg, neck and facial muscles. Unlike other congenital myasthenic syndromes, symptomatic muscles are atrophic.

RNS shows a decremental response. Repetitive discharges are seen after nerve stimulation, similar to those seen incholinesterase inhibitor toxicity or congenital deficiency of endplate acetylcholinesterase. The underlying defect is a prolonged open time of the ACh channel. Quinidine sulfate and fluoxetine may improve strength in this condition (Harper CM, 2003).

Table 2.4 Drug alert for patients with MG

1. Alpha-interferon, botulinum toxin, d-penicillamine and the ketolide, telithromycin (Ketek®) should never be used in myasthenic patients.

2. The following drugs produce worsening of myasthenic weakness in most patients who receive them. Use with caution and monitor patient for exacerbation of myasthenic symptoms. *This list is **not** complete but is used to give the reader and idea of possible problems.*

o **Succinylcholine, d-tubocurarine**, or other neuromuscular-blocking agents
o **Quinine, quinidine** and **procainamide**
o **Antibiotics**

- o **Aminoglycosides**, particularly **gentamicin**, **kanamycin**, **neomycin** and **streptomycin**
- o **Quinolones** (e.g. **ciprofloxacin, levofloxacin, norfloxacin, ofloxacin** and **pefloxacin**)
- o **Macrolides** (**erythromycin**, **azithromycin [Z-pack]**)

o **Beta blockers** (systemic and ocular preparations): **propranolol, timolol maleate eyedrops**
o **Calcium-channel blockers**
o **Magnesium salts** (including laxatives and antacids with high Mg^{2+} concentrations)
o **Iodinated contrast agents**

3. Many other drugs are reported to exacerbate the weakness in some patients with MG. All MG patients should be observed for increased weakness whenever any new medication is started.

An up-to-date reference document for such adverse interactions is maintained on the web site of the Myasthenia Gravis Foundation of America (www.myasthenia.org/docs/MGFA_MedicationsandMG.pdf).

2.15 Drugs That Adversely Affect MG and LES

Drugs that impair neuromuscular transmission make patients with MG weaker (Table 2.4) (Howard JF, 2007). Some drugs have a direct effect on synaptic transmission and may unmask subclinical MG or exaggerate the weakness in patients with disordered neuromuscular transmission (MG, LES, botulism). A familiar scenario in MG is delayed recovery of strength, particularly respiratory function, following general anesthesia during which neuromuscular blocking agents had been used or a patient with a respiratory syndrome who is given an antibiotic that worsens neuromuscular function.

Other drugs may induce a disturbance of the immune system that results in the development of MG. This is most commonly seen in d-penicillamine-induced MG. There are reports of similar occurrences in patients receiving tiopronine, pyrithioxine, hydantoin drugs, trimethadione and chloroquine.

The effects of competitive neuromuscular blocking agents, such as d-tubocurarine and pancuronium, are exaggerated and prolonged in patients with MG. Depolarizing agents such as succinylcholine also must be used with caution. Some antibiotics (particularly aminoglycosides, macrolides and ketolides), antiarrhythmics (quinine, quinidine and procainamide) and calcium channel and adrenergic blocking drugs also block neuromuscular transmission and increase weakness. Because of reports of severe exaceration of MG in patients taking telithromycin, a ketolide antibiotic, this drug carries a specific FDA warning against its use in MG (Turner M, 2006). Iodinated contrast agents have been reported to produce transitory worsening in patients with MG and LES, possibly because of their calcium-chelating effects. Ophthalmic β-blocker and tobramycin preparations may unmask or exacerbate myasthenic weakness. Many other drugs have been reported to increase myasthenic weakness in isolated cases but many of these reports are merely anecdotal, often involving isolated cases of patients with increased weakness while using a particular drug.

The potential adverse effects of medications must be taken into consideration when deciding which drugs to use in MG. Although it is desirable to avoid drugs that are known to impair neuromuscular transmission, this is not always possible. Patients with disorders of neuromusuclar transmission should be observed for clinical worsening after any new medication is started. It useful to place a list of potentially hazardous drugs on the front of the hospital chart of patients with MG (Appendix II.5). An up-to-date reference document for such adverse interactions is maintained on the web site of the Myasthenia Gravis Foundation of America
www.myasthenia.org/docs/MGFA_MedicationsandMG.pdf

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3

Nursing Issues

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Nursing care of the person with myasthenia gravis (MG) is individualized and can be challenging. It requires an understanding of its symptoms, causes, diagnostic tests and treatment in order to maximize the patient's recovery and to promote a healthy life.

Myasthenia Gravis is a chronic autoimmune neurological disease, which affects all genders, ages and races (Sanders and Howard, 2008). Although MG currently has no cure, it is one of the best-understood autoimmune diseases and much is known about its pathophysiology and autoimmune nature. It is caused by a defect in the transmission of nerve impulses at the neuromuscular junction to voluntary (striated/ skeletal) muscle groups (ocular, oropharyngeal, facial, neck, shoulder, intercostals, diaphragm, trunk, hip, upper and lower limbs). These are the muscles, which the patient can voluntarily move and control (unlike the heart muscle). In MG, antibodies block, alter, or destroy the receptors for the neurotransmitter acetylcholine (ACh). Acetylcholine binds to receptors on the muscle membrane to transmit nerve impulses for muscle contraction.

Autoimmune MG can be divided into two clinical presentations: restricted ocular MG or generalized MG. Each may be one of three serotypes. The largest group is antiacetylcholine receptor (AChR) antibody positive, the smallest group is muscle-specific tyrosine kinase (MuSK) antibody positive and the third group does not appear to have any antibodies and they are termed seronegative (SN) MG. (See Section 2 for a full description of types of MG). In SN-MG the source or site of the immune system attack has not yet been identified, but the patient responds to the same clinical treatment for MG.

The name Myasthenia Gravis is derived from Latin and Greek. It literally means, "grave muscle weakness". MG varies uniquely among individuals. Some persons have a mild course with little progression, while others have more exacerbations and less periods of remission. In the patient with myasthenia gravis, muscle weakness often occurs after exertion and improves with rest. Stress, over or under medication, illness, medication interactions and non-compliance with the healthcare regimen can also trigger symptoms and even an MG exacerbation. Symptoms and exacerbations can usually be managed with medications, other MG treatments and lifestyle interventions.

Weaknesses in the voluntary muscles cause the characteristic symptoms of MG:

- *ptosis (droopy lids) and/or, lid lag when opening and closing eyes due to levator palpebra / orbicularis oculi muscle weakness;*
- *diplopia (double vision) due to weak ocular muscles affecting gaze;*
- *swallowing problems (gagging, choking, difficulty clearing secretions, hoarseness and nasal speech) due to oropharyngeal muscle weakness;*
- *poor facial expression (flat smile, poor brow movement, drooping lips, weak pucker);*
- *chewing fatigue due to facial/jaw muscle weakness;*

- *shallow breathing, decreased chest expansion, shortness of breath due to intercostal muscle/ diaphragm weakness;*

- *neck, shoulder, hip, upper and lower limb weakness.*

The majority of individuals with MG will have an excellent life expectancy and quality of live with optimal medical, nursing and psychosocial management and patient compliance. The goal of treatment is to normalize muscle strength and limit disease exacerbations and associated complications. To this end, the following nursing principles should be implemented.

3.1 Critical Elements of the Patient History

A health history is subjective data and a prerequisite to the assessment of the myasthenic patient. It is an important part of interacting and developing a trusting relationship with the patient and useful to identify the patient's problem(s) and health strengths and weaknesses. This will be helpful in understanding why the patient is experiencing an exacerbation of MG symptoms and aid in the development of an individualized care plan.

To facilitate obtaining a correct history it is important to have an environment which insures privacy and addresses maximum possible comfort (room temperature, lighting, noise, etc.). Include family or significant others with permission of the patient who can provide additional or supplemental information if necessary. It is important to establish rapport and address the person by his or her surname unless otherwise directed. Sit facing the patient or informant, watch your posture, use eye contact, express a caring and non-judgmental attitude, ask one question at a time and communicate in words understandable to the individual's learning/cultural level. Family and psychosocial history will also be helpful.

Use of open ended and closed or direct questions can have a different function during information gathering. Begin with open ended questions. These can help patients to tell their story, "What brings you to the hospital?" "What is your chief concern? " Directed questions are useful to get more specific details and can be better controlled by the clinician. MG symptoms should be described using the seven basic attributes:

1. location (where/what is the weakness – eyes, speech, swallowing, breathing, upper/lower limbs, etc.),
2. quality or character of the weakness,
3. quantity or severity of the weakness,
4. timing (onset, duration, frequency) of the weakness,
5. setting,
6. aggravating /alleviating factors and
7. associated factors

Factors that may aggravate myasthenic weakness include various forms of stress (e.g. change in emotional state, depression, anxiety, fear), heat and humidity, infection, surgery, menses to name but a few. It is therefore important to question the patient about these possible triggers as their identification will allow the health care team to develop appropriate coping strategies or modifications in behavior (Moos RH, 1989).

It is also helpful to understand the patient's perception of what the symptoms mean. Some specific MG questions may include:

- Is the patient a newly or previously diagnosed myasthethic?
- Was the patient perviously in remission?
- What does the patient know about MG?

• What are his or her sources of information?

• How is the patient coping with the diagnosis?

• Did the patient follow the prescribed medication dosing and frequency schedule?

• Does the patient understand the medication regimen and frequency schedule?

• Is the patient experiencing unpleasant side effects?

• What is the response after taking the cholinesterase inhibitors? (pyridostigmine, neostigmine, etc.)?

• Is fatigue/weakness noticeable before the medication is due? (over or under medication can worsen MG symptoms)

• Do symptoms increase after activity or stress?

• Is the patient being treated for a recent infection or illness?

• Has the patient been started on new medications?

• What is the patient's learning level?

• What type of family support is available?

• Are there cultural/religious issues that can affect compliance?

An understanding of MG will facilitate the nurse's comprehensive history which is a bridge to the assessment and nursing care plan.

3.2 Nursing Assessment of the MG Patient

The principle characteristic of myasthenia gravis is fatigable weakness that may involve any or all of the muscles that the patient can control voluntarily that is often improved with a short period of rest only to worsen with resumption or repetition of the activity. The muscle weakness fluctuates and varies in location and severity in individuals with MG. The muscles used in controlling movements of the neck, eyes, eyelids, face, chewing, swallowing, speaking, breathing and the limbs may be affected. It is important for the nurse to assess muscle strength and the presence of fatigability. This information will enable the nurse to identify potential or existing problems, to assist the individual with myasthenia and family members to develop strategies in the prevention and management of problems and to assist in the evaluation of the effectiveness of the treatment plan. The goals are to enable the individual with myasthenia achieve maximal function and to promote quality of life.

3.2.1 Assessment of Muscle Strength

Assessment of muscle strength of all voluntary muscles provides the essential data to determine the severity of the patient's myasthenia and their risk of developing secondary complications. Muscle strength testing includes the neck, face, ocular/bulbar, respiratory muscles and

the proximal/distal limb muscles. A reliable Quantitative Myasthenia Gravis (QMG) score has been developed for research purposes. An MG nursing examination tool has not been developed, however, in some centers the spinal cord testing or other nursing assessment tools are adapted for this patient population. In selected centers, the physical therapist will team with the nursing staff to quantitatively assess muscle strength (See Section 7 on Physical Therapy). Documentation of MG muscle testing needs to include time of day and time of recent cholinesterase inhibitor (ChI) medications. There is no single optimally testing time of muscle strength and it is depended upon the question that is being asked. For instance, if the question is to determine the maximal response to pyridostigmine then testing should be performed at a consistent time that would capture peak drug efficacy usually 1 to 2 hours following the dose. If one is trying to determine how weak one is despite pyridostigmine therapy then testing the patient just prior to the administration of medication may be most helpful. During ChI titration it is useful to test muscle strength predose and 60-120 minutes later for efficacy and tolerance.

Eye (ocular) weakness can be assessed by observing for lid lag, ptosis and weakness of extraocular movements. If ptosis is not readily apparent the patient can fixate on a finger or object above his head. Observe if and how long (at least 90 seconds) it takes for the eyelid to fall to the top of the pupil. Ptosis may be unilateral or bilateral and may increase when looking upward. Gazing in all directions (H-pattern) may elicit blurred or double vision that results from asymmetrical weakness of the extraocular muscles. Take note of the presence of symptoms (blurred or double vision) and/or inability of the eye to completely move in all directions of gaze. Fatiguing of extraocular muscles may occur with fixation on an object, e.g. a pin or pen for 60 seconds resulting in double vision. It is important to remember that double vision can only be elicited if both eyes have visual capacity, i.e. if the eyelids cover the pupil or other reasons exist for monocular vision (e.g. macular degeneration, blindness in one eye,) double vision cannot be elicited. Testing should be done with the patient wearing corrective lenses as those who have a severe refractive error may experience the phenomenon of ghosting where an object may appear blurred or double when in fact it is not.

Facial strength is assessed for mobility; the ability to smile, flattening of the nasolabial fold, frowning, eye closure (able to bury eyelashes), blowing up cheeks and symmetrical facial muscle strength. All tests should be done repeatedly (e.g. 3-5 successive attempts in order to assess for fatigability). Test the ability to chew bilaterally by asking the patient to clench the jaw, while you attempt to open it. Jaw opening is tested by asking the patient to keep the jaw open against resistance. Observe the quality of speech such as pronunciation, enunciation, volume intensity, hypernasality, breathlessness and whether the voice alters with prolonged talking (dysphonia). Observe for any weakness of the palate and pharynx that would result in an inability to handle secretions and swallow food or liquids. Note the presence of any drooling.

Observe the position of the head, the ability to hold the head up and whether it falls forward or is being supported by the patient's hand. Test muscle strength of the neck muscles. Neck weakness can be assessed by having the patient push the forehead against your hand and sustain it, then have the patient push the back of his head against your hand. This test can be repeated 3-5 times to assess fatigability.

Test the strength of each proximal and distal limb muscle group using the following widely accepted motor scale of 0 to 5:

Grade 5 = normal muscle power
Grade 4 = movement against gravity and against resistance
Grade 3 = movement against gravity without resistance
Grade 2 = movement in the plane of action with gravity eliminated
Grade 1 = flicker of muscle movement in the gravity eliminated position
Grade 0 = no muscle movement even with gravity eliminated

Since the weakness of individuals with myasthenia gravis may be asymmetrical, it is important to compare each muscle group on both sides of the body. Note the ability to hold or pick up objects. Fatigue testing may be done by having the patient raise his arms to shoulder height and out to the side, parallel to the floor. Observe and record (in seconds or minutes) how long it takes for the arms to fatigue.

Muscle testing should be done at peak medication time and also at a time when the patient may be weak (e.g. trough medication time) for comparison. Note any differences in strength and record using the scale. Remember that when doing strength testing that the test itself can fatigue the patient and that repetitive movement can also tire muscle groups. This observation would suggest that the patient might be weaker than thought and has no functional reserve.

3.2.2 Assessment of Respiratory Function

Respiratory muscle function can be assessed by observing breathing activity and listening to the patient talk. Ask the patient to count to 50 and record at what number he needs to stop to take a breath. Assess whether the patient is able to lie flat or bend over without shortness of breath. Assess chest expansion and auscultate the chest in all quadrants for air entry or crackles. Observe for shortness of breath, increased respiratory effort or frequent inspiratory gasps. Note the rate, rhythm, depth and quality of the respirations. Individuals who are short of breath often appear anxious and restless.

Pulmonary function tests may be used to measure the degree of respiratory compromise. Measurements of the patient's negative inspiratory force (NIF) are informative. The forced vital capacity (FVC) is not an accurate parameter of respiratory muscle work and muscular fatigue. However, measuring the FVC in both supine and sitting positions will assist in determining diaphragmatic involvement. A change of 15% to 20% or greater between the lying and supine FVC indicates

diaphragm involvement. The NIF will change before abnormalities of FVC are seen. Patients with NIF of -20 to -40 should be closely monitored for impending respiratory failure and the physician notified. It is important to recognize that patients with significant facial weakness may not achieve a good seal on the mouthpiece. NIF and FVC measurements will be often abnormal in these situations. Performing the test while using a mask may eliminate this problem.

Oxygen saturation and blood gas analysis provides additional data in determining respiratory status. However, a distinctive characteristic of the MG patient during evaluation of respiratory strength is that the blood gas or oxygen saturation percentage is not a good indicator of respiratory strength. Myasthenia gravis does not interfere with gas exchange itself, but impaired diaphragm function and the reduced capacity of the chest muscles to support respiration is the manifestation of the respiratory involvement. Respiratory failure, producing a myasthenic crisis could occur in the most severe situation.

3.3 Nursing Care of the Patient with Myasthenia Gravis

The specific problem areas and severity vary from patient to patient and over the course of the disease process. The identification of these patient problems with the implementation of the appropriate interventions will serve to manage fatigue, prevent complications and aid in maintaining a quality life-style appropriate to the course of the disease. The following patient problems (nursing diagnoses) are the most commonly encountered in these patients.

A few sample nursing care plans are provided in Appendix 3.1 – 3.5. The reader is encouraged to develop their own to fit with the specific needs of the treatment team.

PATIENT PROBLEM	EXPECTED OUTCOMES	NURSING INTERVENTIONS
3.3.1 Activity intolerance related to muscle fatigability and weakness.	1. Maintains muscle strength, endurance and activity level. 2. Demonstrates energy conservation techniques 3. Patient verbalizes a decrease in muscle fatigue.	1. Identify factors that increase activity Intolerance. 2. Rest periods prior to and following activities. 3. Develop energy conservation strategies to decrease fatigue and optimize activities. 4. Adjust medications to maximize effectiveness.
3.3.2 Impaired verbal communication related to weakness of the larynx, pharynx, lips, mouth, and jaw muscles.	1. Decreased frustration with communication. 2. Uses an alternative methods to communicate.	1. Determine the most effective mode of communication including the use of alternative methods (e.g. gestures, written, communication cards). 2. Encourage the patient to speak slowly and louder. 3. Reduce environmental noise. 4. Observe for nonverbal clues. 5. Ask patient questions that require short answers. 6. Discuss the frustration associated with the inability to communicate. 7. Explain the need for patience by family and friends. 8. Consult a speech pathologist.
3.3.3 Alteration in nutrition related to fatigue of the muscles for chewing and impaired swallowing.	1. Maintains weight within normal limits. 2. Absence of dehydration.	1. Rest prior to eating and drinking. 2. Provide foods easy to chew. 3. Provide highly viscous foods and thickened liquids. 4. Offer frequent, small meals including high-calorie and high-protein foods. 5. Instruct patient on principles of good dental hygiene. 6. Instruct patient to take rests while chewing and in between bites to restore strength. 7. Serve meals at times of maximum strength (usually in the earlier part of the day and ½ hour after cholinesterase inhibitor medications). 8. Serve larger meal in the morning and smaller meals in the evening. 9. Review food preparation techniques so that food is easier to consume because of softer consistencies. 10. Review principles of nutrition and basic food groups so that the patient can select food that provides a balanced diet. 11. Consult a dietitian to determine appropriate food choices. 12. Consult with a swallowing specialist to determine the most effective swallowing techniques.

PATIENT PROBLEM	EXPECTED OUTCOMES	NURSING INTERVENTIONS
3.3.4 High risk of aspiration due to inability to swallow, manage own secretions, and impaired cough and gag reflexes.	1. Absence of aspiration. 2. Breath Sounds within normal limits. 3. Chest X-ray within normal limits	1. Discuss the causes and prevention of aspiration. 2. Position upright with head slightly forward when eating and drinking. 3. Encourage taking small bites, chewing well, and frequent swallowing. 4. Encourage taking small sips of liquids. 5. Encourage eating slowly – make sure patient has swallowed after each bite. 6. Provide meals at times of optimal strength. (after medications, earlier in the day, after rest periods). 7. If swallowing only slightly impaired, instruct patient to lean forward, take a small breath through the nose and cough forcefully to push the irritating substance out of the throat. 8. If choking occurs, apply emergency principles as outlined by the American Heart Association to include the Heimlich maneuver. 9. If aspiration suspected, assess breath sounds and obtain a chest X-ray.
3.3.5 Disturbed sensory perception related to double vision and ptosis.	1. Absence of physical injury associated with impaired vision.	1. Reinforce the need for rest periods. 2. Discuss the risks associated with visual Impairment.
3.3.6 Risk for injury related to visual disturbance, muscle fatigue and weakness.	1. Uses safety measures to decrease risk of injury. 2. Absence of falls.	1. Use eye patch to eliminate double vision. 2. Use safety measures to prevent injury, e.g. remove or anchor throw rugs, use handgrips in bathroom, and railings on stairs. 3. Moderate exercise to maintain muscle strength. 4. Use of an alert system/mechanism in case of increased weakness or a fall.

PATIENT PROBLEM	EXPECTED OUTCOMES	NURSING INTERVENTIONS
3.3.7 Ineffective respiratory function related to weakness of intercostal muscles and diaphragm.	1. Absence of shortness of breath. 2.Adequate air exchange. 3. Effective spontaneous cough. 4. Pulmonary Function tests are within normal limits.	1. Assess and document respiratory status, rate, rhythm and breath sounds. 2. Assess gag and cough reflexes. 3. Assess quality of voice – notify MD of changes from baseline. 4. Obtain baseline Forced Vital Capacity (FVC) (normal ≥60 ml/kg) and Negative Inspiratory Force (NIF) (≥70cm H_2O) and continue to monitor 5. Notify MD for any respiratory abnormalities or change in FVC and/or NIF from baseline value or NIF <30, FVC <1.5L. (Values of FVC ≥1.0L <15mL/kg body weight /NIF <20 cm H2O are indications for mechanical ventilation.) 6. Administer oxygen as needed. 7. Suction if patient unable to manage secretions. 8. Teach patient/caregiver how to use oral suction. 9. If facial weakness – obtain NIF/FVC per face mask.
3.3.8 Disturbed sensory perception related to double vision and ptosis.	1. Absence of physical injury associated with impaired vision.	1. Encourage patients to verbalize the meaning of the illness/loss (i.e., “How do you feel about what is happening to you?”). 2. Listen attentively and compassionately. 3. Since appearances may greatly alter and weakness may leave patients unable to take care of grooming needs, help them to look their best. 4. Be honest about realities of the illness; encourage patients to seek help if denial becomes detrimental. 5. Facilitate acceptance; help patients set realistic, short-term goals so that success may be achieved. 6. Encourage patients to do the things that they are capable of doing. 7. Share hopeful aspects of the disease with patients and family. 8. Recognize that the family too will be experiencing grief for the loss of the way the patient “used to be.” 9. Determine what their usual coping mechanisms are, and how they can best be used to cope with the MG. 10. Assist patients in identifying factors in their environment that have the potential to undermine positive adaptation. 11. Involve patients in the planning and decision making regarding care. 12. Give patients and family information regarding the disease, medications, emergency measures, and precautions for living with MG after discharge from the acute care setting. 13. Explore patient role changes so that they will be less threatening. 14. Supply information on local MG chapter. Relationships can be formed with others with the disease and be a great source of strength to patients and family.

PATIENT PROBLEM	EXPECTED OUTCOMES	NURSING INTERVENTIONS
3.3.9 Self care deficit related to muscle fatigue and weakness and visual Impairment.	1. Able to perform activities of daily living within limits of weakness and fatigability. 2. Demonstrates increased strength, endurance and mobility.	1. Assess ability to carry out ADL's (feed, dress, groom, bathe, toilet, transfer and ambulate). 2. Assess specific cause – weakness, vision. 3. Assess need for assistive devices. 4. Encourage as much independence as possible. 5. Use consistent routines and allow sufficient time to perform each activity. 6. Provide positive reinforcement. 7. Position in optimal position to perform activity. 8. Plan activities so patient is rested. 9. Ensure needed equipment is available. 10. Encourage use of clothing that is easy to put on and remove. 11. Consult with Physical Therapist and/or Occupational Therapist.
3.3.10 Knowledge deficit related to the disease and its management.	1. Verbalizes an understanding of the disease, management, potential side effects and fatigue management.	1. Assess any barriers to learning and readiness to learn by patient and family. 2. Education about the disease process. 3. Education about the treatment options, their effects and side effects. 4. Education regarding fatigue management.

3.4 Nursing Considerations Related to Treatments of Myasthenic Patients

Treatments used to manage and treat myasthenia gravis may include cholinesterase inhibitor medications (pyridostigmine [Mestinon®, Regonol® and Mestinon TimeSpan® formulations] and neostigmine [Prostigmin®]), immunosuppressive; corticosteroids (prednisone or prednisilone) and immunomodulatory drugs (azathioprine, cyclosporine, cyclophosphamide, methotrexate and mycophenolate mofetil), plasma exchange (PLEX), intravenous human immunoglobulin (IGIv) and surgical thymectomy (Table 3.4) (Sanders and Howard, 2007). The nurse plays an important role with each of these therapeutic modalities in terms of patient assessment, administration and education. The duration of treatment is individualized and variable depending on disease course, comorbidities and treatment adverse effects, tolerance and efficacy. Information regarding management options to newly diagnosed patients is beneficial when given in both written and oral avenues, including a discussion of their unique situation. Individuals who have been treated for a longer period of time are often experts on their treatment regimes and its effectiveness. The treatment decisions are often shared between the patient and the health care team.

Every patient is wise to keep a medication list or diary with them at all times outlining the name of the drug, reason for taking it, name of ordering physician, dose, dosing schedule and date started. Changes in drug schedules or drug dose should be clearly documented (see Table 3.4). Changes made to drugs or drug schedules for side effects should also be documented. All medications and treatments including overthe-counter drugs, herbal preparations, injections, immunizations and intermittent drugs or treatments such as antibiotics should be kept in the medication diary.

Many medications (e.g. azathioprine, methotrexate, mycophenolate mofetil and cyclosporine) take several months to take effect. However, prednisone has a much faster onset time (weeks or few months determined by the protocol used). Prednisone may precipitate a steroid-induced exacerbation of the MG during the first several days after beginning treatment with high dose daily therapy or several weeks into therapy when treated with an incrementing dose protocol.

Many medications such as certain anesthetics, antibiotics are to be used with caution or not at all with the Myasthenia Gravis patient (See Section 11, Pharmacy Considerations). Live vaccines should not be used in those patients being treated with immunomodulatory therapy (See Section 2.15 and 11). The MGFA maintains a web-site listing possible drugs that could be dangerous or require special monitoring (*see references*).

3.4.1 Cholinesterase Inhibitors (ChI)

Several cholinesterase inhibitors are available for the treatment of MG. These include pyridostigmine bromide (Mesti-

non®, Regonol® and Mestinon TimeSpan® formulations) and neostigmine ([Prostigmin®).

These medications should be given with small amounts of food to minimize the risk of gastrointestinal upset. Some patients may experience gastrointestinal problems, commonly nausea, loose stools or diarrhea particularly in the initiation of the drug. They may be given a liquid form if there is a problem with dysphagia. The following nursing administration guidelines should be adhered to with these medications:

If oral intake is safe ChI may be administered 30-45 minutes pre-meals

- Be sure and have the physician prescribe the schedule and dose of the cholinesterase inhibitor that the patient takes at home, so that the pharmacy will not automatically place this medication on a default or standard schedule.
- These medications **MUST** be given on time, at the same schedule as the patient takes at home. The usual nursing rule of a 30 minute administration window before or after scheduled dose time does **NOT** apply with this patient population as the win dow of safety is much shorter. Medication admin istered too late may result in excess weakness and even the inability to swallow. Medication administered too early may result in excess cholinergic stimulation and toxicity. A 5 minute administration window may be used if the medication cannot be given precisely on time.
- **BE CAREFUL** and be sure and check the dosage before administration of any cholinesterase inhibitor. These drugs can cause a life-threatening myasthenic crisis if overdosed. If an overdose of drug is given there is no practical antidote available and the patient must be supported for respiratory or bulbar compromise.
- Post a sign above the patient 's bed indicating the schedule of each dose throughout the day. This information is helpful to other health professionals, for example physical therapy which can be evaluated when the patient is the strongest, approximately 45 - 60 minutes after a pyridostigrnine dose.
- Pyridostigrnine can be crushed and given per nasogastric tube, around the clock. The long acting pyridostigrnine (Mestinon TimeSpan®) should not to be crushed and administered through a gastric tube.

The most important concern with this class of medication is that of cholinergic crisis due to drug overdose. This can be hard to evaluate since the symptoms of muscle weakness could also be due to a myasthenic worsening or under medication. In such cases, the time of the cholinesterase inhibitor dose could provide crucial information. If the acute worsening of strength is 3 to 4 hours after dose, then it could be under medication due to the relatively short half-life of the drug. If increased weakness, e.g. slurred speech, dyspnea, increased diplopia, occurs within 15 to 60 minutes after dosage, this would indicate signs of an over-dosage, a possible cholinergic crisis. In some situations, the cautious administration of edro-

phonium with careful assessment of changes in examination may be useful. If this is to be considered, one must have the necessary emergency equipment available and extra personnel should there be an abrupt worsening of strength with the administration of edrophonium. If one is convinced the patient is overdosed on a CHI medication consideration should be given to holding the drug after thorough discussion with the treating physician. Careful and intense monitoring for signs of respiratory failure and increased weakness is mandatory.

3.4.2 Corticosteroids

Many MG patients are treated chronically with corticosteroid therapy. Prednisone is the most common corticosteroid used. The nurse must be an astute observer during the initial stages of corticosteroid treatment. Patients receiving high doses of prednisone are at significant risk for a steroid-induced exacerbation of their myasthenic weakness (See Section 2.8.3). This exacerbation may be severe enough to result in respiratory failure. Patients should be fully informed about the potential side effects of steroids so that appropriate preventive measures can be initiated. These include weight gain, Cushingoid appearance, acne, edema, hypertension, depression, insomnia, cataracts, glaucoma, osteopenia/osteoporosis, avascular necrosis of the hip, infection risks and possible diabetes mellitus.

The patient may have difficulties with body image should these side effects occur. The nurse can reassure the patient that these side effects will lessen or resolve as the steroid dose is reduced. Calcium and vitamin D supplementation should be included in this treatment to reduce the risk of bone demineralization. Bisphosphates may be necessary in more severe situations. Occasionally potassium salts are also indicated and serum potassium should be maintained in the mid-4 range as myasthenic patients often feel worse when their serum potassium is low normal or low. Nutritional counseling is recommended to help with food choices to offset weight gain and diabetes. Close follow up of these patients by the patient's local medical physician is essential.

3.4.3 Immunosuppressive and Immunomodulatory Drugs

Other medications (e.g. azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil) may be used to treat MG. Important considerations with these drugs are to inform the patient that these often take months to take effect and should be taken on a regular schedule. Blood tests for renal, liver or hematological side effects should be performed on a regular basis and monitored by the treating physician. The rationale for this should be explained to the patient in order to improve compliance. Education on immunosuppressive precautions against infection includes: good hand washing techniques and avoidance of individuals who have obvious viral or bacterial illnesses. It should also be emphasized that the patient should seek medical attention immediately when an infection is suspected.

TABLE 3.4 MYASTHENIA GRAVIS TREATMENTS COMPARISONS

DRUG	**Pyridostigmine Bromide (Mestinon®, Regonol®)**
DOSE	Usual dose 30-60-90 mg every 3-4 hrs during the day. Variations and further dose increases may occur per physician orders
ACTION	Prevents the breakdown of the neurotransmitter acetylcholine (ACh) allowing more ACh to accumulate at the neuromuscular junction. ACh is the chemical that transmits nerve impulses to the muscle. Increased ACh improves strength of muscles involved in eye movements, limb strength, swallowing and breathing.
POTENTIAL SIDE EFFECTS	• Abdominal cramps, diarrhea • Increased salivation, sweating, tearing or rhinitis • Muscle twitches, muscle cramps • Urinary urgency and frequency • Nausea and vomiting • Increased muscle weakness (at higher doses)
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	• May dissipate with time or if taken with food (e.g. crackers) . • Patients may require anti-diarrheal agents (eg. Kaopectate, Lomotil etc. per physician orders), especially if new to pyridostigmine or recent increased dose.

DRUG	**Mestinon TimeSpan®**
DOSE	180 mg at bedtime
ACTION	Same as pyridostigmine except long-acting may not be evenly absorbed/or tolerated. Therefore some patients prefer or respond better to short acting pyridostigmine during the night.
POTENTIAL SIDE EFFECTS	Same as pyridostigmine but more likely to occur
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	• Usually taken at night, in individuals who are very weak first thing in the morning, so a night-time regular Mestinon dose is not required • Should not be crushed, broken or chewed • Should never be substituted for regular Mestinon • Pill coating may be excreted in the stool, but this does not mean the drug has not been absorbed.

3.4.4 Plasma Exchange (PLEX)

Therapeutic apheresis or plasma exchange (PLEX) is widely accepted as a means of rapidly reversing myasthenic weakness. Plasma exchange protocols [volume of exchange, frequency of procedures] will vary among centers and the reason for which the procedure is being performed. The PLEX procedure requires transient anti-coagulation with acid-citrate-dextrose solution or heparin and an extracorporeal fluid volume be removed from the patient. Replacement solutions include saline, albumin, hydroxyethyl starches: hetastarch (Hespan and Pentaspan) or fresh frozen plasma. Each has its own benefits and risks and the nursing staff should be aware of them. Because large bore infusion needles are often used, the antecubital region should be protected from random blood draws. Heat and squeezing exercises may help preserve these veins for the PLEX procedure. In some instances, a central line maybe necessary if more peripheral access is not available.

During the PLEX procedure, the nurse should monitor the patient for changes in weakness, hypovolemia and possible allergic reactions. Close observation of administration sites for evidence of infection particularly if a central catheter or administration port is used. Dosages and timing of medications may need to be altered during the PLEX procedure. For example,

DRUG	**Prednisone/Prednisilone**
DOSE	5 -60 mg daily or alternate day schedule
ACTION	Is a steroid, which is normally produced by the adrenal glands (a small gland above each kidney) and is responsible for essential body functions. In higher doses, prednisone can suppress an overactive immune system. In MG prednisone may be used as long-term therapy or for an acute exacerbation.
POTENTIAL SIDE EFFECTS	• Stomach upset • Increased appetite and weight gain • Swelling and shortness of breath (due to fluid retention) • Hypertension • Hyperglycemia/diabetes • Muscle cramps • Mood changes **With long-term use:** • Oteopenia/osteoporosis • Cataracts, glaucoma • Acne • Easy bruising • Delayed wound healing • Prone to infections • Muscle weakness (rare) • Change in menstruation • Cushingoid appearance • Buffalo hump In children, may delay growth
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	Prednisone often works to improve symptoms within 1-2 months depending on the dose and disease severity. • Prednisone needs to be gradually tapered and not stopped suddenly • Take with food to reduce stomach upset • Unless instructed otherwise, the entire dose can be taken in the morning • Prednisone may interact with other medications, all doctors, dentists and pharmacists need to be informed • If prone to stomach ulcers, may require protective medications • Low sodium (2000 mg), low fat, low carbohydrate diet to prevent weight gain and fluid retention • Check blood pressure regularly • Watch for signs and symptoms of diabetes • Bone building medications, extra calcium and vitamin D may be ordered • Monitor weight • Encourage a healthy potassium rich diet • Nutrition counseling • Encourage exercise within ability

DRUG	**Azathioprine**
DOSE	2-3 mg/kg, (50-300 mg)
ACTION	Myasthenia gravis (MG) is an autoimmune disorder where the body's immune system attacks a protein on the muscle surface. By suppressing this abnormally active immune system, Imuran may allow some recovery from this autoimmune attack. The exact way that Imuran works in MG is unknown. It is thought that treatment with Imuran results in fewer antibodies available to attack the acetylcholine receptors at the neuromuscular junction. This may allow a return of motor function and strength.
POTENTIAL SIDE EFFECTS	• Stomach upset • 5-10% chance of increased liver enzymes • 5-10% chance of decreased white blood cell count • 1% chance of flu-like illness with 1 week of starting lmuran • theoretical risk (probably not in MG) of cancer - lymphoma, skin cancers • Gl upset • Mild nausea, vomiting • Loss of appetite • Mild hair loss • Skin rash • darkening of the skin and fingernails
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	If azathioprine is working, there is a gradual improvement after about 6-12 months with: • Increased strength • Need for less pyridostigmine and possibly corticosteroids Symptoms of concern that should be reported to physician include: • Fever, chills, sore throat • Muscle or joint pain • Flu-like symptoms • Unusual tiredness or weakness • Stomach pain with nausea and vomiting (severe) • Unusual bleeding or bruising • Yellowing of the eyes and skin

DRUG	**Azathioprine *continued***
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	• Azathioprine may cause mild bone marrow suppression or elevation of liver enzymes. • Blood tests (complete blood count, ALT, AST, ALP, GGT) need to be done regularly to monitor for significant changes. This is usually done once a week for the first 8 weeks and then every month or two thereafter for as long as you are taking Imuran. • To prevent or lessen stomach upset, the drug and be taken with meals, and with spreading out the doses through the day. • The medication should be stored away from heat and direct light. • Before receiving immunizations check with the doctor. • Avoid direct contact with other persons who have an infection. Regular hand washing is a good preventative measure to lessen the risk of infection. • Inform physician if taking any other medications, especially allopurinol, or blood pressure/heart medication. In some cases these might interact with lmuran. • The physician needs to discuss other rare complications such as infertility in women of childbearing age or an increased risk of certain types of cancers.

longer acting medications may be held if the procedure is performed in the morning and given immediately following the procedure. In contrast, cholinesterase inhibitors should not be held. There is the potential that the exchange procedure may clear the drug from the patient. It is therefore necessary that close monitoring of patient's strength be done. A unique idiosyncratic reaction may occur in patients undergoing PLEX and receiving concurrent angiotensin-converting enzyme (ACE) inhibitor therapy (Owen and Brecher, 1994). Anaphylactic or atypical reactions, characterized by flushing, hypotension, dyspnea and bradycardia, have been reported. It is recommended that ACE inhibitors be withheld for at least 24 hours before that procedure.

3.4.5 Intravenous Human Immunoglobulin (IGIv)

Intravenous human immunoglobulin (IGIv) is also used in situations similar to PLEX. The IGIv protocols will vary among treating physicians and the specific problem for which it is being administered. Allergic reactions are uncommon and most adverse effects are of minor significance. Fever and chills are frequently seen during or within 24 hours of the administration of IGIv. This may be treated with aspirin, acetaminophen, or anti-inflammatory medications such as ibuprofen or small doses (25 mg to 50 mg orally) of diphenhydramine (Benadryl®). Intense headache is relatively common and may be treated as if it were a migraine headache. Rarely

DRUG	**Cyclosporine**
DOSE	Dosage variable dependent on height, weight, and other medications Monitored and adjusted according to serum trough levels. Doses to be given q 12 h.
ACTION	Potent immunosuppressant and may be used in serious case of MG where other treatments have been less effective
POTENTIAL SIDE EFFECTS	• Stomach upset • Hand tremor • Increased hair growth (face and arms) • Gingival hyperplasia • Headaches • Visual changes • Hypertension • Hyperkalemia • Hypercholesterolemia • Renal failure • Prone to infections • Swelling • Seizures • Gallbladder problems
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	Trough blood levels of cyclosporine are required (e.g. 2x per week) until ideal drug dose is determined. Extreme vigilance is also required with frequent cyclosporine monitoring during any drug change i.e. old drugs stopped, doses increased or decreased and when new drugs are added. Blood tests are to be done fasting and before your morning dose. Interaction with other medications and grapefruit juice is high. Pregnancy and breastfeeding is contraindicated. Drugs are to be kept away from children and stored at a stable room temperature.

the patient may experience aseptic meningitis, thrombosis of renal, coronary or cerebral vessels. IGIv products differ regarding their composition but whether this has any impact on patient response is not know. It is, however, recognized that those individuals with vascular occlusion risk should receive product low in osmolality.

DRUG	**Mycophenolate Mofetil**
DOSE	500 -1500 mg q 12 h
ACTION	Suppresses the immune system, that is overactive in MG.
POTENTIAL SIDE EFFECTS	• Gl upset • Nausea, vomiting • Heartburn • Diarrhea, constipation • Acne • Tremors • Headache • Prone to infections • Bone marrow suppression • May slightly increase risk of skin cancer or lymphoma
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	• Take on an empty stomach, 1hr before or 2 hrs after a meal • No antacids which contain magnesium, or aluminum hydroxide • Must use birth control • Breast feeding contraindicated There are many drug interactions, have pharmacist check. CBC and differential blood monitoring required q 2 weeks x 6 then monthly.

DRUG	**Intravenous Immunoglobulin (IGiv)**
DOSE	1-2 gm/kg over 2-5 days May be administered via mediport, portacath, PICC line, heplok, saline lok or direct venous access. IGiv must be infused in a separate dedicated infusion line.
ACTION	IGiv is a blood product. It is prepared from thousands of healthy donors and processed to separate the immunoglobulins (antibodies) from other blood products, and then purified and concentrated. The length of time required for each treatment is approximately 4 to 6 hours, depending on the amount of IGiv that is being given and the infusion rate. The onset of improvement may take a few days to a week or two, although this is variable IGiv therapy may be done in combination with other therapies (e.g. immunosuppressant) IGiv is composed of immunoglobulins, also known as antibodies. These antibodies seem to regulate or control the abnormally active immune system.
POTENTIAL SIDE EFFECTS	• Gl upset • Nausea, vomiting • Heartburn • Diarrhea, constipation • Acne • Tremors • Headache • Prone to infections • Bone marrow suppression • May slightly increase risk of skin cancer or lymphoma
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	Common but mild side effects consist of: • flu-like symptoms (headaches, rash, low grade fever, joint pains, muscle aches, chest and abdominal pain) More serious side effects but fortunately these are rare. • As with any blood product there is always a possibility of an allergy and an "anaphylactic" reaction • More severe headache can occur during or after treatment with IGiv. This is called "aseptic meningitis", and is not secondary to an infection but instead is because of a chemical reaction, which produces inflammation of the covering of the brain (the meninges). • IGiv may increase the tendency for blood to clot, which may produce clots in the leg veins (a deep vein thrombosis) or rarely a pulmonary embolus. • In rare instances, a cerebral stroke has occurred. • Other rare complications include a form of anemia (hemolytic anemia), or more serious skin rashes, which can produce the loss of skin over the palms of hands and soles of feet. • Infection with a virus such as HIV, hepatitis B or hepatitis C. is rare.

DRUG	**Intravenous Immunoglobulin (IGiv)** ***continued***
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	They are almost always short-lived, lasting only for the duration of the infusion (which usually takes several hours per day) or up to several hours after the infusion has stopped. These side effects can be treated by either changing the rate of infusion (how fast it is given through the intravenous) or with simple treatments such as acetaminophen (Tylenol). Some patients may require pre-medication with Acetaminophen, an anti-inflammatory agent or Diphenhydramine, to prevent known side effects in susceptible individuals. • Anaphylaxis can be life threatening but fortunately is extremely rare (less than one in ten thousand). During the initial stages of IGiv administration close monitoring and if this occurs the infusion is stopped and treatment is required. • The severe headache is usually short-lived (several days at most) but can be severe. This also is uncommon, probably less than one in one thousand at most. • Some individuals may experience side effects due to a specific brand of IGiv and its components. Therefore the prescriber may change the brand of IGiv at subsequent infusions in order to reduce the side effect profile. • Kidney failure is usually reversible. Individuals who already have kidney disorders or who are dehydrated are more at risk of this. • There has not been a documented case of transmission of one of these viruses from an IGiv preparation for at least the last five years. There cannot be an absolute guarantee that some as yet unrecognized virus, which cannot be tested for, could not make its way into the blood product and be passed on. The methods of preparation used should inactivate all known viruses and therefore should protect against this possibility.

DRUG	**Plasma Exchange (apheresis, PLEX)**
DOSE	4-6 treatments over 6-14 days or 1-2 x per week until improved and then tapered off. PLEX protocols are individualized. PLEX may be performed via arm veins or a central line e.g. perma-cath system.
ACTION	Plasma exchange appears to help many of the same neurological diseases that IGiv is used to treat. The plasma that is removed during PLEX is replaced by another blood product called albumin, with similar risks. In MG, the abnormal anti-acetylcholine receptor antibodies are removed and this improves muscle strength, at least temporarily.
POTENTIAL SIDE EFFECTS	Common: • Hypotension • Feeling faint • Dizziness • Blurred vision • A "cold" feeling • Sweating • Abdominal cramps Rare: • Bleeding due to anticoagulants used to keep blood from clotting during treatment • Tingling of lips, eyes, fingers, toes • Allergic reaction to replacement solutions (albumin, a blood product) • Infection risk with indwelling catheters
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	Plasma exchange generally shows similar benefit to IGiv, but usually has a slightly higher rate of side effects than IGiv.

DRUG	**Thymectomy**
DOSE	Surgical removal of thymus gland (hyperplasic or a thymoma in some patients) Approach: • Transcervical • Transthoracic • Endoscopic
ACTION	Done by surgeon by when MG is stable and/or immunosuppressive drugs are low dose. Done to decrease the severity of myasthenic symptoms and improve long-term outcome.
POTENTIAL SIDE EFFECTS	• Post-operative chest pain • Post-operative recovery is individualized (4-8 weeks) • Scarring
MANAGEMENT OF SIDE EFFECTS & SPECIAL ISSUES	Treatment with Plasma exchange or IGiv preoperatively may be arranged. Benefits of thymectomy may take months to years.

NOTE:

1. This is only a partial list of some of the more common or serious potential adverse effects.
2. These medications and treatments may be used in combination. It is not unusual for pyridostigmine, prednisone and one of the other immunosuppressant agents to be used to control MG. The treating physician will determine and monitor the treatment regimen.

3.4.6 Thymectomy

Thymectomy, the surgical removal of the thymus gland, reduces or stabilizes symptoms in many cases. The patient should be educated as to the OR experience, recovery room and ICU facilities prior to surgery. Tours of these facilities are often a way to help ease the patient's anxiety particularly if the patient is a child. Preoperative teaching regarding incentive spirometry is important as post-operative chest discomfort will inhibit deep inspiration and predispose the patient to atelectasis and pulmonary infection. Education on how to turn in bed, compress the chest when coughing and the irritation of the trachea with suctioning are important points. Close post-operative observation of the patient's pain level, respiratory status and muscle strength is necessary. Women should be instructed in the use of a post surgical bra to minimize tension on the sternotomy wound and sutures.

3.5 Myasthenic Exacerbation and Crisis

Myasthenic crisis is a term that is used to describe a condition where the muscles that control breathing weaken to the point that ventilation is inadequate, creating a medical emergency and requiring a respirator for assisted ventilation. This condition can happen quickly with little or no warning and requires immediate emergency medical care. Monitoring of the respiratory status should be done routinely. Observe the patient for signs of shortness of breath or increased respiratory effort. Obtaining NIF and FVC measurements may give clues to potential problems. One distinctive characteristic of the MG patient during evaluation of respiratory strength is that the blood gas or oxygen saturation percentage is not a good indicator of respiratory strength. Myasthenia gravis does not interfere with gas exchange itself, but the capacity of the chest muscles to support respiration.

3.6 Nursing Education of the MG Patient

Most educational needs have been addressed as the specific topic was discussed. Some other recommendations include:

- Reinforce to the patient and their family that this disease can be controlled in most cases and that the patient can live a normal and productive life with MG.

- Contact support groups" such as the Myasthenia Gravis Foundation of America (MGFA) state chapters to receive literature and meeting schedules.

- Be sure the patient is aware of all interactions that other drugs have on MG. Recommend a Drug Inter action Card be carried. This is available from MGFA. Wear a Medic-Alert bracelet or medallion inscribed with: "Myasthenia Gravis. Use Drug Precautions.

- Consult with the treating physician before taking any other drugs, e.g. antibiotics.

- Be sure the patient is aware of the possible birth defects that can occur with some MG drugs. If the patient wants to become pregnant, consult with her treating physician.

- Adjust eating routines so that the patient's medication is optimal, approximately one hour after medication dose. Small frequent meals and soft foods are recommended.

- Plan ahead activities that require more energy during the strongest time of day.

3.7 Lifestyle Management of the MG Patient

The best management of Myasthenia Gravis includes education to understand MG, compliance with the medical regimen and following a healthy lifestyle. The points listed below can be used to discuss health and wellness for patients with MG.

3.7.1 Good Nutrition

- Weight Control -low fat foods, lean protein, good carbohydrates and caloric intake based on age, gender, height, weight and activity level. If on steroids excess calories and carbohydrates can increase risk for diabetes and weight gain. Healthy weight pro motes well-being.

- Low Sodium -to reduce edema, breathing and other health problems. This is especially important due to fluid retention secondary to steroid medication.

- Potassium (bananas, avocado, broccoli, potato, citrus fruits, fish, dairy). Potassium depletion can occur due to corticosteroid treatment.

- Calcium (dairy, green leafy vegetables, broccoli, cauliflower, egg yolks, lentils, soft bones of salmon and sardines) for strong bones and teeth. This is especially important for patients on long term corticosteroids (prednisone) who are at risk for bone loss. The recommended daily amounts via supplements or foods are Calcium 1500mg + 800 IU Vitamin D daily.

3.7.2 Physical Activity and Exercise

- Patients should check with their doctor regarding exercise restrictions especially if they have been sedentary for a long time, are overweight, have heart disease or other chronic illnesses.

- Start slow and gradually increase the intensity and duration of activities as an individual becomes more fit.

- Choose activities which are enjoyable, add variety, bring along a friend.

- Wear comfortable clothing, proper fitting footwear. Do not over exert or become fatigued.

- Adjust the Cholinesterase inhibitors (Pyridostigmine) dosing before exertional activities as directed by neurologist or plan activities at the peak of Pyridostigmine effect.

3.7.3 Stress Management and Coping Skills

- Stress can worsen symptoms of Myasthenia Gravis.

- Progressive relaxation, yoga, deep-breathing, physical activity, visualization, adequate rest and proper nutrition help reduce stress.

- Support groups, stress management programs, socialization and religious/spiritual activities enhance coping skills and reduce stress.

- Psychological counseling may also be beneficial.

3.7.4 Infection Control and Health Maintenance

- Proper hand washing (20 seconds with soap and water, dry well, lotion on dry skin)

- Maintain good dental care and oral hygiene.

- Avoid large crowds and individuals with upper respiratory infections or other contagious illnesses.

- Keep current on immunizations as advised by the health care provider.

- Note: "live" vaccines are to be avoided (see medications and MG in this manual). The timing of immunizations is important especially if patients are immunosuppressed and should be discussed with the treating physicians.

- Keep medical appointments for health care monitoring and treatment.

3.7.5 Medication Guidelines

- Patient should keep a current medication card/list.

- Patient should have copy of MG contraindicated medication list.

- Have physician contact the neurologist, pharmacist as needed or check MGFA web site for "Medications and MG reference for health professionals" for further information regarding medication guidelines for MG. Patient can also check with neurologist regarding new meds.

3.7.6 Emergency Alerts

- Use emergency alert such as bracelet, neck chain and wallet card.

- ICE (In Case of Emergency) use on cell phone to contact family members or significant others.

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For medication interactions listings:
www.myasthenia.org/docs/MGFA_MedicationsandMG.pdf

For educational material or Support Groups contact the Myasthenia Gravis Foundation of America:
www.myasthenia.org.

4

Anesthesia Issues

Brian Barrick and Robert Kyle

4.1 Anesthetic Considerations in Patients with Myasthenia Gravis

As with any patient, a preoperative evaluation begins with a focused but complete history and review of systems. It almost goes without saying that a myasthenic patient should be under the care of a neurologist who specializes in treating these individuals. Initial questioning should focus on current symptoms. Patients with no symptoms or ocular symptoms only will tend to fare better than those with limb weakness or bulbar symptoms (dysarthria, dysphagia, etc.). Patients with more severe symptomatology should be referred to their treating neurologist for adjustments or additional treatment before elective surgery. For more urgent cases, more severe symptoms may point to a need for continued postoperative ventilation. The anesthesiologist will want to know how long the patient has been diagnosed with myasthenia gravis, what the presenting symptoms were and how this compares to current symptoms.

Every patient with this condition should be asked if he or she has trouble laying flat. Stridor or subjective shortness of breath in the supine position may indicate thymic hyperplasia severe enough to compress the trachea. These patients present a challenge because the induction of general anesthesia (with cessation of respiratory drive and relaxation of the tracheobronchial tree) may lead to airway compression severe enough to prevent ventilation of the patient even with an endotracheal tube in place, a potentially deadly situation. Such patients require airway management (intubation) with maintenance of spontaneous respiration, perhaps even awake.

The patient should be asked about symptoms of cholinergic excess. Symptoms such as excessive salivation and respiratory secretions, GI symptoms, weakness, bronchospasm, or bradycardia (manifest as syncope) especially recent, may indicate that the dose of cholinesterase inhibitor should be adjusted. Many patients with cholinergic excess will have symptoms severe enough to present to an emergency department and will have been managed appropriately before elective surgery.

4.2 Anesthetic Considerations of Concurrent Medications in the Myasthenic Patient

Several medications taken by myasthenic patients have safety implications for the patient undergoing anesthesia. Cholinesterase inhibitors which act by blocking the degradation of acetylcholine include pyridostigmine (e.g., Mestinon®, Regonol®) and neostigmine (Prostigmin®) may be necessary to maintain the patient's strength. Arrangements should be made so this medication can be administered prior to anesthesia induction and at appropriate time intervals after recovery from anesthesia. Intramuscular administration of the drug should be use if a parenteral route is necessary. Adjustments in the dose are necessary (see Table 2.2, Section 2). Intrave-

nous injections may exert their effects too quickly and may precipitate cholinergic excess.

Corticosteroids are a commonly used immunosuppressant drug. As anesthesiologists are well-aware, steroids can produce many side effects. These include impaired wound healing, increased blood glucose, GI ulceration, osteoporosis and increased infection risk. Patients who have been on chronic steroid therapy may need supplemental steroid doses to deal with the stresses of moderate to major surgery, though this is a source of controversy.

Cyclosporine is a drug that selectively inhibits activation of T-cells. Its most important side effect is nephrotoxicity that may pose some difficulty for the anesthesiologist. It can also interact with neuromuscular blocking drugs, an important consideration in MG (Marczin N, 2004). Azathioprine, a purine analog, and methotrexate, a folic acid analogues, target immune cell replication. They may lead to bone marrow suppression, liver toxicity, nephrotoxicity and other less serious effects (Marczin N, 2004). Again, these complications may alter the anesthetic management of the patient.

In addition to the usual focus on the airway and the cardiopulmonary system during the physical exam, the anesthesiologist should focus on exam findings that demonstrate the patient's strength and point to the possibility of an anterior mediastinal mass. The patient should have brisk, coordinated eye movements. With the patient supine, one should listen over the trachea with a stethoscope for stridor and check for tracheal deviation. Ask the patient to breathe deeply and assess his/her vital capacity. Lastly, do a brief neurologic exam to assess the strength of all four limbs.

Laboratory studies are dictated by the patient's current medications, the anticipated stress of the surgery and any other comorbidity. A chemistry panel (including blood glucose) is usually warranted for moderate to major surgery. Abnormalities in electrolyte concentrations can interfere with neural conduction and exacerbate muscle weakness. Patients on immunosuppressive drugs should be evaluated for renal function (BUN, creatinine) and current potassium level. A complete blood count may indicate bone marrow suppression (anemia, leukopenia and/or thrombocytopenia) and a potential need for blood products. Liver function tests (coagulation studies can be grouped here) are also indicated in patients taking immunosuppressant agents. Drug levels (cyclosporine, etc) are probably of more value to the treating neurologist and to those who will care for the patient postoperatively. A chest x-ray is a good screening tool. One can look at lung volumes and gauge a patient's vital capacity. One can also look for mediastinal widening or tracheal deviation.

One area of controversy, not only for myasthenic patients, is which patients should receive pulmonary function tests (PFT's) preoperatively. These tests may be of use in patients undergoing thoracic surgery, especially lung resection. Lung volumes can be directly measured and spirometry can determine the presence of restrictive or chronic obstructive pulmonary disease. In addition, flow-volume loops can be used to de-

termine if there is an intrathoracic obstruction as one might see with an anterior mediastinal mass, especially if there is decreases flow during the expiratory phase. Most of the information above can be derived from the history and physical. There are two groups of patients who may benefit from PFT's. The first is those who are undergoing lung resection. Spirometry and lung volumes can be used to gauge if a patient will tolerate the planned resection. The second is those who are undergoing thoracic or upper abdominal surgery who have a pulmonary comorbidity (COPD, etc). The combination of disease processes may severely hamper respiratory mechanics. This may lead an anesthesiologist to consider epidural analgesia for a procedure that opioid medications would cover for most patients, or plan for postoperative ventilation earlier in the course of evaluation.

Some myasthenics may benefit from being admitted to the hospital before the planned procedure. Such patients include those undergoing a relatively urgent procedure who have not yet been medically optimized and those undergoing thymectomy because they are refractory to medical treatment and those with a recent cholinergic crisis. In addition to adjustments in medication doses, these patients may benefit from plasma exchange or intravenous immunoglobulin therapy. The decision to admit a patient is usually made by either the treating neurologist or attending surgeon. However, an anesthesiologist who encounters a myasthenic patient whom he/she feels is not optimized prior to surgery should consider postponing surgery and suggesting that additional therapy take place as an inpatient.

4.3 Role of Neuromuscular Blocking Agents in the MG Patient

Patients with myasthenia gravis (MG) may present for surgery for multiple reasons. In particular, patients who require general anesthesia present additional challenges. Based on their pathology, these patients have altered neuromuscular function and as such, altered (exaggerated and prolonged) response to neuromuscular blockade (NMB). In the non myasthenic patient, we frequently use NMB as an adjunct to our anesthetic agents to provide akinesis and a "balanced anesthetic". The use of NMB in MG patients may defeat the goals of avoiding prolonged intubation/ventilation and limiting impairment of neuromuscular function postoperatively. If at all possible, we avoid the use of NMB in MG patients. However we would consider use of NMB to improve surgical exposure and provide an element of patient safety for certain procedures. In particular, delicate procedures such as neurosurgical, neuroradiologic, microvascular and perhaps ophthalmologic procedures deserve this consideration.

In order to safely and effectively use NMB in patients with MG, the anesthesiologist must have a sound understanding of the altered response to these drugs in association with MG. For example, the decreased number of motor end plates at the neuromuscular junction makes these patients more resistant

to the depolarizing NMB agent succinylcholine (SCh). MG patients require a larger dose to obtain the same degree of relaxation as seen in a patient without MG. Eisenkraft, et al (Eisenkraft JB, 1988) demonstrated in a limited study that the ED50 and ED95 for SCh for MG patients were 2 and 2.6 times respectively what one observes for non myasthenic patients. However, the dose of SCh we typically use for induction (1 to 1.5 mg/kg) greatly exceeds the ED95 of non myasthenics, so the dose may have to be increased only slightly to achieve adequate, rapid relaxation (1.5 to 2 mg/kg). SCh is metabolized by the enzyme pseudocholinesterase in the bloodstream, normally within minutes of administration. In patients treated with cholinesterases, pseudocholinesterase activity is also decreased. This means that the patient may have a more prolonged effect of the drug.

By contrast, MG patients are extremely sensitive to nondepolarizing NMB agents. They display profound weakness after much smaller doses than would be expected from the non-MG patient. This is due to the decreased number of acetylcholine receptors at the motor end plates becoming more saturated by the NMB agent, not because MG patients have altered clearance of these drugs. By this same reasoning, a given dose of a nondepolarizing NMB will have a more prolonged effect in an individual with MG than a nonmyasthenic. However, it should be noted that an equipotent dose of nondepolarizing NMB (measured as suppression of twitch height in a train of four) probably has the same duration of effect in a myasthenic patient (Nilsson E, 1990). When one chooses to use these agents as part of an anesthetic, the use of small doses, the use of a neuromuscular twitch monitor and vigilance on the part of the anesthesiologist are essential.

When choosing the appropriate anesthetic management for a patient with MG, several things should be considered. The first is whether a general anesthetic is required for a particular case. Perhaps a regional technique (spinal, epidural, or nerve block) may be all that is required. This is especially true of orthopedic and peripheral vascular cases. In cases where a regional anesthetic is contraindicated, general anesthesia can be used, with the patient maintaining spontaneous ventilation through a device such as a laryngeal mask airway (LMA). The majority of surgical cases, however, require controlled ventilation, particularly intrathoracic, intra-abdominal and intracranial cases. In general practice, NMB are used during induction of anesthesia along with narcotics and IV induction agents to achieve intubating conditions (e.g., akinesis, vocal cord relaxation and reduced hemodynamic response to airway manipulation). During the maintenance phase of anesthesia, NMB's are often used to facilitate mechanical ventilation. For MG patients, other means of achieving these ends are available.

One option for induction is to use an increased dose of the chosen IV induction agent (e.g., propofol, thiopental, etomidate). Propofol is often chosen because is it more effectively cleared than other agents (barbiturates in particular) with more complete arousal and fewer residual effects. A dose of 3-4 mg/kg has a rapid onset and, from experience, effectively blunts hemodynamic response to airway manipulation. This technique

is not without consequences. Increased doses of all induction agents cause profound vasodilation and a resultant decrease in blood pressure which may be detrimental to patients with cardiovascular or cerebrovascular disease.

Situations where use of NMB for anesthetic induction has merit in patients with MG include the need to emergently secure the airway in unstable patients or those with high risk of aspiration, induction of anesthesia for patients in whom profound hypotension is contraindicated and those cases where NMB is deemed necessary for the maintenance of anesthesia. For emergent cases where rapid sequence induction for securing the airway is essential, the use of SCh is standard of care. As stated above, a larger dose may be required in a myasthenic patient to achieve rapid intubating conditions. One must keep in mind the potential for prolonged duration of action and the need for post-procedure ventilation. When using a nondepolarizing NMB for induction, neuromuscular twitch (NMT) monitoring is used to titrate the agent to the desired effect. This means the patient should maintain at least one pretetanic twitch in a train of four. During the maintenance phase, the desired effect is also to maintain at least one pretetanic twitch so that paralysis is readily reversible with IV cholinesterase inhibitors (e.g. pyridostigmine, neostigmine).

Akinesis during the maintenance phase of an anesthetic can be achieved without NMB. The basic technique involves using one of a variety of agents to achieve a deeper plane of anesthesia than is typical for the particular case in a non-myasthenic patient. Agents at one's disposal include an increased dose of inhaled volatile agent (e.g., isoflurane) as well as various adjuncts, including propofol infusion, narcotic boluses or infusion (remifentanil can be considered if rapid emergence is desired), or dexmeditomidine infusion. Bear in mind that all of these agents have the potential to cause hypotension and may need to be countered by a pressor agent (usually a vasoconstrictor such as phenylephrine).

4.4 Anesthetic Monitoring of the MG Patient

Anesthetic monitoring of these patients deserves some discussion. We use ASA standard monitors (ECG, blood pressure cuff, pulse oximetry, capnography and temperature) for every patient. The use of the NMT monitor is especially important to use in all patients who receive NMB, but more frequent monitoring of twitches and more attention to redosing NMB are warranted in MG patients. The bispectral index (BIS) is a tool that allows anesthesiologists another gauge of anesthetic depth (in addition to vital signs, akinesis, pupillary response). It uses a proprietary algorithm to process a frontal EEG and display a number to represent sedation level, with 0 being no EEG activity and 100 meaning awake and alert. Its most frequent use is in trying to prevent intraoperative recall, with a BIS below 60 considered low likelihood for recall. Since most cases with MG patients involve using a relatively deep plane of anesthesia, recall is not likely. However the BIS can be used to titrate anesthetic depth toward the end of a case. For example,

the BIS can be used to lessen anesthetic depth with skin closure (allowed to drift toward 60) so that emergence can occur in a timely fashion. Other hemodynamic monitors, such as arterial lines and central lines, should be dictated by the patient's other comorbidities and the complexity of the case, not simply because the patient is myasthenic.

Optimization of neuromuscular function preoperatively is paramount for successful perioperative outcome.

Anesthetically, we need to limit any agents we administer during surgery that may inhibit muscular strength or depress respiratory function. This is not limited to NMB, as will be discussed below. The struggle is to combine optimum preoperative treatment with effective intraoperative management such that the patient can emerge from anesthesia with peak strength and have limited or no respiratory compromise. Effective postoperative analgesia is an important link in this chain as well.

4.5 Concurrent Medications During Anesthesia

As previously mentioned anesthesia is accomplished with no or only minimal muscle relaxants. This serves to preserve the function at the neuromuscular junction (NMJ) and removes a major source of confusion should the patient have weakness postoperatively. Despite the anesthesiologist's best efforts, other medications given either preoperatively or adjunctively during anesthesia can interfere with neuromuscular function. The best example would be aminoglycoside antibiotics, which can impair both preand post-NMJ function. Aminoglyciodes may be administered for perioperative infection or infection prophylaxis. These drugs can lead to weakness by themselves or prolong muscle relaxant action when administered during the case. Myasthenics may be exposed to antidysrhythmics intraoperatively, which have also been linked to impaired NMJ function. Lastly, anticonvulsants and antipsychotics have been shown, at least in experimental settings, to impede NMJ function. These drugs would include phenytoin, lithium, haloperidol, droperidol and amitriptyline that may have been administered prior to surgery and anesthesia (Adams SL, 1984).

4.5.1 Pain control in the Post Anesthetic Myasthenic Patient

Narcotics have a blanket warning for myasthenic patients. This is not due to NMJ dysfunction, but rather the depressant effect on respiratory drive. There is some evidence that cholinesterase inhibitor medications can exacerbate the depressant effect of narcotics (Adams SL, 1984). This combined effect, together with the baseline neuromuscular dysfunction in myasthenic patients, makes it critical that narcotics be given in a monitored setting. This does NOT mean that narcotics should be avoided postoperatively. Narcotic analgesics are very effective and necessary to treat postoperative pain, even in myasthenic patients. Patient controlled analgesia (PCA) works well for postoperative pain. PCA allows more timely titration of medications, limits large narcotic peaks and troughs and with

the appropriate dose and lockout limits provides and element of safety. Regardless of the method used, prudent administration and monitoring is mandatory (Dillon FX, 2004).

Other modalities of postoperative pain management are useful in myasthenic patients. Non-steroidal analgesics (NSAIDS), acetaminophen and local anesthetics placed at the surgical incision are helpful adjuncts for postoperative pain. Regional anesthetics (nerve blocks, epidurals, spinals) might be useful for certain procedures and can often be both the anesthetic and postoperative mode of analgesia. The benefits of these modalities need to be weighed against the unique risk of myasthenic patients.

For example, spinal anesthesia to the level of T4 in a normal patient may be sensed as mild shortness of breath in normal patients. This is due to some of the accessory respiratory muscles being impaired by neuromuscular blockade to the T4 spinal nerve level. This same spinal spread in a myasthenic, however, may cause outright respiratory failure due to the spinal's effect and the already impaired function (weakness) of the primary and secondary muscles of respiration. Next, case reports of thoracic epidurals for thymectomy in myasthenics have been linked to profound bradycardia. The proposed mechanism is that the cardiac accelerator fibers in the midthoracic region are being blocked by the epidural's local anesthetics (transient sympathectomy), combined with the parasympathetic effect of concomitant cholinesterase inhibitor medications and relatively higher acetylcholine levels (White MC, 2004). While these are usually rare occurrences, these examples illustrate that there is no single and simple method to caring for these complex patients.

4.6 Emerging Anesthetic Strategies for the MG Patient

Anesthesia for myasthenic patients continues to evolve. What is emerging from the data, though, is that what is given for anesthesia is not as important as how anesthesia is administered (with the exception of muscle relaxants). Della Rocca, et al (Della Rocca G, 2003) demonstrated that patients maintained during anesthesia with either sevoflurane (an inhaled anesthetic) compared to those maintained with propofol (an intravenous anesthetic) were equally successful at being immediately extubated postoperatively. The rate and type of postoperative complications were both minimal and similar in both groups. Both groups did not receive muscle relaxants during anesthesia. The bottom line is that the exact agent used isn't as important as the conduct of anesthesia, namely goal directed anesthesia designed to affect respiratory function and drive the least. The foundation (as emphasized throughout this text) is to avoid muscle relaxants and preserve ventilatory function throughout anesthesia when at all possible.

Effective respiratory function is the goal for all patients receiving general anesthesia, particularly the patient with MG. The ability to both ventilate effectively, as well as protect one's airway by having intact reflexes and sufficient coughing strength are the usual endpoints. Objective data for successful extuba-

tion would include the ability to follow commands ("open your eyes," "stick out your tongue"), regular respiratory pattern (>10 and <24 breaths per minute), tidal volumes of 5-7ml/kg ideal body weight, negative inspiratory force of at least –20cm water and a sustained head lift of at least 5 sec. (Banoub M, 2001). Research has shown that respiratory failure is most strongly related to preoperative pyridostigmine dose, reflecting the patient's illness severity. Banoub and Kraenzler (Banoub M, 2001) state that pyridostigmine doses of >750 mg/day place a patient at highest risk for postoperative ventilation, while Mori et al (Mori T,2003) showed risk of postoperative reintubation and ventilatory support to be strongly related to a dose of only 240mg/day.

Medical management, including cholinesterase inhibitor medications, intravenous immunoglobulin therapy and plasma exchange are effective at treating and alleviating myasthenia gravis symptoms. A chance of curing myasthenia gravis requires surgery, namely thymectomy. Thymectomy has been shown to either cure or reduce symptoms in a significant number of patients. White and Stoddart (White MC, 2004) state that in children a remission rate of 60-67% has been reported using 7.7 to 10.1 year follow-up periods. Banoub and Kraenzler (Banoub M, 2001) more generally state that thymectomy, in combined age reporting, produces 20% remission, 40% marked clinical improvement with reduced cholinesterase inhibitor use, 20% clinical improvement with no change in preoperative medication dosage, while 6% have no benefit.

Patients presenting for thymectomy need to be prepared maximally for surgery. Symptomatic patients should take their cholinesterase inhibitor medications up to the point of surgery. Those patients who require plasma exchange should have it as close to the surgical date as possible. Myasthenic patients should be the surgeon's first case of the day, to limit the risk of prolonged NPO periods and missed oral medication doses. A general anesthetic is required. Muscle relaxants should be avoided, if possible, or titrated closely with the use of neuromuscular twitch monitoring. Following surgery, these patients should be followed in an intensive care setting to allow close respiratory monitoring, surgical blood loss recording and to provide the safest environment for intensive but closely monitored analgesic administration. Surgery should only take place in a facility able to provide ICU monitoring (with or without mechanical ventilation), expert nursing care and a skill ed neurology service (White MC , 2004; Della Rocca G, 2003).

Myasthenia gravis patients face numerous challenges in the perioperative period. Virtually any medication administered during the perioperative period can have potentially adverse effects for the patient. Surgery and anesthesia may impair, either physically or pharmacologically, respiratory function. Postoperative pain management and neuromuscular monitoring require specialized and intensive care. A strong understanding of medication pharmacology, myasthenia gravis pathophysiology and teamwork will allow these patients to be treated effectively and safely. Putting our egos aside and asking for assistance when caring for these patients is of utmost

importance. The managing neurologist, surgeon, ICU and ward nurses and the anesthesiologist are a team that must dedicate themselves in an integrated fashion to the care of these unique patients.

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5

Emergency Care Issues

H. Alexander Krob

5.1 Myasthenia Gravis in the Emergency Department

Myasthenia Gravis (MG) is an acquired disorder of fatigable weakness of ocular, bulbar, respiratory, and other striated muscles. The prevalence of disease is about 20 per 100000 population, and the incidence is 2 to 5 cases / yr / 1000000 population. Many cases are undiagnosed (Harrison T, 2006; Sanders DB, 2008). In myasthenia gravis, auto-antibodies are formed against the nicotinic acetylcholine receptor (AChR) on the postsynaptic (muscle) membrane of the neuromuscular junction, leading to inactivation or destruction of the AChR and to variable failure of neuromuscular transmission. Prompt and correct identification and treatment of the myasthenic patient in the emergency department is critical.

5.1.1 Modes of Presentation

Emergency department encounters with the myasthenic patient typically involve one of three scenarios:

1. The stable myasthenic patient with unrelated issues

2. The myasthenic patient with an acute exacerbation of myasthenic symptoms

3. The patient with previously undiagnosed MG with new onset of symptoms

The first scenario is the most common. In these patients, the challenge for the emergency practitioner is to identify the presence of the disease through history taking, and to avoid therapies that may aggravate the weakness. The second scenario is discussed below under Myasthenic Exacerbation and Myasthenic Crisis. The third scenario, although uncommon, represents a diagnostic challenge for the emergency practitioner that can be answered by careful history taking, evocative physical examination techniques, and bedside confirmatory testing.

5.1.2 Symptoms

Case reports demonstrate that MG can present with symptoms ranging from isolated vocal cord paralysis to those mimicking vertebrobasilar stroke (Cridge PB, 2000; Libman R, 2002).

The hallmark of myasthenia gravis is fatigable or variable weakness. This temporal variation is often not noticed or spontaneously reported by patients. The examiner must elicit this key element of the history through directed questions to reveal symptoms that are worse at the end of the day, following exertion, or after prolonged activity.

The most common symptoms of myasthenia include ptosis or diplopia, which together account for two thirds of all presenting complaints. Ptosis often begins as a unilateral or asymmetric problem that can be unnoticed by the patient but revealed in photographs. Diplopia is usually variable and worse with activities requiring sustained gaze (watching television, driving, reading). Around one-sixth of patients present with com-

plaints of bulbar muscle weakness such as difficulty chewing (especially with tough foods, e.g. meat, lettuce), problems swallowing (both food boluses and thin liquids), and trouble speaking (hypophonia, nasal or breathy voice or dysarthria). Ten percent of patients present with complaints of limb weakness (Sanders DB, 2008). Limb weakness may be frank, subtle (such as stumbling when walking over rough and uneven surfaces), or vague (exercise intolerance). Respiratory symptoms and respiratory failure are uncommon presenting symptoms, although many patients have measurable respiratory weakness.

It is unfortunate that many patients with MG go undiagnosed, or improperly treated, despite numerous evaluations by various primary care practitioners and specialists. MG should be included in the broad differential diagnoses of numerous ophthalmologic, gastrointestinal, pulmonary, and neurologic complaints.

5.1.3 Physical Examination

Immediate attention must be directed towards evaluation of the airway, breathing, and circulation in patients presenting with respiratory compromise, or who are otherwise unstable,. Respiratory muscle weakness is common in MG, and it is important to note that patients with respiratory weakness may be severely dyspneic, hypoxic, or hypercarbic without evidence of tachypnea, agonal respirations, or distress.

Formal breathing capacity testing should be performed on patients with known or suspected MG. Negative inspiratory force (NIF) should have a magnitude greater than 30 (less than 20 is an indication for mechanical ventilation). Vital capacity (FVC) should be greater than 1.5 liters (values less than 1.5 mL / kg are an indication for mechanical ventilation). When formal breathing capacity tests are not immediately available, screening can be done at the bedside by having the patient count slowly upwards from 1. Patients should be able to count to 20 without taking a breath. Elevation of the head of the bed to 30 degrees or more may reduce aspiration risk, intrathoracic pressure, and work of breathing.

Bilateral positive airway pressure (BiPAP) may delay or eliminate the need for endotracheal intubation (Mazia CG, 2003; Rabinstein A, 2002). Rapid sequence intubation may be performed without the use of neuromuscular blocking drugs that may cause further respiratory deterioration (Politis GD, 2007).

Routine general and neurologic examinations may be augmented by provocative physical examination techniques. Ptosis and ophthalmoplegia may be elicited by asking the patient to maintain gaze for 180 seconds. Sustained resistance or repetitive testing may elicit proximal limb weakness.

5.2 Testing for Myasthenia Gravis in the Emergency Department

Although the diagnosis of myasthenia gravis is usually confirmed by antibody testing and neurophysiologic techniques (see Section 2), these techniques are time consuming and not useful to the emergency clinician. In the emergency department, two methods are recommended to aid in the diagnosis of myasthenia gravis: the ice pack test, and the edrophonium (Tensilon®, Reversol®, Enlon®) test (see Section 2.7.1 and 2.7.4).

5.2.1 Ice Pack Test

Subphysiologic temperatures are known to improve neuromuscular transmission, possibly by reducing the activity of acetylcholinesterase. In patients with unilateral or bilateral ptosis, a bag or surgical glove filled with ice and wrapped in a towel is placed over the ptotic eye for 2 minutes. A positive test results when ptosis is measurably reduced in the cooled eye. Ideally, the results can be demonstrated with before-and-after photographs. The degree of ptosis can also be measured by considering the iris as a clock face and noting where on the face of this clock the lid intersects the iris. The test is reported to be 80% sensitive, and highly specific for myasthenia gravis. Added benefits of the test are that it utilizes materials commonly found in the emergency room, it is noninvasive, and lacks side effects (Saavedra J, 1979; Golnik KC, 1999).

5.2.2 Edrophonium Test

A more standard, but invasive, test is the edrophonium (Tensilon®, Reversol®, Enlon®) test (see Appendix 2.4; Osserman KE, 1952). Edrophonium chloride is a cholinesterase inhibitor with an effective duration of action of less than five minutes. The first step in the edrophonium test is to identify a clinically weak muscle. For limb muscles, this requires that the patient exert full effort both before and after the test. It is generally considered more reliable to evaluate ptosis or ocular muscle weakness. The test is often done in a blinded or double-blinded fashion with the use of a placebo, but this may not be practical in an emergency setting.

Administration of edrophonium chloride can have cardiac side effects including bradycardia, hypotension, loss of consciousness, and asystole. The test should be performed in a setting with immediate access to a “crash cart” with appropriate resuscitative equipment and medications (including atropine). The complication rate is reported to be 0.16%, but may be higher in patients with asthma, cardiac dysrhythmia, or in those taking atrioventricular blocking agents (Roberts JR, 2004; Ing EB,2000). Furthermore, a number of patients are sensitive to the effects of edrophonium and develop cholinergic side effects (salivation, lacrimation, and increased bronchial secretions). For this reason, pretreatment with atropine 0.5 mg IV is recommended.

After pretreatment with atropine, 10 mg of edrophonium chloride (available at a concentration of 10mg/mL)

is drawn up into a 1cc syringe. Direct injection into a vein is preferred rather than using IV tubing in order to be assured of the amount of drug administered. Additional syringes of normal saline should be available to be used as placebo (if desired) and as flush. A test dose of 2 mg (0.2 ml) of edrophonium is injected. The observer should assess for signs of intolerance and of improvement in the weak muscle. If no effects are noted after 1 minute, the remaining dose is given as aliquots of 3 mg and 5 mg at 1 minute intervals. Any change in the weak muscle is considered a positive test and no further injection is needed. This may then be followed by testing using the placebo. A positive test occurs when the observer notes objective improvement in the weak muscle over a period of 2 to 5 minutes, followed by return of the weakness over the next 5 minutes.

The edrophonium test is about 90% sensitive under ideal conditions, but false negative results can occur (Osserman KE, 1966).

5.3 Management of Myasthenia Gravis in the Emergency Department

Patients with MG present a management challenge to the emergency provider. Those with stable disease may develop worsening of symptoms following treatment with drugs commonly used in the ED, while patients with unstable disease may experience variability in symptoms due to various influences on immunologic and cholinergic tone.

5.3.1 Medications to Avoid

The list of medications that must be avoided or excluded completely in the treatment of the myasthenic patient is extensive. A list is maintained on the Myasthenia Gravis Foundation of America website (www.myasthenia.org; Pascuzzi RM, 2000). Some of these medications are commonly used by the emergency physician and are categorized below by class.

- Antibiotics: especially fluoroquinolones ("-floxacin" drugs), aminoglycosides ("-mycin" and "-micin" drugs), and ketolides (telithromycin)
- Beta blockers: metoprolol, labetalol, and ophthalmic beta blockers (timolol)
- Calcium channel blockers: verapamil
- Psychiatric drugs: haloperidol
- Critical care drugs: neuromuscular blocking agents (all)

Please refer to Section 11 for a more complete discus sion of medications that adversely affect MG.

5.3.2 Myasthenic Exacerbation and Myasthenic Crisis

Myasthenia gravis is a fluctuating disease. The disease state is a function of immunologic and cholinergic tone as the final

endpoints in a complex physiologic relationship. Myasthenia exacerbation is a broad term that may be defined as any provoked increase of weakness of bulbar, respiratory, or limb muscles. Myasthenic crisis may be defined respiratory failure necessitating assisted ventilation resulting from myasthenic weakness (Juel VC, 2004). The approach of the emergency provider towards either of these conditions must be to ensure the stability of the patient's airway, breathing and circulation. After the patient has been stabilized, attention can be directed towards discovering the underlying cause of the worsening symptoms. The list of possible causes is protean and can include:

- infection or inflammation
- drugs
- idiopathic processes (such as physiologic or psychological stress)
- endocrine disorders
- metabolic imbalance

With prompt identification and appropriate treatment, myasthenic crisis has a mortality of less than 5% (Lacomis D, 2005).

5.3.3 Cholinergic Crisis

A particular challenge to the emergency provider is the identification of cholinergic crisis. This condition is defined as respiratory failure due to overdose of cholinesterase inhibitors, and may present with symptoms very similar to those of myasthenic crisis. The condition is arguably less common in the current era, in which these drugs are no longer a mainstay of treatment, and are used in smaller doses. However, unintentional overdoses of cholinesterase inhibitor medications can occur. It is also important for the emergency provider to be aware that numerous compounds of commercial, agricultural, military and bioterrorism uses have cholinergic properties (see below). The mnemonic DUMBBELLS can be used to identify signs of cholinergic excess:

- Diaphoresis
- Urination
- Miosis
- Bradycardia
- Bronchial secretions
- Emesis
- Lacrimation
- Loose stools

The edrophonium test (described above) has been used to assess states of cholinergic excess or deficit. When administration of edrophonium results in worsening of symptoms, cholinergic excess should be suspected.

5.4 Transport of the Myasthenic Patient

Appropriate treatment of the unstable myasthenic patient requires consultation by a neurologist (preferably with neuromuscular expertise), access to an intensive care unit, and access to plasma exchange. If these resources are not immediately available, the emergency provider should consider referral and transport to an appropriate facility.

Transportation of the unstable myasthenic patient by surface or air ambulance must include the ability to provide continuous monitoring of respiratory function and breathing assistance such as BiPAP or endotracheal intubation and ventilation. As stated above, BiPAP may delay or eliminate the need for endotracheal intubation and ventilation, and rapid sequence intubation has been successfully performed without the use of neuromuscular blocking agents (Mazia CG, 2003; Politis GD, 2007; Rabinstein A, 2002).

5.5 Bioterrorism Posing as Myasthenia Gravis

Numerous compounds of commercial and agricultural use are readily available as agents of bioterrorism. These include organophosphates and carbamates that are commonly used as pesticides, and compounds with purely antipersonnel uses (the nerve agents sarin, VX, and soman). These agents have been employed for the purposes of bioterrorism such as the March 1995, terrorist attack on the subway system in Tokyo, Japan (Yokoyama K, 2006; Yokoyama K, 1996). The emergency provider must be aware of the uses of these compounds and alert to any suspicious circumstances. It is possible that patients with MG may be among the first to present with acute exacerbations in the event of a bioterrorism attack involving these substances.

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Psychosocial Issues: From Diagnosis to Lifetime Management

Kimberly M. Johnson

Myasthenia Gravis, as a chronic disease, has psychosocial aspects that are similar to those shared by other disease populations as well as aspects that are unique to the disorder itself. An individual with a newly diagnosed chronic disease begins the cycle of grieving a loss of health and elicits the cycle of denial, fear, anger, depression and eventual acceptance (Kübler Ross E, 2005). The newly diagnosed patient will spend a lifetime of cycling through these feelings as various life events create challenges for coping with the disease. As one patient noted, "As soon as you think you've come to grips with one thing, something else happens". It is important for the health care provider to incorporate the bio-psycho-social approach to treating these patients as psychosocial issues can impact the management of the disease. The challenge for the health care provider is to identify triggers that may lead to problems in disease management, such as stress, extreme heat, medication side effects, etc. and provide the resources needed to manage the disease effectively.

6.1 Impact of Disease on Body Image

Body image is a significant issue for the myasthenia gravis patient who may be faced with drooping eyelids, masklike facial expression (myasthenic snarl), surgical scars from a thymectomy and changes related to corticosteroid treatment. These changes can be frustrating and embarrassing for a patient who is very conscientious about being in the public eye. Changes in body image may lower self esteem and some may seek to cope by socially isolating themselves from the public. This may have an even greater impact for the patient who was socially active prior to diagnosis. A patient who withdraws socially may isolate themselves from the informal support network available (e.g. friends, special interest groups, church, etc.) that may play a vital role in helping the patient cope with the daily stressors that can impact the disease process. Patients may choose treatment options based on feelings about body image. For example, they may refuse prednisone therapy for fear that the drug's potential side effects will alter their body image. Further, a patient may ultimately self-discontinue the use of medications if they are dissatisfied with changes in body image associated with their use. A patient may opt out of having a thymectomy if having a surgical scar is an issue. Of critical concern is that the patient may not be forthcoming with this information to their treating physician. This may lead to disease management changes that would not have occurred otherwise and such changes may increase the treatment risk. For example, the patient may self-discontinue their immunodulatory treatment and the unknowing physician "increases the medication dosage with the belief that the previous dose was ineffective. Should the patient resume taking the drug the dose may then be "toxic"; increasing the risk for an adverse reaction. It is helpful to assess feelings related to body image to gauge what is important to the patient so that treatment options can be tailored toward the best possible outcome. It is also worthy of noting that sometimes family members may not understand the impact that the disease and side effects of medications may have on a patient. One patient describes the scenario of her husband purchasing a spa membership for her as he found her weight gain while taking prednisone to be unacceptable. She underutilized this spa membership and her husband became angered by the "waste of money". As is noted in the section on Physical Therapy, exercise must be carefully planned for the patient with myasthenia to avoid overexertion and exacerbation of symptoms.

6.2 Emergency Services

Muscle weakness is a unique aspect of the disease that is unpredictable and feared as it relates to problems that may be encountered in severe situations with breathing, swallowing and talking. This may pose an even greater fear for the patient who lives alone. The Lifeline® emergency response system is a device that may be worn by the patient and when activated, signals calls to individuals that can quickly check on the patient (Lifeline®, 2006). This alleviates the fear of not being

able to utilize a phone to contact emergency personnel in a crisis situation... The First Alert system can be installed and has an activation fee and monthly service fee. Many medical centers administer this service as well as local Council on Aging agencies. It is also a good idea for a patient to educate their local emergency personnel regarding potential respiratory/ communication issues so that emergency personnel can respond to a call in which a patient may not be able to effectively communicate their needs. Patients with myasthenia gravis should also consider purchasing a MedicAlert® (or similar) bracelet (www.medicalert.org; 1-888-633-4298) that can be worn at all times and alerts first responders that they have myasthenia gravis.

6.3 Advanced Directives

Completion of an Advanced Directive is a topic that is worthy of consideration for any patient with a chronic disease and a patient with myasthenia gravis is no exception to this rule. Advanced Directives are known as a Living Will and Health Care Power of Attorney. These documents are quite useful should a patient not be able to communicate their wishes during a time of crisis. A Living Will allows a patient to document wishes regarding the use of mechanical ventilation or artificial feeding should a patient be in a non-communicative state, terminally ill or in a vegetative state. Local hospitals usually have these documents available for patients to complete. Of important note, completion of these documents requires a witnessed and notarized signature. Copies of these documents should be filed with all treating physicians and medical institutions. The patient should keep the original documents in a secure place where they can be easily retrieved by family or friends should the need arise. A Living Will document does not allow for specifications in treatment such as "I would like to be on a ventilator for a week and if no improvement, taken off". With this document, a patient either chooses the treatment or not.

6.3.1 Health Care Power of Attorney

The Health Care Power of Attorney is very confusing to many in that this document is only valid should a patient not be able to make decisions regarding their own health care. In this case, the patient may appoint an individual to act as their health care agent during this time period. This document is commonly confused with a Durable Power of Attorney in which a person appoints an individual to handle financial affairs on behalf of the patient. A Health Care Power of Attorney is for health care only; however, a Durable Power of Attorney may include health care if this is written into the document. Durable Power of Attorney documents are prepared by attorneys not by the patient or their designee. Health Care Power of Attorney documents can be obtained from local medical institutions and must be witnessed by two individuals unrelated to the patient and share no common interests so that there can be no secondary gain from executing this document. Health care personnel are not allowed to witness these documents as this may be interpreted as a conflict of interest. The document must be notarized. If a patient has no Health Care Power of Attorney, the order for decision making on behalf of

the patient goes to the spouse and if the patient has no spouse, the children and if no children, the parents and lastly siblings and other extended family. A common issue that arises in these situations is with a patient who may be separated from a spouse. Until legally divorced, this spouse has decision making power unless another agent is specified in the Health Care Power of Attorney document. It is a good practice to complete both a Living Will and a Health Care Power of Attorney so that a patient is certain that health care directives are clear and the desired health care agent is making decisions should a situation arise that requires intervention. Common mistakes that patients make with these documents are:

1. not completing the documents accurately,
2. not having the documents witnessed and notarized and
3. not having the documents available when in need of them.

A patient should always make sure that a copy of these documents is given to all treating physicians and medical institutions and a copy accompanies the patient when traveling. The patient should keep the original documents in their personal files and make certain that family members or any health care agent has a copy. Many states have Legal Aid services available to disabled individuals with limited incomes to assist with legal issues such as Durable Power of Attorney, Disability Denials, or other issues that require legal counsel.

6.4 Energy Conservation

One of the perplexities for a patient with myasthenia gravis is judging the degree of muscle strength and not overtaxing the muscles. This is a balancing act that requires a patient to be in tune with their body and to “listen” to their body. Our bodies often remind us when we have overtaxed ourselves but for the myasthenic patient, it is important to avoid this altogether. This is an extremely important issue for the patient who exercises regularly. What may seem to be a simple walk from a parking lot, may prove to be overtaxing for the myasthenia patient who has overly exerted themselves on a given day. For this reason, a handicapped parking license may be a good resource so that a patient can conserve energy and avoid a potentially harmful situation. Handicapped parking applications may be obtained from the Division of Motor Vehicles for temporary or permanent handicapped parking. The application requires a physician signature to verify that such parking is needed by the patient. The Division of Motor Vehicles charges a nominal fee for this special parking permit. Of course, one of the issues with this is that muscle weakness cannot be outwardly seen and patients may be publicly ridiculed for “looking perfectly fine” and using handicapped parking. Educating the public about the disease will be a lifelong endeavor for those who have the disease and for healthcare providers. It is important for us to assure the patient that public ridicule is temporary but managing weakness is for a lifetime and “managing” is part of the balancing act.

Managing muscle weakness may evoke a major change in lifestyle for the patient with myasthenia gravis. Many times we hear people refer to themselves as a “morning” person or an “evening” person and this refers to times when an individual feels the most alert and energetic. For the myasthenic patient, the focus is on the time of day when they are feeling their strongest. This often coincides with rest and medication administration, but; nonetheless, it is important for the patient to be in tune with their body and know when they are feeling the strongest. This is the time to plan activities that require extra energy and strength and even this must be done in moderation [see section on occupational therapy]. The difficulty exists when life’s activities cannot be planned according to “best strength” time for the patient. Frustration arises as the patient is forced to make lifestyle changes centered on the disease process and may foster greater losses such as giving up old roles, finding new interests that are less physically taxing, or establishing shortcuts in daily routines. Adaptation to this change in lifestyle will vary from individual to individual based on personality types, where they are in the grief cycle and the degree of support available to them.

Patients may find themselves in need of assistive devices for walking or adaptive equipment for activities of daily living throughout the course of the disease. Physical and Occupational therapists can be instrumental in assessing these needs and facilitate obtaining necessary equipment. In the event that home modifications are needed, therapists can be helpful in determining the needed modifications. Agencies such as Independent Living or Vocational Rehabilitation may be resources for facilitating these modifications. The Americans with Disabilities Act of 1990 requires that all structures built after 1990 have handicapped accommodations as well as parking The ADA web site for information is www.ada.gov or a patient may contact the organization at 1-800-514-0301.

Residential structures built before the ADA Act are not required to make accommodations within a dwelling but are required to make accommodations for parking and accessibility outside of the dwelling.

6.5 Stress Management

Body image and muscle weakness may have a profound effect on sexual expression of the patient with myasthenia. Due to the sensitive nature of this topic, patients may not feel comfortable discussing this with a healthcare provider. It is helpful for the health care provider to affirm that in some cases, patients may experience functional limitations and decreased endurance during sexual practices due to muscle weakness. Medications may influence a patient’s ability to conceive and increase susceptibility to infections. This affirmation alone may encourage open communication about any issues that the patient may be experiencing. Couples should be encouraged to talk openly with each other. The myasthenic patient may want to consider planning intimacy during peak strength times, using techniques that require minimal energy and developing other frequent expressions of love and affection to strengthen

and reinforce sexuality in the relationship. Patients may consider seeking professional counseling services should this become an issue that jeopardizes the relationship.

Adapting to a major lifestyle change can be difficult for any individual and can create a stressful environment. Stress is a part of life and can be positive for motivational purposes and can be negative depending upon the severity and reaction to the stress. Even in a healthy person, emotional and physical responses to stress can compromise health. For a myasthenic patient, stress is one of the factors that may exacerbate the illness and have harmful affects on overall management of the disease. So, how do we alleviate stress you may ask? Since this is virtually impossible, we as health care providers must promote the use of stress management techniques and encourage patients to explore activities that lower stress levels. Patients may benefit from counseling services offered through local mental health centers or through the private sector in the community.

Support groups may also help the myasthenic patient develop strategies for coping with stress. Many states have local myasthenia gravis chapters that promote patient services, research, education and advocacy. Meeting other individuals with myasthenia gravis through these local chapters can be an invaluable resource for patients as well as afford them an opportunity to become involved with activities of the organization. The Myasthenia Gravis Foundation of America offers support and education and is a resource for information about local resources available to patients. The web site for obtaining this information is www.myasthenia.org or a patient my contact the MGFA Patient Services Division at 1-800-541-5454. While assessing a patient with myasthenia, it is important to understand what triggers stress, how they have coped with stress in the past and what kinds of activities may help them to relax and lower stress levels. Unfortunately, since stress will always exist to some degree, the health care provider should closely monitor its' effects on a patient with myasthenia.

Most individuals with a chronic illness have to plan special events, such as traveling, very carefully and the patient with myasthenia gravis is no exception to this rule. It is important for the patient to have access to medical information. There are some web based programs for purchase that will allow patient access to their medical information but whatever modality the patient pursues for obtaining this information, timeliness is of the utmost importance. Patients should be encouraged to discuss this issue with medical information administrators prior to any travel plans and know the most efficient means of obtaining medical information if needed. Patients need to know how to reach their treating MD and should have extra medication when traveling to avoid any complications that may occur in the event of lost or misplaced medication. The MedicAlert® bracelet would be especially helpful to wear during travel times and anyone traveling with the patient should at least be made aware of the illness in case a crisis arises and the patient's health care agent has to be notified. The patient should always have pertinent information such as a list of medications and those that are contraindicated, as

well as a copy of their Advanced Directive. There is a certain level of planning that occurs for anyone planning to travel but for the patient with myasthenia, more effort is needed to carefully address issues that may arise in management of this chronic disease.

6.6 Financial and Insurance Issues

Management of the disease with medication is also an important component when treating the myasthenia gravis patient. It is important to closely monitor the patient for side effects as adverse effects may discourage a patient from taking the medication. Encourage patients to talk freely about medications so that adjustments can be made if medications are found to be unsuitable. The goal is to achieve maximum increase in strength with minimum side effects. Some medications are taken on a fixed schedule that may require that a patient awaken during the night to take them. This may pose a problem for a patient who has difficulty awakening during the night. Some patients may require assistance from family members to awaken them or patients may need to set alarm clocks to coincide with medication administration. Regardless, this all equates to another lifestyle change as it is imperative that medications be taken timely and in proper dose. A patient with myasthenia gravis should have their medications with them at all times and should have extra medication, especially when traveling so that they are prepared in case the unexpected happens.

6.6.1 Medicare

The costs associated with medications for treating myasthenia gravis can be exorbitant and patients should be encouraged to closely review their insurance plans to determine medication coverage. In some instances, pharmaceutical companies may offer assistance programs for patients who meet criteria for financial hardship. The Medicare Part D program, which is effective beginning January 1, 2006, is a prescription drug program offered to Medicare recipients. Medicare Part D offers patients many different plans to choose from. Plan designs vary; therefore, patients should be cautious in choosing a plan that meets their coverage needs. Not all plans cover medications for the treatment of myasthenia. Once a patient has chosen a plan, the patient is not allowed to make a change in plans for at least a year. Individuals may apply for “extra help” with the Medicare D program by completing an application and submitting it to the Social Security Administration. “Extra help” eligibility equates to a waiver or reduction in certain fees. There are penalties involved for those Medicare recipients who did not choose a plan by the open enrollment deadline of May 15, 2006. Penalties may also be applied to those future Medicare eligible patients if they do not choose a plan within a certain period of time after becoming Medicare eligible.

So, how do we as health care providers assist our patients in choosing a plan? First, we should advise our patients to compile a comprehensive list of medications and dosages before exploring plan options. For assistance in choosing a plan, pa-

tients may visit www.medicare.gov or contact Medicare directly at 1-800-633-4227. Medicare published a handbook entitled, Medicare & You 200x that patients may find helpful in understanding the new drug program. Other outreach options for assistance include: SHIPP (Seniors Health Insurance Information Plan) at 1-800-443-9354. Patients with access to the internet may visit www.shiptalk.org. Local agencies such as Council on Aging; Elder Care; or Senior Centers may have representatives available to assist elders in choosing a plan. It is most important for the health care provider to address with the patient a plan for obtaining medications since medication management of the disease is a crucial part of the treatment.

The financial burdens associated with the disease can be overwhelming for a patient with myasthenia gravis. The patient is faced with the costs of medications, hospitalizations and periodic visits to physicians and other health care providers for maintenance of the disease. Patients should be encouraged to speak with financial counselors in the treating institutions to determine if payment plans can be established to reduce stress associated with payment for services rendered that are not covered by insurance. As discussed earlier, stress can have an adverse affect on the outcome of treatment and should be monitored in all aspects of disease management.

6.7 Vocational Challenges

Another aspect of myasthenia gravis is the vocational challenges that a patient may face. Beginning in the early stages of diagnosis, health care providers are often asked by patients, "Will I be able to continue working?" This is a question that cannot be easily answered and warrants much discussion with the patient since being gainfully employed equates to maintaining their livelihood.

One of the difficulties with myasthenia is that diagnosis may take some time and many remain uneducated about the disease. Symptom management may be inconsistent throughout the course of the disease such that a patient, who is capable of working one week, may not have the same capabilities the following week. Extreme absenteeism from work may present a problem for the patient with myasthenia. Decisions regarding vocational issues can be difficult to make since symptom presentation varies and it is often a fine line between consistently performing job duties and being disabled as a result of the disease. A major variable in this decision is, of course, the type of work that an individual with myasthenia does as it is important to factor in the amount of exertion required. The Americans with Disabilities Act of 1990 was instrumental in requiring employers to accommodate disabled workers and outlawed discrimination based on hiring, firing, or pay. Making reasonable accommodations for a disabled employee in no way negates the need for the employee to be able to perform the essential job duties on a consistent basis.

6.7.1 Employment Issues

Patients who have jobs that require physical exertion are at most risk for having difficulties performing job duties since

myasthenia gravis weakens muscles and manifestation of this muscle weakness is unpredictable. The Americans with Disabilities Act, which applies to all state and local government employers and private employers with 15 or more employees, requires that employers make “reasonable accommodations” for employees who can otherwise perform the “essential functions” of the job. Reasonable accommodations may include written material in large print or Braille, audiotape, sign language, interpreters or readers, or modified equipment or devices. In some cases, the employer may transfer the employee to a different position if a patient cannot perform “essential functions” of an existing job. If an employer does not have a transferable position, the patient may have to seek other alternatives. These patients may wish to consider a referral to Vocational Rehabilitation Services that provides skills assessment, job search and training for individuals with limitations due to a disability who may need to pursue another employment path. Vocational Rehabilitation Agencies are generally located in each county and the agency will schedule an interview with the patient once the health care provider initiates a referral. Vocational Rehabilitation may support patients in pursuing higher education for purposes of obtaining a new skill set for employment. A patient must be committed and medically able to continue gainful employment.

6.7.2 Disability

There certainly exists the category of patients who absolutely cannot participate in gainful employment of any nature or who work for a period of time and eventually have to terminate work because of the increasing manifestations of the disease. Social Security Disability may be available for patients who are not expected to be able to maintain gainful employment for a period no less than a year. SSDI (Social Security Disability Income) is for those individuals who have a previous work history and benefits are based on their contributions in the system. SSI (Supplemental Security Income) is for those individuals who may not have a work history but clearly are not able to be gainfully employed. These benefits are reduced but can provide a source of income for the disabled patient. Patients should visit their local Social Security Administration to inquire about these benefits or visit www.socialsecurity.gov . It is important to note that due to lack of education and the unpredictability of myasthenia gravis, disability is often difficult to obtain. Disability determination personnel may request that a patient visit one of their physicians for screening. This physician may not have sufficient knowledge about the disease thus leading to disability denial. It is important for the treating physician to carefully document the patient’s limitations when completing the documentation required by Social Security Disability. This will help clarify work limitations and alleviate any misunderstandings about the disease. A patient may appeal a disability denial three times.

Insurance coverage is another concern for patients with myasthenia gravis as medical care needs span over a lifetime. Patients who are employed may be vested with an employer who provides insurance even if a patient becomes disabled. Some

patients, who are employed, but are unable to continue with employment, may have the option of cobra coverage for at least a year once employment is terminated. The patient is required to pay a monthly fee to continue this coverage. Others may be eligible for Medicare two years after becoming disabled and others may qualify for Medicaid for the disabled based on income eligibility. The Social Security Administration administers Medicare benefits and The County Departments of Social Services administer Medicaid benefits. Patients are also encouraged to check with the State Insurance Commission to explore potential resources for insurance coverage through private plans.

6.8 Assisted Living

We have discussed extensively patients who are able to manage their disease and care for themselves at home. Now we must turn to the group of patients who are considered a very brittle myasthenic and cannot effectively care for themselves at home and lack family who can assist with their care. This is, in fact, a small percentage of the myasthenic population but; nonetheless, is worthy of attention. Patients have housing options such as Assisted Living or Skilled Nursing facilities that can provide the level of care needed and the choice is largely dependent upon the patient's capacity to care for self. Assisted Living facilities are not funded by Medicare but can offer assistance such as medication administration, meals and assistance with activities of daily living. These facilities are for the more independently functioning patient and can provide supervision for the patient 24 hours a day. Skilled Nursing facilities are covered, in part, by Medicare, Medicaid and some commercial insurances and can provide a higher intensity of care such as 24 hour nursing services and skilled services such as physical, occupational and speech therapy. Obviously, a huge concern of patients with myasthenia going into Assisted or skilled facilities is the degree to which staff are familiar with the intricacies the disease. Medication administration is of utmost importance as it must be timely and accurately dosed. It is important for therapies to be done at peak medication dosing in order to maximize a patient's strength and not overfatigue. It is important for the staff to understand the disease and know warning signs of crisis. Facilities are governed and licensed by State facilities services and patients should be encouraged to contact their respective State Facilities Services agencies to review strengths and deficiencies of any facility they are considering for housing.

Assisted Living facilities can offer therapy services through Home Health agencies and these services are covered by Medicare, Medicaid and some commercial insurance companies if patients qualify for services under the "homebound" status criteria of their policy. These services can also be provided in a home setting as well. Counties generally have numerous agencies that can provide these services. Therapists in these agencies are licensed to provide therapy services but, as mentioned previously, the degree of education about myasthenia gravis varies from agency to agency as well as professional to professional. Home Health services require a physician order prior

to arranging. The health care professional who is arranging these services should be cognizant of the degree to which the treating agency and therapists understands the disease and should use this referral process as an opportunity to provide additional education about the disease as indicated. Services should be closely monitored and any problems encountered should be directed to the attention of the physician.

6.9 Caregiver Issues

Just as it is important to know about myasthenia gravis and the psychosocial aspects of the disease, it is equally important to know how to care for ourselves as caregivers. Compassion fatigue among health care providers is often under recognized as our focus in the helping profession is on the patient, not ourselves. I would argue that a healthier approach to patient care would be to focus on caring for both ourselves as well as our patients. The only way we as health care providers can consistently and effectively manage patients is to consistently and effectively manage ourselves first. Just as the patient with myasthenia must recognize triggers to an exacerbation of illness, the health care provider must recognize when it is time to nurture and care for self. Nurturing one's self, in whatever form that takes for the provider, will lend itself to richer relationships with patients and a clearer perspective of the challenges facing patients in every day life. Patients are more apt to follow by example rather than follow the advice of a health care provider whose unspoken message is "Do as I say, not as I do". Sometimes, our actions as providers speak louder than words and the impressions we instill in our patients can have a lasting impact.

A patient once said, "Some of the most valuable lessons to learn about MG are the smallest ones which are

1. a power nap,
2. honesty with your doctor and
3. doing small things that make you feel good about your self".

Sorting through issues and feelings about the disease is a life-long challenge that will have ups and downs. A patient states, "The question is "Are you an MG patient simply coping with life or are you a real person who just happens to have MG?" Part of our goal as health care providers is to help every patient see that they are a person who just happens to have myasthenia gravis. We are there to provide the support and resources needed to make sure that every patient discovers that yes, there is life after a diagnosis of myasthenia gravis and while it may seem like a roller coaster ride, we are on that roller coaster together. We can truly make a difference.

6.10 References

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Lifeline® medical alert system. www.lifelinesys.com. Telephone: 1-800-797-4191.

MedicAlert Foundation International, 2323 Colorado Avenue, Turlock, CA 95382. www.medicalert.org. 1-888-633-4298

7

Physical Therapy Issues

Michael Thomas

Physical therapists should play an important role in evaluating muscular weakness, fatigability and functional mobility with patients with myasthenia gravis. With all neurological disease, competent physical therapy clinicians should use a thorough evaluation to link impairments and disabilities to appropriate, effective treatment and functional prognostication. This discussion will focus on specific components of the physical therapy evaluation which require special attention in the patient with MG, specifically, muscle weakness and fatigue. Each MG patient is unique and deserves meticulous attention to objective detail. There exists a significant disagreement in clinical practice and poverty of research data on the topic of exercise with MG patients.The physical therapy clinician must utilize a symptom-specific, objective approach with every evaluation. A close interdisciplinary approach with the primary or consulting MD is imperative to insure the patient's safety and best functional outcome.

7.1 Muscle Weakness in the Myasthenic Patient

The weakness presentation in generalized myasthenia gravis can be diverse from patient to patient but usually follows a specific pattern of proximal greater than distal involvement. Patients with significant bulbar disease can present with neck flexor weakness so that cervical postural alignment is difficult. Patients with proximal upper extremity weakness will have problems with activities of daily living (ADLs) above shoulder level. Patients with proximal lower extremity weakness will have difficulty with ambulating long distances and climbing stairs. The severity of the patient's weakness can be variable. Some patients may have generalized weakness so significantly that they can't lift their extremities against gravity more than a few repetitions. Other patients may only be affected by activities that are repetitive and induce fatigue. Medications such as pyridostigmine or neostigmine can also cause peak and trough dose strength variability. Diurnal variability also plays a significant role with patients that have significant myasthenic fatigue problems.

Because the myasthenic patient's weakness can be so variable with individual pattern and magnitude and can be influenced by many other factors, the clinician must use the most objective and quantitative motor evaluation measures available.

7.2 Using Hand-Held Dynamometry in Myasthenia Gravis

Manual muscle testing (MMT) has been used with many types of neuromuscular disease. MMT can be used in diagnosis and treatment evaluation with MG when the baseline weakness severity and post treatment changes are large. MMT has been shown to have questionable reliability within professional groups, and in our experience, is worse with comparisons across professional groups (Andrews WA, 1991; Van der Ploeg RJO, 1991; Nicklin J, 1987; Aitkens S, 1989). HHD conversely has better reliability when used by occupational and physical therapists who have clinical experience with the technique (Andrews WA, 1991). When evaluating MG weakness, HHD provides a more quantitative and reliable strength measure with muscle groups that can produce up to 70 pounds of force (Wikholm JB,). The use of HHD enables the therapist to provide more objective and quantitative strength measurements to assist in diagnosis, treatment effectiveness, and exercise prescription.

There are many types of HHD devices, both analogue and digital (Andrews WA, 1991). The sensitivity of either type is sufficient for testing human strength (Andrews WA, 1991, 1996; Van der Ploeg RJO, 1991; Bohannon RW, 1993; Nicklin J, 1987). The devices are relatively inexpensive, portable, and an experienced examiner can complete a strength exam in ap-

proximately the same time as with MMT (Andrews WA, 1991; Bohannon RW, 1997; Hyde SA, 1983).

7.3 The Clinical Application of Hand- Held Dynamometry

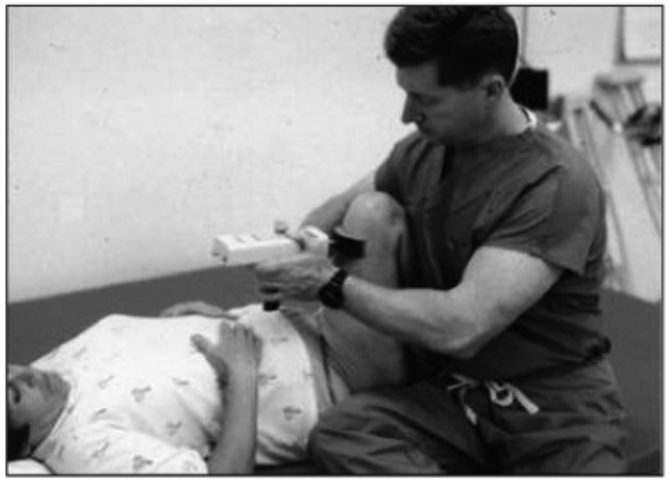
The type of test used with HHD is an isometric make test as compared to MMT, which utilizes an isometric break test (Andrews WA, 1991; Bohannon RW, 1990). The make test enables the patient to have more effort control and produces less force which helps to prevent pain from being a deterrent to producing their best effort. The pattern of motor involvement in MG is usually symmetrical, often is worse proximal and can be mild, moderate, or severe in magnitude. Bulbar weakness can also be present. The physical therapy motor exam in MG includes neck flexors, proximal and distal musculature. The pattern of motor involvement in MG is often stereotypical and usually correlates with the patient's primary functional complaints. The motor testing evaluation includes neck flexion, shoulder flexion, elbow flexion, elbow extension, wrist extension, hip flexion, hip abduction, knee extension, knee flexion and ankle dorsiflexion (Figure 7.1). Other musculature may need to be evaluated. The clinician will base the exam upon an initial general screening and the patient's history and comorbidities.

The testing protocol (Andrews WA, 1991, 1996; Bohannon RW, 1997) involves a series of 2 maximum effort repetitions, generated in two to three seconds, in standardized gravity eliminated positions that sample proximal to distal musculature (Andrews WA, 1996) (Appendix 7.1-3). A one-minute rest period between repetition one and two is maintained to insure the patient's best effort and to minimize the bias of MG fatigue. The variance between repetitions should be less than 15 percent and the higher of the 2 efforts is considered the patient's current level of strength. The criteria for significant worsening and improvement are also 15 percent variance. Comparison to available normative HHD values can be utilized to establish the severity and pattern of motor involvement (Andrews WA, 1996). Other important factors that must be recorded are the patient's current medicines and dosages, the time of day, and a statement regarding the patient's effort. Patients who are being treated with pyridostigmine will need to be tested consistently in regards with peak and trough dosages. If the patient's individual test integrity is partially compromised by substitution patterns, or any change from the standardized test positions is utilized, all deviations must be well documented to insure reliability. Every effort must be made to test at specified time intervals pre and post treatment protocols. (Table 7.1) Patients who have just been plasma exchanged must have a minimum of 2 hours to recover from the procedure before a posttest is done.

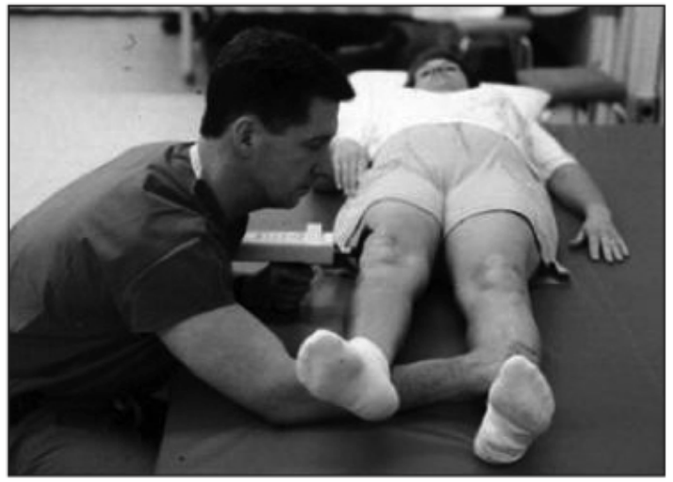
Hand Held Dynamometry

Strain Gauge

Lower Extremity



Hip Flexion



Hip Abduction

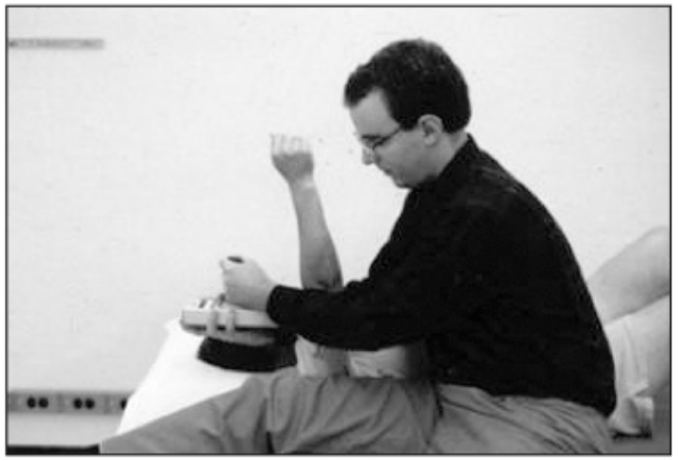
Knee Flexion

Knee Extension

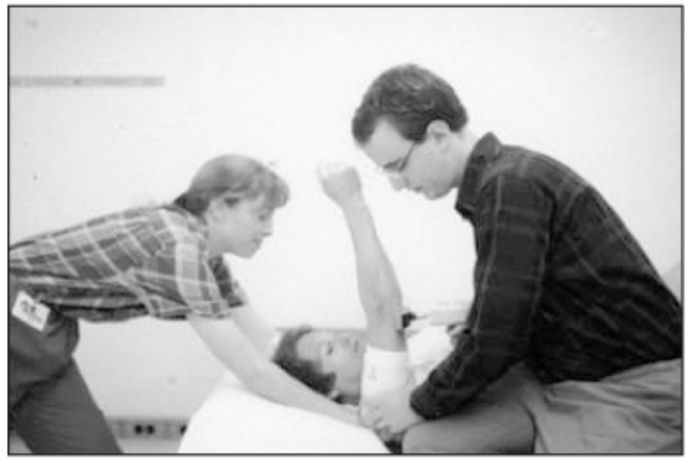
Ankle Dorsiflexion

Figure 7.1. A*. The testing positions for hand held dynamometery (HHD) in the lower extremity.*

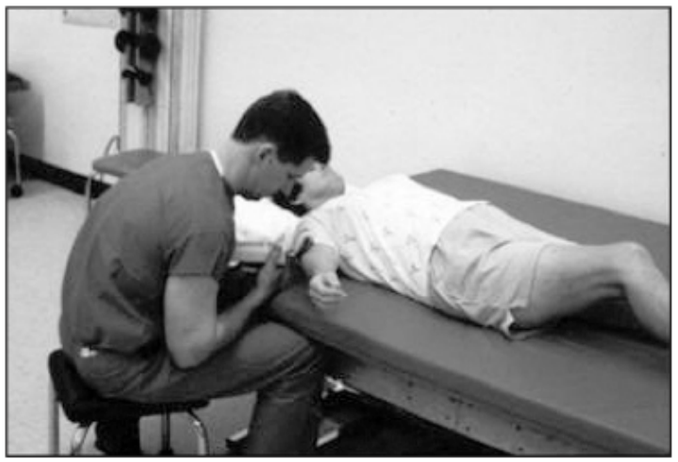
Upper Extremity



Shoulder Flexion



Shoulder Extension w/ Assist

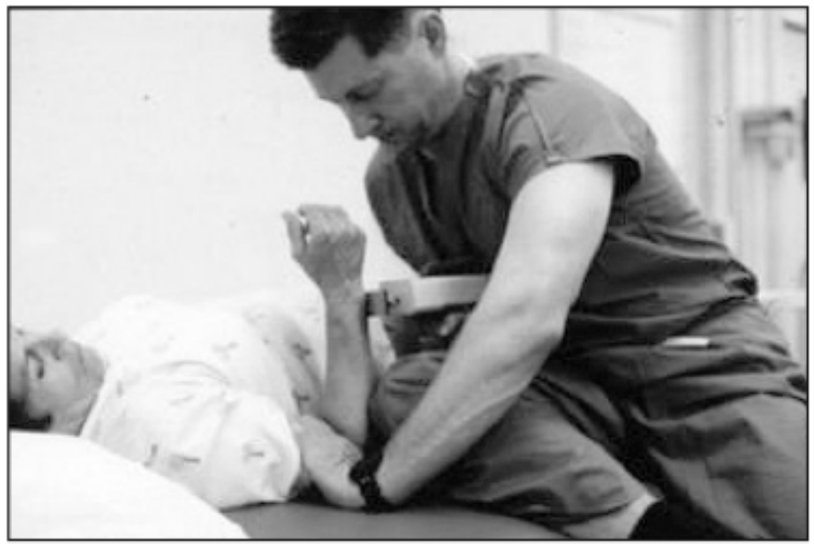


Shoulder Abduction

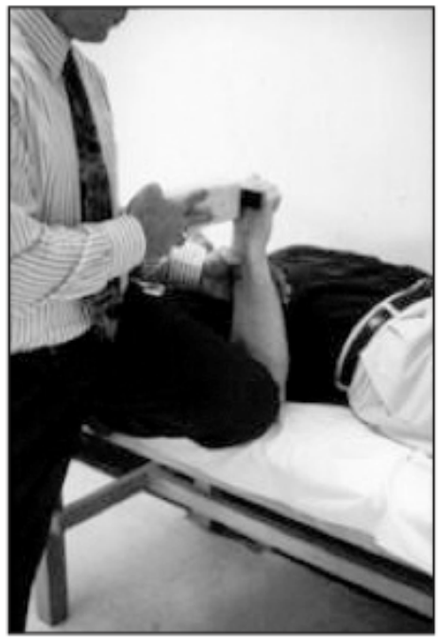
Shoulder Internal Roatation

Shoulder External Rotation

Elbow Flexion



Elbow Extension



Wrist Extension

Figure 7.1. B. *the testing positions for hand held dynamometery (HHD) in the upper extremity. Copyright Michael Thomas.*

TABLE 7.1 PHYSICAL THERAPY DIAGNOSTIC STUDIES

Patient Status	Manual Muscle Test	Hand-Held Dynamometry	Cardiopulmonary Tests
Diagnostic Evaluation	Yes	Preferred	Preferred
Edrophonium Test	Yes	Preferred	No
Pyridostigmine Dose Adjustment	Yes	Preferred	No
Pre & Post Plasma Exchange	Yes	Preferred	Preferred
Pre & Post Prednisone Induction	Yes	Preferred	Preferred
Pre & Post IGIv	Yes	Preferred	Preferred
Pre & Post Thymectomy	Yes (Pre only)	Preferred (Pre only)	Preferred

Fatigue can also be measured by HHD (Nicklin J, 1987). A series of 10 repetitions is utilized with 1-minute rest intervals between each contraction. A percent difference of the patient's worse and best efforts is calculated. If the difference is greater than 50 percent, the patient's fatigue is considered significant. This fatigue ratio is helpful to assist the clinician to adjust the level of activity and exercise for each patient. HHD values have been published for normal subjects ages 50 through 79 for strength levels but not for fatigue (Andrews WA, 1996). Strength values obtained by HHD also have been shown to have significant predictive value with ambulation ability (Bohannon RW, 1996).

7.4 Evaluation of Functional Endurance in Myasthenia Gravis

Evaluation of the ambulation parameters of distance and time has been used as an indicator of functional endurance with many diseases (Steele B, 1996; Butland RJA, 1982; Bohannon RW, 1996). Patients with MG, especially those with generalized motor weakness, often present with poor functional mobility. After significant proximal lower extremity muscle fatigue, gait compensation begins to require more cardiopulmonary support. Invariably, MG patients' ability to ambulate functional distances at reasonable speeds diminishes or fails. Pulmonary medicine has utilized the vigorous 6 minute walk test for many years (Steele B, 1996; Butland RJA, 1982), but MG patients can present with such incapacitating fatigue that the severe generalized or "brittle" patient would not tolerate a 6 minute long walk at maximum speed. Walk test literature reveals that the fastest ambulatory velocity occurs in the first 2 to 3 minutes (Butland RJA, 1982). After the initial burst of speed, the patient self paces his ambulatory velocity to the

length of the test (Butland RJA, 1982). Researchers have revealed that fast ambulatory speeds are required in functional emergencies such as crossing a street after walking a block. Lower extremity strength (measured by HHD) has been significantly correlated with maximum ambulatory velocities (Bohannon RW, 1996).

A 3-minute walk test is long enough to be functional and short enough to be tolerated by most MG patients not in crisis. When severe generalized MG patients present with poor respiratory function tests such as a low NIF or FVC, their ambulatory endurance can be too low for a 3-minute walk. In those cases, both the shorter ambulatory distance and ambulatory velocity can be used as a functional ambulatory endurance indicator (Bohannon RW, 1996). The PT clinician should always time the patient's ambulation for a specified distance and then calculate the patient's ambulatory velocity (distance divided by time). Normative ambulatory velocities are available in the literature to assist in determining functional deficit severity. All of the previously mentioned objective measures should be utilized to assist the treatment team to evaluate treatment efficacy.

When performing a 3-minute walk test, specific and standardized performance instructions are given to the patient before the test (Steele B, 1996; Butland RJA, 1982).

A distance-measured course with minimal turns and no distractions is used. Adequate and constant vocal encouragement throughout the walk must be used to facilitate the patient's best effort just as with all strength measurements. Objective monitoring of vital signs, ocular, and generalized symptoms must always be done. The measured parameters of the 3 minute walk, distance over time, can be compared to normal data and provide the individual patient's ambulatory baseline. Changes of greater than 1.5 feet/second are considered significant. The patient's total ambulatory distance in 3 minutes can also be referenced to normative data (Steele B, 1996; Butland RJA, 1982).

7.5 Exercise Prescription in Myasthenia Gravis

MG is classified into 5 symptom presentations. Treating stable MG with exercise is an interdisciplinary task. The specific symptom exercise programs given by the occupational and physical therapists and the speech pathologist must be coordinated with the patient's medical treatment. Consideration of the patient's total daily activity tolerance must be considered so that the patient is not overwhelmed by the sum of all the individual areas of therapeutic exercise. MG patients must also have the aptitude to learn how to monitor their symptoms at rest, with activity, and exercise. Progressive exercise overload must be individualized, of a moderate intensity only and tolerated by the MG patient. Exercise has not been shown to improve postsynaptic endplate dysfunction. The principle of specificity of exercise will produce and improve physiologic adaptations that occur as the consequence

of training. It is imperative that exercise is only used in conjunction with a stable patient whose medical treatment is actively managed. Clinicians must understand that MG patients who are exacerbating, can not monitor their own symptoms, and are not compliant with their medical care are at high risk of making their disease worse with progressive exercise. An exercise prescription is not appropriate until their MG is stable. Consistent exercise will elevate the patient's baseline functional capacity, which will diminish the effect of MG exacerbations

7.6 Patient Exercise Considerations

All stable MG patients who are exercising should consider the following 5 items:

"The dollar per day" rule: Patients should always use energy conservation with all daily activities. Patients should not exhaust themselves in the morning by using 75 cents of their "dollar" with exercise.

2. Exercise at "your best time of the day": Most patients feel their best in the morning regarding fatigue. But, some individuals are not "morning people".

3. Exercise at "peak dose pyridostigmine": the half- life of pyridostigmine is 4 hours. Patients should exercise at peak dose, which is usually 1.5 to 2 hours post dose.

4. Exercise large muscle groups: Patient exercise programs for MG should be short and build up to moder ate intensity only. Proximal muscle groups should be emphasized (such as shoulders and hips).

5. Moderate intensity ONLY: Patients have done too much when:

a. Patient's pulse increases greater than 30 BPM from resting to peak exercise.

b. Patient becomes short of breath at the peak of exercise.

c. Patient's MG symptoms become worse during exercise (example: ptosis or diplopia becomes worse).

d. Patient is still tired 2 hours post exercise.

e. Patient has severe residual muscle soreness next day(s) post exercise.

It should be always be remembered that the patient should consult with their treating physician before starting any exercise program.

7.7 Types of Exercise and Devices Utilized in MG

The following are available exercise methods for MG patients:

1. Walking: Begin on flat surfaces, comfortable pace, controlled environment (no busy streets, no temperature extremes).

2. Stationary ergometer: Both upright and recumbent bicycle can be used; exertion can be measured and controlled. Upper extremity ergometry can also be used.

3. Weight training: Use machines with safety mechanisms or light free weights. Utilize a 10 to 12 repetition system and no more than 3 sets per exercise. DO NOT OVERDO RESISTIVE EXERCISE TO THE POINT OF FATIGUE!

4. Treadmill: Is not a self-paced exercise, has the increased problem of the patient doing too much and causing fatigue.

5. Swimming: Patients should swim in water where they can touch the bottom. Deep water is dangerous and can cause patients to overexert. Always swim with a partner. Never swim in water with extreme temperatures. Extreme temperatures can significantly increase fatigue.

7.8 Clinical Case Studies

7.8.1 Outpatient/Clinic Example— New Diagnosis

Patient demographics: Female, mid-40's

Diagnostic workup: manual muscle exam, edrophonium test, single-fiber EMG

Current Symptoms: mild ptosis, mild proximal lower extremity and neck flexor weakness, mild dysphagia, unable to continue working eight hours per day

Medical history: none
Current Medications: Pyridostigmine 30 mg every 4 hours

Baseline Function (prior to onset of MG): independently ambulation without an assistive device at a community level; independent with all activities of daily living

Appropriate evaluative tests: Baseline motor weakness with HHD, utilize HHD to assist MD to improve objectivity and sensitivity with differences in motor weakness during edrophonium test, 3 minute walk to establish a functional ambulatory calculating both total distance and ambulatory velocities

Treatment strategies: Progressive ambulation as exercise in the AM at peak dose pyridostigmine. Patient taught to self-monitor exercise utilizing ptosis exam, talk test, and post exercise recovery (rest) time. Patient also documents status before, during, and after exercise in a daily exercise

7.8.2 Inpatient Example

Patient demographics: Male, 60's Diagnosis: myasthenia gravis five years ago

Current Meds: Prednisone 30 mg QOD, mycophenolate mofetil 1000 mg every 12 hours

Admitted: for a six-treatment course of plasma exchange (previously treated with plasma exchange six years ago, with improvement)

Current Symptoms: Diplopia in three out of four visual field quadrants

Moderately significant bilateral ptosis – OD: 1/3 of pupil covered at rest; worse with fixed gaze at 30 seconds, OS: covers entire pupil

Proximal upper extremity weakness, with MMT score of 3+/5; fatigues after five repetitions of active bilateral shoulder flexion

Fatigues with attempt to walk outside of hospital room and requires minimal assistance

Unable to perform activities of daily living that require prolonged shoulder flexion, such as combing/washing hair

Medical history: COPD, hypertension, osteoarthritis, chronic low back pain, prior myocardial infarction 10 years ago and status post Coronary Artery Bypass Graft on 3 occasions

Baseline Function (prior to current MG exacerbation): ambulates independently for limited community distances using single-point cane; needs some assistance with activities of daily living

Appropriate evaluative tests: Baseline motor weakness with HHD, 3 minute walk to baseline functional mobility pre and post plasma exchange, utilize pre and post plasma exchange HHD and 3 minute walk data to assist MD to evaluate treatment efficacy

Treatment Strategies: Progressive ambulation, stationary ergometry (bicycle, upper extremity ergometer), repetitive functional maneuvers (example-sit to stand), supervised pool/aquatic therapy, all closely monitored (self or assisted) with vital signs, Talk Test, ptosis scale, diplopia in visual fields, NIF's and FVC's. Use all tests to document patient's status before, during, and after (recovery) to establish patient's exercise tolerance, discharge activity levels, and home exercise program

7.8.3 Intensive Care Unit Example

Patient demographics: Female, 70's

Diagnosis: myasthenia gravis 10 years ago; has had four courses of plasma exchange treatments in the past for exacerbations of her weakness

Current medications: pyridostigmine, 60 mg every 4 hours, azathioprine 150 mg daily for the last 5 years; prednisone 30 mg daily, started three months ago at her local hospital

Admitted: from emergency department with respiratory distress for further management

Current Symptoms: bilateral ptosis, no diplopia, severe dysphagia with aspiration of thin liquids; severe fatigue with attempts to chew food, poor pulmonary function but not requiring mechanical ventilation, bilateral lower extremity weakness—unable to lift legs against gravity, fatigues after 3-4 repetitions; needs assistance to roll over; dependent for all activities of daily living

Medical history: osteoporosis of spine with history of thoracic and lumbar compression fractures, steroid-induced diabetes mellitus with a history of blood sugars >300 at times, frequent urinary tract infections

Baseline Function (prior to current MG exacerbation): resident of skilled nursing facility for two years; ambulatory with rolling walker with assistance for distances

<200 feet; requires moderate to maximal assistance for all activities of daily living; has required thickened liquids and mechanical soft diet in the past due to problems with dysphagia

Appropriate evaluative tests: Baseline motor weakness with HHD, utilize evaluations for ocular dysfunction (ptosis, diplopia), and vital signs during AROM to determine patient's tolerance for active or resistive exercise, when progressing severity of exercise, utilize HHD fatigue test to more objectively evaluate patient's activity or exercise tolerance. Utilize HHD to assist MD to adjust pyridostigmine dose (especially if patient has more generalized than ocular symptoms)

Treatment strategies: Frequent reevaluations to determine if patient has the ability to tolerate active versus passive exercise, slow and conservative exercise progression to patient tolerance only, consideration of more important patient issues (such as extubation) when exercising the patient

The inclusion of physical therapy in the evaluation and treatment of myasthenia gravis can be an integral component that contributes to maximum functional outcomes.

Active participation of patients with objective exercise prescription enables the patient to actively contribute to their own improvement. Each MG patient will be more aware of their symptoms, the effect of their treatment, and will avoid the complacency often associated with chronic disease.

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8

Occupational Therapy Issues

Timothy Holmes

8.1 Occupational Therapy Guidelines for Myasthenia Gravis

The philosophy and approach of occupational therapy is to use occupations i.e., tasks that are personally relevant and meaningful, as a means to facilitate optimal performance and improve one's ability to participate in daily life roles and valued activities (Christiansen and Baum, 2005). These concepts guide occupational therapy evaluation and intervention for a wide variety of impairments and practice settings. Occupational therapy intervention for persons with myasthenia gravis may be thought of as a three-fold process. Once the evaluation is complete and goals are set, occupational therapy strategies may include remedial tasks to improve activity tolerance, compensatory techniques and/or equipment to optimize independence and safety and client education to enhance awareness of disease characteristics and how they may affect occupational performance. While this approach is not unique to persons with MG, priorities and goals are established based on a patient/client-centered process that takes into account patient symptoms and the desire to return to one's previous lifestyle.

Myasthenia gravis is a disorder that alters neuromuscular transmission by impairing interaction of acetylcholine at the receptor site of the neuromuscular junction. Seqeulae include muscular fatigue, ocular motor paresis/palsy, dysarthria and dysphagia. From a functional perspective, this means difficulty engaging a wide array of activities that might include basic self-care, reading, driving, performing household management, or parenting.

Along with the physical manifestations of myasthenia gravis, psychosocial concerns may also arise. As this is a chronic disease which has a fluctuating course and is managed rather than cured, a client may experience concerns of uncertainty of what the future may hold. Exacerbation will be a possibility throughout the lifespan and coupled with the need for continuous monitoring of exertional activity, one may develop a self-perception that may include feelings of anxiety, depression and role inadequacy (Christiansen and Baum, 2005; Kaminski, 2003).

8.2 The OT Evaluation of the Myasthenic Patient

The occupational therapist may select any number of evaluation tools that currently exist that may or may not have been developed with this population in mind. They may range from self-reported questionnaires or scales that reflect one's subjective perception of fatigue such as the Perceived Exertion Scale to objective measures of strength like hand-held dynamometry (see Physical Therapy Section). The evaluation process may combine a bottom-up approach to impairment issues and patient factors e.g., amount of diplopia or ptosis along with top-down performance measures as in the Assessment of Motor and Process Skills.

The first step is the completion of the client's occupational profile which would include the history of typical life roles, routines and habits. The context in which these occur is also paramount to understanding the potential impact myasthenia gravis has on each individual. This helps establish priorities for setting goals and directing the plan of care.

Regardless of the evaluative approach, the patient should always be at the center of this process. Measurement of performance should reflect both the objective, observable qualities and subjective experiences for each client. (Christiansen & Baum, 2005). Table 8.1. is a list of evaluations that might typically be used by the occupational therapist.

Documentation of the evaluation results should also include information from additional contexts of environment and time. Performance in the hospital room or clinic setting may differ from performance in one's own home depending factors such as floor surface, location of commonly used items, or distance of objects. Performance will also vary greatly if the patient is receiving certain medical interventions such as cholinesterase inhibitors or plasma exchange. Typically peak effect of pyridostigmine is approximately 1.5 to 2 hours following the dose and documentation of the time of assessment in relation to the administration of medication should always be noted. Likewise, temporal notation should be noted if the assessment is completed when one is several hours post medical intervention when the effects are greatly diminished. Only in this manner can the therapist or physician correctly interpret the assessment findings.

TABLE 8.1 MEASURES OF FUNCTION FOR THE OCCUPATIONAL THERAPIST

Activities of Daily Living

- Functional Independence Measures
  - Barthel Index
  - Klein-Bell
- Canadian Occupational Performance Measure
- Myasthenia Gravis Activities of Daily Living Profile
- Quantitative Myasthenia Gravis (QMG) Score

Strength

- Grip strength dynamometry

Fatigue

- Perceived Exertion Scale
- Modified Fatigue Scale

Vision/Ocular Motor Function

- Extra Ocular Motility Exam
- Hirschberg Light Reflex
- Maddox Rod
- Ptosis measurement in millimeters

Instrumental Activities of Daily Living

- Assessment of Motor and Process Skills
- Canadian Occupational Performance Measure

8.3 OT Interventions for the MG Patient

Once goals are established, the occupational therapist will develop interventional strategies based under broad categories of education, remedial activities and/or compensatory techniques. The specific course of therapy will depend on some of the same factors that guide the evaluation process. Additionally, the client's understanding of the disease process, the level of impairment and the desire to return to one's previous lifestyle will also influence the course of therapy.

8.4 Patient Education

The primary goal of educational activities for the persons with myasthenia gravis should focus on how the effects of fatigue impact one's daily living performance. Activities that utilize larger muscles will expend more energy than activities that use smaller ones. Therefore, one would expect a quicker onset and a longer recovery period with tasks such as yard work or manual labor compared to relatively easier activities like reading or preparing a light meal.

A significant portion of the occupational therapist's time should be spent on reviewing energy conservation strategies. Table 2 lists some specific suggestions for performing various daily occupations that potentially reduce exertion and fatigue: This is not a comprehensive list but rather one of suggestion as recommendations should be specific to one's individual needs.

8.5 Use of Therapeutic Occupations for Remediation/ Restoration

Occupational therapist and occupational therapy assistants have been guided for decades by the premise that one's participation in activities that are personally relevant and meaningful may facilitate improvement in one's health and well-being. Occupations used for remediation have certain characteristics that provide a therapeutic value. For example, along with being inherently relevant, they may be graded to provide success and yet simultaneously be of enough challenge to facilitate improvement at the impairment level. Other therapeutic elements include utilizing activities that are within the client's capability and are of meaning to the client (Trombly & Radomski). Various methods may be used to grade therapeutic occupations. These might include changing position of the client or materials, changing lever arms, increasing physical resistance, or increasing the duration of sustained activity.

The therapist will be able to determine what activities to include for intervention during the completion of the occupational profile which may include an interest check-list. Using activities that is part of one's typical lifestyle provides many benefits. It facilitates motivation to participate, builds rapport

between the client and therapist, fosters a sense of normalcy and provides an assessment tool to determine the level of progress.

It is important to monitor the myasthenic patient's level of exertion to avoid extreme fatigue. It is advisable to stop an activity prior to fatigue rather than waiting for obvious signs of over-exertion. This will avoid a prolonged recovery time and reduce the risk of a crisis episode. Indicators of fatigue may include a heart rate greater than 20 bpm of the resting heart rate, labored breathing, ptosis, diplopia and fatigue. The remedial program should be tailored to one's specific level of tolerance.

TABLE 8.2. ENERGY CONSERVATION RECOMMENDATIONS

Task & Energy Saving Techniques

- **Basic Self-Care**
  - Use bathroom durable medical equipment to allow one to shower and groom while seated.
  - Organize supplies and clothing such that minimal energy is spent obtaining items.
- **Home Management**
  - Perform laundry in smaller loads. Use laundry hampers on casters that allow for ease in rolling rather than lifting.
  - Organize frequently used cooking equipment/ utensils to allow ease in reaching and reduced trips to collect.
  - Use lightweight equipment rather than heavy vacuum cleaners or mops
- **Shopping**
  - Plan shopping trips during the time of day that one has the most energy.
  - Consider grocery stores that provide a "call-in" and pick-up service.
- **Parenting**
  - Arrange diaper changing stations to allow performance while seated.
- **Care of Pets**
  - Use elevated food container on casters.
  - Use elevated feeding stations.
  - Hire someone to take pets for a walk.
- **Leisure Activities**
  - Perform more strenuous activities during peak medication response.
  - Learn early signs of fatigue and allow sufficient recovery time.
  - Balance strenuous activities with ones that require less physical exertion
- **Sexual Activity**
  - Plan sexual activities at times when concern for fatigue is not a factor
  - Utilize positions that require less energy for posture.

Some of these indicators include a heart rate greater than 20 bpm of the resting heart rate, labored breathing.

As each individual has a specific level of activity tolerance know to them before the onset of myasthenia gravis, the remedial program should be tailored to their specific background.

8.6 CompensatoryTechniques/ Adaptation

Compensatory techniques may include use of equipment and/or strategies and are of value when typical performance is not feasible. Several ideas were mentioned in Table 8.2 Compensation is most readily considered for the debilitating factors in myasthenia gravis that impact performance on the most obvious daily living skills such as basic self-care, shopping, work related tasks, etc. But one would also consider techniques for specific tasks such as child care or work related tasks.

Special consideration needs to be given to the effect of visual impairment as ocular muscle weakness is a hallmark of myasthenia gravis and frequently a first indicator of the disease. While it is possible that any of the three cranial nerves that innervate ocular muscle function can be affected, the oculomotor or third cranial nerve is most often impaired. Subsequently, one might expect ptosis, reduced ocular adduction, upward and downward gaze and reduced diagonal gaze movements. However, pupillary function is spared. Given this ocular paresis and dysconjugate gaze, the client often reports diplopia (von Noorden and Campos, 2002). Functionally this results in difficulty with occupations such as reading, computer tasks, home repair, driving and safely negotiating stairs.

The first step in developing compensatory strategies for diplopia is to perform an assessment to determine which cranial nerves are paretic and causing the diplopia. This is done by observation of ocular movements, cover test and/or the Maddox rod test. These can be performed by the occupational therapist. Additional tests such as Hess Screen or prism cover test would typically be conducted by a neuro-ophthalmologist. The particular cranial nerves involved will determine whether the diplopia is vertical or horizontal and the degree of impairment. It is imperative to document the amount of fatigue a client is experiencing as severity of diplopia will change accordingly. The most common technique to reduce the effects of diplopia is to have a client wear an opaque eye patch. An alternate strategy would be to use translucent tape or cling-on film that would be less cumbersome, more aesthetic and comfortable and yet allow light stimulation. Prisms are not typically indicated as ocular paresis fluctuates, thus the amount of diplopia is too variable for optical correction.

Ptosis may be partial or full. Many clients experience gradual worsening during activity such as reading. Rest will temporarily reduce the symptoms. Medication such as cholinesterase inhibitors may also provide improvement with ptosis although it may cause diplopia if the eyelid is lifted and there is a slight amount of ocular muscle weakness (Kaminski, 2003). Ptosis crutches may also be of benefit, if tolerated by the client.

Regardless if monocular vision is induced by ptosis or an eye-patch, the resulting issue is loss of stereopsis or depth. Typically, the most significant impact is with near tasks such as pouring liquids, accurate reach and grasp, or tool use (Holmes, 2004). Therapist should provide education to help the client learn what to expect and how to compensate.

Another significant area of dysfunction is eating and swallowing secondary to muscle weakness. Evaluation and intervention may be necessary to prevent aspiration. Occupational therapists with advanced training for dysphagia may provide these services (Pendleton & Schultz-Krohn, 2006).

8.7 Summary

The role of occupational therapy is to promote and facilitate independence in areas of basic and instrumental activities of daily living, education, work, play, leisure and social participation. Myasthenia gravis is a disease process that has the potential to disrupt the potential to engage in any or all of these performance areas. It is my hope that this chapter is the beginning of a model that reflects best practice for occupational therapy with clients diagnosed with myasthenia gravis

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9

Speech Pathology and Swallowing Issues

Susan G. Butler

Speech and swallowing deficits are a frequent manifestation in individuals with myasthenia gravis (MG), especially those with oculopharyngeal symptoms. The speech language pathologist (SLP) should be prepared to assess and address a patient's swallowing needs during a myasthenic exacerbation and also follow, assess and treat during periods of improvement. Once the SLP obtains a patient with MG, many times s/he will continue to offer diagnostic and rehabilitation services to that patient for their lifetime. That is, swallowing ability and speech/voice abilities change frequently during the life of an individual with MG. For example, after a myasthenic crisis, a diet may be restricted and modified; however, the SLP will follow the patient and improve the diet level as the myasthenic patient remits and returns closer to their baseline. Once a patient is stable, the SLP will continue to follow the patient periodically to assess if swallowing function deteriorates over time. If it decreases, the SLP will modify a patient's diet or methods of eating again, as indicated, in order to decrease the likelihood of pulmonary compromise and possible myasthenic crisis. With proper diagnostics and management strategies, the individual with MG can avoid pulmonary complications from dysphagia and enjoy quality of life maintaining eating by mouth and using his/her own voice to communicate.

This manual has been prepared to aid the practicing SLP in the assessment, management and rehabilitation of swallowing and speech/voice deficits in individuals with MG. A reading list is provided and should be consulted for further details about management.

MG is a chronic, autoimmune neuromuscular disease manifested by fatigability in striated muscles. The muscle weakness of MG results from an incomplete nerve transmission at the neuromuscular junction. Hallmarks of the disease include the following:

- *Fluctuating weakness of voluntary muscles, particularly the facial and ocular muscles*
- *Muscle weakness that increases with activity*
- *Muscle strength that improves after rest*
- *Muscle strength that improves in response to (cholinesterase inhibitor) medications.*

9.1 Characteristics of Dysphagia in MG

Individuals with MG may present with none of, or varying degrees of the following symptoms that may result in aspiration:

- Decreased lingual bolus propulsion secondary to lingual weakness of decreased lingual to palatal contact, lingual bolus containment, or lingual bolus preparation manipulation which results in post-swallow oral cavity residue
- Decreased mastication secondary to decreased masticatory muscle strength and efficiency which results in prolonged oral phase and/or post-swallow oral cavity residue
- Decreased velopharyngeal seal which results in nasopharyngeal regurgitation
- Decreased base of tongue to posterior pharyngeal wall approximation which results in valleculae residue
- Decreased pharyngeal contraction which results in valleculae and pyriform sinus residue
- Decreased anterior and superior displacement of the hyoid which results in decreased upper esophageal sphincter (UES) opening
- Decreased pharyngeal peak pressure as measured by manometry
- Hypotonic DES resting pressure as measured by manometry
- Delay in pharyngeal response which may delay in aspiration before and/or during the swallowing
- A decreased in:
  - o laryngeal closure (level of true and/or false vocal folds)
  - o tightening of the aryepiglottic folds
  - o approximation of the arytenoid to the base of the epiglottis
  - o epiglottic retroversion
- Loss of residue from the following areas:
  - o oral cavity
  - o valleculae
  - o pyriform sinuses
  - o lateral channels
  - o post-cricoid/inter-arytenoid space
  - o laryngeal vestibule

9.2 SwallowingAssessment

It is important for SLPs to work closely with neurologists, so that when MG is diagnosed, the neurologists will immediately refer the patient to the SLP for swallowing and speech evaluations. Detecting dysphagia early is paramount in managing silent aspiration which can not only lead to aspiration pneumonia but can cause continuous damage to the lungs making rebound from future myasthenic crises more difficult.

A swallowing assessment begins with a clinical swallow evaluation and then is followed with an instrumental swallowing evaluation, as indicated. There are many characteristics of dysphagia in MG as described bellow, but the hallmark is weakness. Research has demonstrated that the presence of penetration and/or aspiration is highly correlated with weakness of pharyngeal muscles (Oda, Chiappetta, Annes, Marchesan, Oliveira, 2002). When performing the swallowing assessments described below, testing for weakness and fatigability is a crucial factor.

9.3 Clinical Swallowing Exam

A comprehensive oral mechanism examination evaluating the musculature functioning of cranial nerves V, VII, IX, X, XI and XII is needed in all individuals with MG, especially patients with bulbar manifestations. In addition, the clinician will test the fatigability of the facial, lingual and laryngeal functioning by having a patient perform repetitive labial eversion and protrusion tasks, lingually push repetitively against a tongue depressor or against a lingual manometric device (e.g., Iowa Oral Performance Instrument or Kay Pentax Swallowing Signals Lab) and count out loud to the number 100, respectively. The clinician will note the rate of fatigue for later judgments in how to instrumentally assess speech and swallowing and make therapeutic recommendations.

If dysphagia is suspected to any degree, an instrumental swallowing assessment is recommended. Silent aspiration is a high risk in the MG population. Literature has demonstrated that it occurs in approximately 50% (Higo, Nito, Tayama, 2005) of those with MG who aspirate. The clinical swallowing exam is poor in its ability to predict aspiration. Subsequently, an instrumental swallowing exam is necessary, especially in this population which is at a high risk for pulmonary complications where clinician error can not be easily afforded.

Following the oral mechanism examination, clinical test boluses may be administered to prepare the clinician as to what to expect and look for during the instrumental assessment. Small test boluses of water are frequently utilized as water has a neutral pH and is relatively benign to the lungs especially if oral care is good. The water test boluses provide an opportunity for the clinician to palpate the larynx and to assess laryngeal elevation. Studies have shown that duration of superior hyolaryngeal elevation is significantly correlated to aspiration (Higo et al., 2005) in individuals with MG. Thus, clinically palpating the larynx during swallowing (i.e., Logemann Four

Point Test) provides information as to what to expect in the instrumental examination.

If the patient is already eating, more viscous or solid boluses may be administered to assess masticatory functioning. The clinician will observe efficiency of mastication/ fatigability of masticatory muscles with various solid boluses in order to better plan the instrumental exam. However, it is best to administer only small water test boluses or no test boluses and proceed quickly to the instrumental assessment. The instrumental assessment is the only means to directly visualize swallowing and aspiration. During the clinical examination, administering boluses other than water place the patient at undue risk for aspiration. Silent aspiration can lead to pulmonary complication since aspiration is frequently silent and undetected in the MG population.

9.4 Instrumental Swallowing Assessments

The Modified Barium Swallow Study (MBS) and the Fiberoptic Endoscopic Evaluation of Swallowing (FEES) are commonly used instrumental swallowing assessments in the evaluation of oropharyngeal and pharyngeal dysphagia in individuals with MG. Frequently one or the other is used, although occasions exist where both exams are needed. Each exam holds some strength over the other depending on the questions asked.

Various swallowing issues in MG are described below. The role of FEES and MBS is also discussed relative to each issue, to better guide the clinician in deciding which instrumental exam best addresses their's patients swallowing needs.

9.4.1 Sensitivity of Detecting Aspiration

FEES has been repeatedly demonstrated in the literature to provide increased sensitivity to the detection of aspiration compared to the MBS. That is, if aspiration is the question, especially trace aspiration, FEES is likely the best choice. Many populations of patients can tolerate trace aspiration and if missed on a MBS, results in no pulmonary complication. However, given that respiratory compromise is paramount in MG, missing trace aspiration is not acceptable because it may lead to a MG crisis. FEES provides direct visualization of the airway and aspiration is easy to detect.

Many SLPs have been concerned that aspiration is not visualized during the swallow on a FEES; however, for the clinician performing FEES, aspiration is not missed during the swallow because if aspiration was not observed before white out (i.e., pharyngeal swallow) and is present following white-out, then the aspiration occurred during the swallow. In addition, literature has consistently and non-refutably borne-out that FEES is more sensitive than the MBS on aspiration. Thus, given the high prevalence of decreased pulmonary functioning in this autoimmune disease, the more sensitive exam in detecting aspiration is the best choice when the question of silent aspiration needs to be answered.

9.5 Fatigability of Pharyngeal Functioning

One of the hallmarks of muscle functioning in MG is the fatigability of muscles. FEES exams are preferred over the MBS to address the question of whether fatigue will negatively affect the swallowing safety of a patient with MG. FEES is not a time-limited exam. MBS involves the use of radiation and is subsequently a time-limited assessment. Thus, a long swallowing exam is paramount to determine how long a patient can swallow without aspirating if aspiration has not already been detected on the first few swallows.

Often, an individual with MG in crisis will not be able to tolerate all consistencies and/or viscosities but once a consistency and/or viscosity that is initially tolerated without aspiration is identified, the clinician needs to make special effort to fatigue the patient. That is, s/he must continue evaluating the safety of those consistencies over the duration of a simulated meal, to assure those consistencies can be tolerated despite fatigue. Some patients will fatigue quickly while others may be able to eat or drink for five to ten or 15-20 minutes before aspirating those consistencies. Factors that may influence fatigue rate include whether or not the patient is in crisis, how responsive they are to cholinesterase inhibitor drugs (e.g., pyridostigmine), or where in the dosing cycle of the cholinesterase inhibitor drugs they are (i.e., peak, trough). Clinicians must be prepared to test patients with MG for the time it takes to consume a meal to assure that the patient's fatigue does not overwhelm their swallowing safety.

If a clinician does not have access to FEES, then the MBS should be tailored to test fatigue to the best degree possible. Testing fatigue on MBS requires first fluoroscopically evaluating the patient to determine what consistencies and viscosities are tolerated without aspiration. Once those consistencies and viscosities are identified, then the patient should continue to consume those while the fluoroscopy is off. The fluoroscopy is then turned on periodically to check how the patient is tolerating those consistencies as fatigue increases.

9.6 Visualization of Pharyngeal Physiology

The MBS is the best choice to view hyolaryngeal elevation, tongue base to posterior pharyngeal wall approximation, pharyngeal contraction, upper esophageal sphincter (UES) opening and to perform a screen of esophageal motility. FEES, however, is the best choice to view laryngeal physiology. As stated above, if aspiration is the primary question, then FEES may be the best choice overall. However, if oral or pharyngeal physiology needs to be determined and/or an esophageal screening is needed, then the MBS is the exam to answer those questions.

9.7 Other Instrumental Assessments

Pharyngeal and upper esophageal sphincter (UES) manometry is another means to evaluate oropharyngeal functioning in individuals with MG. Manometry measures the pressures (mmHg) of the oropharynx, hypopharynx and relaxation of the UES during swallowing and measures the pressures in the UES at rest. Manometry provides quantitative information on the strength or weakness of the swallow. Manometry can more accurately grade a patient's pharyngeal weakness and/or decreased UES relaxation compared to a MBS or FEES which relies on a clinician's subjective severity rating of pharyngeal residue to reflect pharyngeal contraction weakness.

Manometry also can be helpful to the diagnosis of MG. Since manometry offers quantitative information on the functioning of the striated muscles of the pharynx, edrophonium testing can be performed on patients with suspected bulbar onset MG. The SLP and neurologist would work together to perform this type of testing. Baseline manometric measurements would be acquired during saliva swallows, edrophonium would be administered and then manometric measurements would be obtained from saliva swallows following edrophonium injection. One would consider the edrophonium test positive if manometric pressures increased. The MBS may also be used (Schwartz, Waclawik, Ringwala, Robbins, 2005) similar to that described with manometry to facilitate diagnosis of MG. However, manometry offers quantitative pressure measurements whereas MBS can only offer quantitative durational measures. Since weakness is the hallmark of MG, manometry is best suited to illuminate the role of edrophonium on changes in pharyngeal strength.

Barium swallows and esophageal manometric testing may also be needed in the individual with MG. The upper 1/3 of the esophagus is striated and the lower 2/3 is smooth muscle. Literature has shown that individuals with MG may present with esophageal dysphagia as well. The esophageal dysphagia may be a pre-existing condition that is worsened by MG's effect on the upper portion of the esophagus.

9.8 Issues in Swallowing Intervention

9.8.1 Pharmaceutical Timing

Regardless of the clinical or instrumental swallowing assessment being performed the SLP needs to be acutely aware of the patient's medication schedule. Generally, the SLP will time the swallowing study to coincide with the peak of the patient's cholinesterase inhibitor medications (e.g., pyridostigmine) which is usually 30 minutes to one hour following administration. In most cases, cholinesterase inhibitor drugs provide marked improvement in a patient's swallowing ability. Many patients are on a schedule of receiving their cholinesterase inhibitor medications every four to six hours. Thus, to optimize the chances that a patient will pass the swallowing study

on some level of consistency and viscosity, care should be taken to schedule the test accordingly. If a patient passes the swallowing assessment during the peak of his/her cholinesterase inhibitor drugs, then s/he will need to schedule all meals around the peak of the drug. If a patient performs very well during an cholinesterase inhibitor peak then the swallowing test may also be administered during the patient's trough on the cholinesterase inhibitor drug (towards the end of the drug activity right before the administration of the next dose) to determine if or what the patient can safely swallow when the cholinesterase inhibitor medication is not in full effect.

Many patients, especially when in the middle of a MG exacerbation, are only able to swallow safely during an cholinesterase inhibitor peak. Scheduling meals around cholinesterase inhibitor medication peaks can be difficult. In addition, if the patient has been shown to fatigue quickly while eating and can only eat for periods of 5-10 minutes at a time during peak cholinesterase inhibitor medication, getting enough nutrition into the patient can be difficult to impossible. In those cases alternative means of nutrition should be considered if the patient is not expected to remit quickly.

9.8.2 Compensatory Maneuvers

Compensatory maneuvers (e.g., chin tuck, head turn) are often extremely helpful in eliminating or decreasing aspiration in individuals with MG. Compensatory maneuvers that require little effort, such as a chin tuck, should be tried first. If a lower effort compensatory maneuver is not successful in eliminating aspiration then a higher effort compensatory maneuver such, such as supraglottic swallow, may be attempted but with caution due to the likelihood of exacerbating quicker fatigue and subsequent aspiration. All compensatory techniques that are identified to be successful should be repeatedly demonstrated during an instrumental exam to assure that they eliminate aspiration at the end as well as at the beginning of a meal to assure fatigue does not negatively affect the usefulness of the maneuver.

9.8.3 Alternative Means of Nutrition

Alternative means of nutrition include nasogastric tubes, small bore tubes, orogastric tubes and gastrostomy tubes. Generally, any type of tube that goes from the mouth or nose through the pharynx into the lower alimentary canal is used as a short-term (e.g., two weeks or less) means of nutrition; whereas a gastrostomy tube is used as a longer-term alternative means of nutrition.

Alternative means of nutrition allow an individual to obtain nutrition while they are too sick, too weak, receiving oral ventilatory intubation, or unconscious. Thus, alternative means of nutrition are helpful. However, alternative means of nutrition should not be implemented unless absolutely necessary for many reasons. First, quality of life is greatly hampered by not being able to consume nutrition orally. Eating is a social experience in our society and not be able to eat a meal with one's family and friends decreases one's opportunity for socialization and may lead to depression. In addition, most people en-

joy eating. Later in life, eating one's next meal is a lot of what one looks forward to when many of their other functions are no longer possible. Second, receiving a tube is often perceived by an individual as a sign of being defeated by their disease and potentially leads to depression or greater depression. With depression the potential for optimal rehabilitation often decreases. Third, receiving an alternative means of nutrition decreases the number of times one swallows and leads to deconditioning and potentially worsened dysphagia. Fourth, the presence of a pharyngeal tube slows the pharyngeal swallow duration, contributes to laryngeal and pharyngeal edema which contributes to post-swallow residue and possibly interferes with epiglottic retroversion negatively affecting swallowing safety. Fifth, the presence of a tube in the upper and lower esophageal sphincters may promote laryngopharyngeal reflux and subsequent aspiration of both acidic and non-acidic material contributing to pneumonitis or aspiration pneumonia. Sixth, a tube is more difficult to manage and may hamper one's ability to live independently or outside of constant medical care.

The aforementioned negative effects of tubes do not mean that alternative means of nutrition are to be completely avoided. They often serve an excellent purpose in helping a patient through a crisis by providing a means for nutrition and medications and/or prolonging one's life. However, one should consider how quickly one will remit before placing a pharyngeal tube (e.g., N-G tube). If a swallowing evaluation reveals that a patient can get their medications down safely in, for example, a few tablespoons of applesauce and the MD believes the patient will remit in a day; perhaps, the NG tube is not worth the negative physiologic effects it will force on the swallowing mechanism.

If an alternative means of nutrition is needed, often a gastrostomy tube may the best choice if the swallowing is not believed to quickly improve. A nasogastric tube will make a patient with a weak pharyngeal swallow that more hampered in their rehabilitation due to the mere presence of the tube in the pharynx mechanically obstructing swallowing physiology and desensitizing the pharynx. By placing a gastrostomy tube, the pharynx is free to rehabilitate both spontaneously and with therapy with the goal of returning to oral nutrition quicker. When making a decision on an alternative means of nutrition, the length of time to remission or improvement should be considered, quality of life and timeline goals of returning to oral nutrition.

9.9 Swallowing Rehabilitation

Many SLPs are taught that we should compensate for, not rehabilitate dysphagia in individuals with progressive neuromuscular disease; however, that may not be true in MG. When a patient is experiencing a myasthenic crisis or exacerbation of symptoms, rehabilitation is not indicated. However, when a patient is stable or in remission, then increasing a patient's functional reserve may be indicated. That is, improving one's oropharyngeal muscular baseline strength may decrease the

degree of dysphagia in a future myasthenic crisis. All active swallowing strengthening programs should be conducted under the supervision of a SLP per MD recommendations. The SLP will be careful to observe that the strengthening exercises are of the proper frequency, intensity and repetition. All oropharyngeal exercises may mildly fatigue the patient but not to the point of interfering with speech intelligibility or current swallowing functioning. If a clinician is unsure as to the degree of aggressiveness of a swallowing therapy program, s/he may choose to perform a baseline FEES and then a post-exercise FEES to assure that swallowing safety is not compromised. If swallowing rehabilitation appears to be negatively affecting function, then it would be best to markedly lighten the exercise repetition and intensity and repeat the FEES in another session or terminate the exercises all together. Swallowing rehabilitation would be best performed during the patient's peak drug therapy and not immediately prior to meals in case fatigue becomes an issue. Again, many patients may be appropriate for active strengthening but only when stable and not in crisis per MD recommendation in consultation with the patient and the SLP.

9.10 Lifetime Swallowing Plan

Patients, even in remission, should be at a minimal clinically assessed every three months to assess swallowing in order to manage potential aspiration before it contributes to pulmonary complication and possible myasthenia crisis. Many SLPs schedule their patients for standing appointments every three months and/or have the patient call-in for a brief phone interview every month. Of course, patients should be instructed to schedule a swallowing assessment with the SLP sooner if they note any changes in their swallowing ability.

The SLP should make sure that patients and their caregivers educated to the signs and symptoms of dysphagia and aspiration. They should be knowledgeable and able to detect wet voice, throat clearing, coughing, increased chest congestion after eating, etc. In addition, patients should be instructed to periodically assess temperature and be alert to indicators of pneumonia. In the event that the patient experiences an increase in temperature, s/he should be instructed to notify their MD and SLP immediately for appropriate medical assessment and management of possible pneumonia before it develops into an aspiration pneumonia.

9.11 Speech and Voice Assessment and Management

Several reasons exist that may cause a patient with MG to lose his/her ability to communicate. One reason is a myas-

thenic crisis requiring oral intubated for positive pressure ventilation. Oral intubation means that the intubation tube is passing through the pharynx, through the vocal folds and into the trachea and lungs. In this scenario, the patient can not use his/her own voice and is dependent on an augmentative communication device. If the patient has fine motor control of his/her hands, then the SLP and occupational therapist may provide the patient with a white board, marker and eraser or paper and pencil. If the patient has limited fine motor movement, then an augmentative communication board or device that requires simple pointing or pushing may be employed. For example, a picture book or a devise that provides an entire sentence with one push (e.g., "I need the bedpan") may be helpful for the short-term. A low-tech device that is easy to use is best for a short-term situation when the patient is expected to wean off the ventilator within two weeks.

A second reason for a patient's inability to communicate is failure to wean off the ventilator, necessitating a tracheostomy tube for prolonged ventilator use. A tracheostomy tube with an inflated cuff is generally required for positive pressure ventilation. When the cuff is inflated, the patient is unable to obtain subglottic pressure to create voice. Thus, two communication options exist in this situation. The first option is a Ventilator Passy-Muir Tracheostomy Speaking Valve (vent valve). The second option is a more elaborate, high-tech augmentative communication device.

A vent valve is the first choice because that allows for the cuff to be deflated and for the patient to use his/her own voice to speak. The vent valve can not be placed by a SLP alone. Typically, a RT and SLP; or a RT, Pulmonary MD and SLP place the vent valve as a team. The reason the SLP can not place the vent valve alone is because the vent valve requires the tracheostomy tube cuff to be deflated, the patient to be suctioned and changes to be made to the ventilator. Typically, the pulmonary MD or RT make the changes to the ventilator after the cuff has been deflated and the vent valve placed in-line with the ventilator. Once, the vent valve is in-line and then airway patency needs to be assessed. That is, the vent valve is a one-way valve. It allows for the ventilator to give the patient an inspiratory breath through the vent valve, but then the valve shuts and does not allow the expiratory air to return through the ventilator. The expiratory air must pass around the trach's deflated cuff and up through the upper airway without substantial obstruction. Comparing baseline ventilator peak inspiratory peak (PIP) to the PIP once the valve has been placed is helpful in determining if the upper airway is patent. Also, it is helpful to have the patient blow on the hand of the SLP to feel if adequate air is coming up through the mouth. If upper airway patency is determined, then the RT or pulmonary MD will make necessary ventilator changes to control for the "leak" of having the cuff deflated. This paper is not intended to offer a full discussion on ventilator changes; however, one can obtain that information by calling Passy-Muir, Inc. (1-800- 634-5397) directly where they have an on-call clinician to help with clinical questions. The Passy-Muir Ventilator Speaking Valve is the only FDA approved valve that can be utilized with the ventilator.

Once, upper airway patency has been identified, the SLP cues the patient to elicit voice. Once voice is elicited, the SLP works with the patient to talk on the expiratory air afforded them from the ventilator. Many patients do well with this immediately, while other patients will require multiple training sessions to improve or increase their tolerance of the vent valve and/or improve their speaking voice with the vent valve.

If a patient requires prolonged ventilator support and can not use the vent valve, then a "high-tech" augmentative communication device is the second best option.

Many devices are available today that verbally communicate for the patient that are controlled by minimal movement of the hand, lips, or eye gaze. Although, these devises may not be readily available, the SLP will need to advocate for the patient to obtain these devises, as the patient will need a means to communicate. Inability to communicate is one of the leading reasons for anxiety in individuals who are trached and vented. Many specialty augmentative communication centers exist in the country. If the SLP does not feel comfortable obtaining the patient their optimal form of augmentative communication, s/he should refer the patient out to an augmentative communication center where the patient can get the devise that best suits his/her abilities and needs.

A third reason for inability to verbally communicate is a patient who no longer needs ventilator support, but still has a tracheostomy tube. A Passy-Muir Tracheostomy Speaking Valve (speaking valve) can be used on the trach hub as long as the trach has no cuff or the cuff is deflated. Again, as described earlier, upper airway patency needs to be assessed. Once upper airway patency is identified to be fine, the patient needs to be assessed for tolerance of the speaking valve. Typically, the clinician will assess for signs of breathstacking. If the patient shows any evidence of breathstacking the speaking valve needs to be removed and the clinician should troubleshoot to remediate the problem. In addition, the SLP will assess the patient's heart rate, respiratory rate, oxygen saturation and subjective response. If the patient demonstrates evidence of increased work of breathing with the speaking valve on and upper airway patency is good then the SLP may want to try a biased-open valve such as the Shiley Phonate.
A biased-open valve may be helpful with patients who have very low tidal volumes and have difficulty breathing through the biased-closed valve; however, the biased-closed valve (Passy-Muir) should be attempted secondary to the many other benefits gained from a biased-closed valve. If a SLP is not familiar with placing Passy-Muir Valves, s/he may obtain further information by contacting Passy-Muir, Inc. directly and speaking to the on-call help clinician (1-800- 634-5397).

With all verbal forms of communication (e.g., Passy-Muir Tracheostomy Speaking Valve), the patient will need to be assessed and counseled in optimal voice maintenance. That is, if the patient is only tolerating the speaking or vent valve for short periods of time, then the valves should initially only be offered during the peak of their cholinesterase inhibitor therapy. Along with pharmaceutical timing, the SLP can instruct the patient

in using content words and eliminating ancillary words when the patient is severely weak or fatiguing extremely quickly. An example would be “need bedpan” instead of “I need to go to the bathroom.” When patients are severely weak, both verbal and augmentative forms of communication should be offered so that the patient can use the optimal form of communication when possible which is his/her voice and then use the augmentative communication when the voice is fatigued or the patient fatigues with the speaking valve. Since individuals with MG are cognitively intact, actively addressing their communication needs is imperative.

9.12 Conclusions

The majority of individuals with MG can live full lives and enjoy eating by mouth and verbal communication. The SLP should carefully assess and treat individuals realizing that the disease typically exacerbates and remits. A diet that was appropriate during a MG crisis may no longer be needed three weeks later. Likewise, while a patient may be in a state of improvement, a progression of dysphagia can occur that requires assessment and a new diet plan. In assessing dysphagia, an instrumental swallowing assessment is indicated due to the high percentage of silent aspirators in this population.

Both FEES and MBS are good instrumental swallowing assessments yet FEES may be the exam of choice if silent aspiration is the main question; whereas MBS may be the exam of choice if visualizing oropharyngeal physiology is the main objective. Pharyngeal manometry offers quantitative information of the pharyngeal weakness and degree of UES hypotonicity and functioning. Esophageal manometry and full barium swallows are useful in providing esophageal functioning in MG.

Swallowing difficulties may be compensated for with compensatory techniques such as a chin tuck and only assessing and eating during the peak of cholinesterase inhibitor medications. Active swallowing rehabilitation such as oropharyngeal strengthening may be indicated when a patient is stable and not in crisis only under the recommendation of MD in consultation with the SLP and patient.

Some form of communication is almost always an option. Verbal communication is the best option when a patient is trached or trached/vented through a Passy-Muir Tracheostomy Speaking Valve or Vent Valve if indicated and tolerated. If verbal communication is not an option, then many forms of both low and high-tech augmentative communication devices are available. Actively managing swallowing difficulties is important due to the potential role of aspiration in the development of aspiration pneumonia and a potential myasthenic crisis; however, actively addressing communication needs in MG is equally if not more important. Providing a “voice” to patients with MG when needed allows them to participate in decisions regarding their medical care, control their environment, reduce their anxiety and improve their quality of life.

9.13 References

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10

Dental Care Issues

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Myasthenia gravis (MG) may manifest neuromuscular weakness in the head and neck region that produces characteristic features that may provide clues to diagnosis and challenges to dental treatment. Consultation with the patient's neurologist is recommended prior to dental treatment in order to ascertain the extent of neuromuscular weakness, frequency of neuromuscular exacerbations or crises and to discuss the need for medical management to optimize the treatment outcome in the unstable patient. Dental management of patients diagnosed with MG is recognized to present a challenge to the dental profession (Yarom, 2005). Although dental care can usually be managed effectively in private dental offices, the dental team should be cognizant of the medication precautions in this population, modify dental care to accommodate existing neuromuscular weakness and drug therapy and be prepared to manage emergent complications.

10.1 Oral and Maxillofacial Manifestations and Complications of MG

Because oropharyngeal features are present in up to 56% of patients with MG at the time of presentation and may be the only symptom in 19%, dental and oral and maxillofacial surgeons need to be aware of presenting signs and symptoms and be able to assist in referral to a neurologist for appropriate diagnostic evaluation (Dhillon, 1984).

10.1.1 Intraoral findings

Lipomatous atrophy of the tongue in MG may result in a furrowed and flaccid clinical appearance (Bassler, 1987). In severe cases, it can result in a triple longitudinal furrowing of the tongue (Gallagher, 1981). Tongue atrophy with associated fasciculation has been reported in an elderly man (Burch, 2006). A case of initial presentation to the emergency department with a swollen tongue resulting in subjective airway distress in a 56-year-old patient, despite a 5-month history of recurrent tongue swelling, which had caused dyspnea, dysarthria and dysphagia, highlights the difficulty with MG diagnosis (Davison, 1997).

10.1.2 Impaired facial expression

In addition to principle signs of ptosis and diplopia, other facial findings may prove helpful in raising a suspicion of MG in the undiagnosed patient. The myasthenic facies is characterized as a sleepy, expressionless, apathetic appearance due to weakness of the muscles of facial expression and bilateral ptosis (Howard, 2000; Mason, 1964; Spicer, 1965). The ability to smile (and the ability to pout the lips) is impaired. Measurement of deficits in the lip length index (degree to which the mouth can be lengthened with function of the buccinators, risorius and part of the zygomaticus major muscles) and the snout index (degree to which the mouth can be shortened with function of the orbicularis oris muscle) in patients with bulbar MG are significantly greater than normal patients (Weijen, 1998). Attempts at smiling often result in a flattened smile or snarl.

10.1.3 Reduced masticatory strength/dysphagia

Lack of muscle strength in the masseter muscle, especially following a sustained chewing effort, may cause the mouth to hang open, unless the mandible is held shut by hand (Mason, 1964; Spicer, 1965). Patients with bulbar MG have been found to have significantly lower values for maximal bite force and maximal electromyography activity of the jaw-closing and jaw-opening muscles than control subjects (Weijen, 1998). Lack of strength of the muscles of mastication can inhibit proper mastication of food. Chewing efficiency has also been assessed by measuring the degree of breaking down and dividing of test food comparable to cheese and has resulted in the mean particle size being larger after 15 chewing strokes among those with MG, than healthy control subjects (Weijen, 1998).

Eating can be further inhibited by dysphagia, when the tongue and other muscles of deglutition are involved and by aberrant passage of food or liquids from the nasopharynx into the nasal cavity, when the palatal and pharyngeal muscles are affected (Mason, 1964; Spicer, 1965). In experimental settings, the maximal tongue force in MG patients was significantly lower than in healthy controls when the tongue was pushed in both upward and sideward directions against a lever (Weijen, 1998). Measurements of the surface electromyography of the submental and swallowing muscles, combined with chin and larynx movement registrations of subjects while swallowing 10 ml of water showed the bulbar MG patients swallowed slower and needed more swallows to ingest 10 ml of water than healthy controls (Weijen, 1998). A significant correlation was found suggesting that those with lower maximal tongue force tend to swallow more slowly (Weijen, 1998).

TABLE 10.1 HEAD AND NECK SYMPTOMS IN THREE LARGE SERIES OF PATIENTS WITH MYASTHENIA GRAVIS (ADAPTED FROM DAVISON ET AL, 2004)

	Case Series 1 (n=147) (Calcaterra et al, 1972)			Case Series 2 (n=175) (Carpenter et al, 1979)			Case Series 3 (n=48) (Dhillon & Brookes, 1984)		
Symptom	1° symptom (%)	2° symptom (%)	**Any symptom**	1° symptom (%)	2° symptom (%)	**Any symptom**	1° symptom (%)	2° symptom (%)	**Any symptom**
Ocular	-	-	**-**	57	25	**82**	51	15	**66**
Voice	18	31	**49**	16	14	**30**	31	23	**54**
Dysphagia	9.5	22	**31.5**	15	12	**27**	27	30	**57**
Mastication	5.5	12	**17.5**	6	6	**12**	16	22	**38**
Facial	1.5	9.5	**11**	6	7	**13**	3	3	**6**

1°= Primary or initial symptom; 2°= secondary or subsequent symptom.

Management approaches depend on the masticatory performance and the severity of dysphagia (Sasakura, 2000; Weijnen, 2002; Van der Blit, 2001; Colton-Hudson, 2002; Llabres, 2005). Patients with prolonged weakness of chewing and swallowing may develop poor nutrition, dehydration and hypokalemia which may adversely affect muscle strength independent of their MG and may be contributing factors in a crisis (Noroian, 1986). Chewing and swallowing functions may be improved by administration of cholinesterase inhibitor medication one hour prior to the meal, allowing one half hour rest periods before meals and frequent rests while eating, eating the main meal in the morning when muscles are stronger and consuming soft foods in small portions (Noroian, 1986) Aspiration risk in the elderly with severe pharyngeal dysfunction related to MG may necessitate prophylactic placement of a feeding tube in some patients with advanced disease (Kluin et al, 1996).

10.1.4 Dysphonia/Dysarthria

Involvement of the palatal and pharyngeal muscles may also result in dysphonia, with thickened, indistinct and hypernasal speech (Mason, 1964). Affected individuals may have continuous breathiness with progression and an increase in severity with prolonged speaking. Impaired phonation and articulation, combined with involvement of the muscles of facial expression, make verbal and nonverbal communication difficult (Noroian, 1986). In a review of studies evaluating a particular symptom or sign in patients both with and without MG, Scherer and coworkers (2005) found that a history of “speech becoming unintelligible during prolonged speaking” increase the likelihood of MG by 4.5 fold.

10.2 Dental Management

Dental care provision for patients with MG requires special management considerations. These include identifying and managing myasthenic weakness or crisis, avoiding the potentiation of harmful drug interactions, monitoring oral side effects of drugs/therapies used to treat MG and modifying dental treatment to accommodate altered muscle strength.

Patton and Howard (1997) reported on responses to dental treatment among 16 MG patients with mean age at presentation of 37 (range of 6-76) years. The duration of MG at the initial presentation to the Dental Clinic varied from <1 to 38 years. Each patient was assigned to a modified Osserman classification of MG based on the Myasthenia Gravis Foundation of America quantitative disease severity scale (See Table 2) (Sanders, 1979). Therapeutic regimens for treating MG in these patients included: cholinesterase inhibitor, corticosteroids and other immunosuppressants, PLEX, thymectomy, immunoglobulin and mechanical ventilatory support for crisis in five patients. Forty-four dental treatment visits were identified for these 16 patients, including one case each of extractions under intravenous anesthesia or general anesthesia in the operating room. Five treatment episodes in four different patients were associated with neuromuscular sequelae.

Patients in incomplete remission (Class IR) had the lowest rate of neuromuscular sequelae (0/10; 0.0%), while those with moderate generalized weakness (Class 4) had the highest rate of neuromuscular problems associated with dental treatment (2/7; 29%). Patients with mild generalized weakness (Class 2) had a low but appreciable rate of neuromuscular exacerbation (3/27; 11%). These preliminary findings suggest that baseline neuromuscular weakness in patients with MG, as identified by clinical classification, may relate to the risk of exacerbated neuromuscular dysfunction associated with dental treatment.

In this retrospective study (Patton, 1997), neuromuscular responses varied from isolated transient jaw weakness, lethargy, or ptosis, requiring no treatment, to combined symptoms of delayed weakness and dysarthria, or dysphagia, ptosis and extremity weakness, necessitating treatment with intravenous edrophonium or plasma exchange. One treatment visit in a patient with moderate generalized weakness (Class 4) resulted in the need for emergent management of the neuromuscular complications by the neurologist.

10.2.1 Identifying and managing myasthenic weakness in the Dental Office

It is important to realize that oral infections and the psychological stress of anticipating or undergoing dental treatment may lead to onset of a myasthenic crisis. Short duration morning appointments will minimize fatigue and take advantage of the typically greater muscle strength during the morning hours. Appointments are best scheduled approximately one to two hours following oral cholinesterase inhibitor medication so as to benefit from maximum therapeutic effect and decrease the risk of myasthenic weakness or crisis (Gallagher, 1981).

While the stable MG patient, with limited or mild neuromuscular involvement, may be safely treated in the private dental office setting, the patient with frequent exacerbations, or significant oropharyngeal, respiratory, or generalized weakness may receive dental care most safely in a hospital dental clinic or other facility with emergency intubation and respiratory support capabilities (Schneider, 1993). Preoperative PLEX may be indicated in the patient with frequent severe myasthenic exacerbations or crises in preparation for significant oral surgical procedures. If an exacerbation is precipitated, the patient should be evaluated for severity of neuromuscular involvement by the patient's neurologist and given an intravenous injection of a rapid onset cholinesterase inhibitor (e.g. edrophonium chloride). The possibility of a cholinergic crisis due to excess cholinesterase inhibitor medication should be considered if the patient shows no improvement or is made worse.

If respiratory collapse occurs, an open airway and adequate respiratory exchange must be established. Removal by suctioning of secretions and debris from the oral and hypopharyngeal regions is important to prevent aspiration and mechanical blockage of the airway. Manual retraction of the weakened tongue may prevent obstruction of the airway. When intercostal, diaphragmatic and accessory muscles of respiration fail to

provide adequate ventilation despite sufficient cholinesterase inhibitor medication and other appropriate measures, the patient must be endotracheally intubated and mechanically ventilated (Gallagher, 1981).

10.3 Avoiding the Potentiation of Harmful Drug Interactions

Certain medications affect neuromuscular transmission, acetylcholine release and metabolism and should be avoided or used with caution in myasthenic patients (Table 10.2). Rarely used today, the ester-type local anesthetics, such as procaine (Novocain®), should be avoided because they are hydrolyzed by plasma cholinesterases. The reduced plasma cholinesterase activity in the MG patient on cholinesterase inhibitor medications leads to enhanced risk of systemic procaine toxicity (Shaw, 1972) The widely used amide-type local anesthetics, such as lidocaine (Xylocaine®) and mepivacaine (Carbocaine®), should be used with caution (Shaw, 1972; Howard, 1981). Care should be observed in avoiding intravascular injection. Use of a vasoconstrictor, such as 1:100,000 epinephrine in combination with lidocaine is beneficial in maximizing anesthesia efficacy at the oral site, while minimizing total anesthetic dose. The periodontal ligament injection and intrapulpal injection techniques should be considered if the dental procedure warrants their use. Aminoglycosides and erythromycin cause neuromuscular blockade and are contraindicated because they may potentiate the myasthenic deficit

TABLE 10.2. COMMON DRUGS USED IN DENTISTRY WITH POTENTIAL COMPLICATIONS FOR MG PATIENTS

Relatively contraindicated	Use with caution	Safe
LOCAL ANESTHETICS		
Procaine*	Lidocaine* Mepivacaine* Bupivacaine* Prilocaine*	
ANALGESICS		
	Morphine & derivatives§ Narcotics§	Acetaminophen, NSAIDS, Aspirin
ANXIOLYTICS/SEDATIVES/HYPNOTICS		
	Benzodiazepines§ Hypnotics§ Barbiturates§	N2O/O2 sedation
ANTIBIOTICS		
Erythromycin* Gentamicin* Neomycin* Polymyxin B* Bacitracin* Clindamycin*	Metronidazole* Tetracycline* Vancomycin*	Penicillin & derivatives
OTHER DRUGS		
	Corticosteroids‡	

Key: * = drugs which may acutely potentiate myasthenic weakness
§ = use with caution in patients with respiratory difficulty or depression
‡ = exacerbation of MG

(Howard, 1981). Intravenous sedation techniques and narcotic analgesics should be used with caution to avoid respiratory depression (Howard, 1981).

10.4 Monitoring oral side effects of drugs/therapies used to treat MG

Cyclosporine, known to induce gingival overgrowth in some organ transplant patients undergoing immunosuppressive therapy, has also been responsible for initiating this fibroblastic response in a patient with MG (Savage, 1987). The pathogenesis of drug-induced gingival overgrowth is uncertain (Seymour, 1996). The gingival response, which may begin as early as the first month of drug use, seems to be dependent upon the presence of dental plaque or other local irritants causing gingival inflammation, individual genetic susceptibility in fibroblasts and pharmacological variables including the dose of cyclosporine used (Butler, 1987; Seymour, 1996). Several medications with common use in dental practice are contraindicated in the patient on cyclosporine. Drugs that exhibit nephrotoxic synergy with cyclosporine include: gentamicin, vancomycin, ketoconazole and the nonsteroidal anti-inflammatory drugs. Drugs that increase cyclosporine levels, possibly resulting in toxicity, include: erythromycin, ketoconazole, fluconazole and itraconazole.

Prednisone and azathioprine are immunosuppressant medications that can predispose the patient to oral infection and delay wound healing (Bahn, 1982). Careful sterile surgical technique, close observation following surgical treatment and consideration for antibiotic coverage with amoxicillin or penicillin are warranted. Additionally, steroid-dependent patients may have adrenal suppression and may benefit from consideration of prophylactic glucocorticoid supplementation prior to complicated or stressful dental procedures, such as multiple extractions or dental treatment under general anesthesia. (Bahn, 1982) Supplementation is usually not needed in patients on high doses (> 30 mg prednisone/day), alternate day dosing schedules, or for uncomplicated, nonanxiety-arousing dental

visits. Adrenal crisis is a rare event in dentistry, especially for patients with secondary adrenal insufficiency and most routine dental procedures can be performed without glucocorticoid supplementation (Miller, 2001). Consultation with the patient's physician may be indicated.

The cholinesterase inhibitor drugs may result in excess salivation as a side effect. Efficient high speed evacuation, application of a rubber dam for restorative procedures and constant saliva ejector use may diminish the risk of aspiration of excess saliva, water, or dental materials (Frankel, 1978). Additionally, because PLEX protocols may involve the use of anticoagulants, including heparin, dental treatment for these patients should be arranged for a non-exchange day in the treatment sequence.

10.5 Modifying dental treatment to accommodate altered muscle strength

Dental treatment procedures themselves may require modification in poorly controlled patients. Oral hygiene efforts may be compromised by muscle weakness in the extremities and a weakened sustained hand grasp. Electric toothbrushes or manual brushes with modified handles may decrease the muscle effort required to accomplish effective oral hygiene. Use of a mouth prop during operative dental procedures may ease masticatory muscle strain and fatigue.

The ability to manage complete dentures may be compromised by the inability of the flaccid muscles to assist in retaining the mandibular denture and to maintain a peripheral seal for the maxillary denture. Overextended and overcontoured maxillary dentures with thick flanges that impinge upon muscle and frenal attachments can lead to muscle fatigue and altered salivation. Ill-fitting dentures may exacerbate symptoms of difficulty in closing the mouth, tongue fatigue, a tight upper lip, dry mouth, impaired phonation, dysphagia and masticatory problems (Bottomley, 1977). The mechanism of denture-induced salivary suppression is thought to be due either to physical obstruction of the duct outlet, stimulation of the sphincter to constrict, or interference with normal milking of the parotid resulting from masticatory and facial muscle paresis (Bottomley, 1977).

10.6 Stress and anxiety management/Dental care under general anesthesia

Management of emotional stress is important in prevention of myasthenic crises and may be needed for the phobic or anxious patient. Effective pain control and a supportive and trusting relationship with the patient should be established (Yarom, 2005). Nitrous oxide/ oxygen sedation may provide anxiety management and reduce the stress associated with dental treatment. When intravenous sedation is required, it should be delivered with supplemental oxygen support in order to as-

sure adequate respiratory support and medication doses should be controlled to avoid respiratory depression (Howard, 1981). Occasionally, general anesthesia may be necessary to accomplish certain maxillofacial and dental treatments and carries its own precautions.

Standard general anesthetic technique usually requires the use of neuromuscular blocking drugs, such as atracurium, pancuronium and succinylcholine, to facilitate control of the airway and allow procedures to be performed on a motionless patient. Standard anesthetic agents and, if needed, judiciously titrated neuromuscular blocking drugs generally allow safe emergence and immediate extubation for most low-risk MG patients (Dillon, 2004). If necessary, postoperative mechanical ventilation is accomplished with the use of specialized monitoring devices that help monitor awareness and depth of sedation. Currently used intravenous sedatives allow titrated depth of sedation and rapid emergence when extubation is appropriate (Dillon, 2004). If general anesthesia is required to accomplish dental treatment, preoperative plasma exchange or IGIV should be considered for patients with advanced disease, bulbar symptoms, or poor pulmonary function (Kernstine, 2005).

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11

Guidelines for the Pharmacist

James F. Howard

The neuromuscular junction (NMJ) is uniquely sensitive to the effects of neurotoxins. Unlike the blood-brain barrier that protects the brain and spinal cord and the blood-nerve barrier that protects peripheral nerve, there are no barriers to protect the NMJ from the deleterious effects of these agents. Several forms of neurotoxins are directed against the NMJ. Many occur as natural substances of plants or animals, other result from the actions of widely prescribed pharmaceutical compounds, and still others are environmental hazards.

In nearly all instances of NMJ neurotoxicity, there is a reduction in the safety factor of neuromuscular transmission by one of several mechanisms. These neurotoxins may affect either the pre-synaptic or the post-synaptic elements of the NMJ. The clinical features of these neurotoxins are quite varied as many have associated toxicity of other parts of the central, peripheral or autonomic nervous systems. Many will have other systemic effects as well. While the most common neurotoxicity of the neuromuscular junction results from envenomation, more concern to the clinical neurologist are those situations that result from the direct effects of various pharmacologic agents routinely used in the practice of medicine that produce significant aberrations of neuromuscular transmission in susceptible individuals.

It is beyond the scope of this manual to discuss all potential drug interactions with the neuromuscular junction. For this purpose the reader is recommended the website of the Myasthenia Gravis Foundation of America and recent reviews of the topic (Howard, 2007). Therefore this section will focus on those pharmaceutical agents that are most commonly implicated in the acute worsening of myasthenic weakness.

11.1 Pharmacological Neurotoxicity

The adverse reaction of drugs on synaptic transmission may be classified either as acting pre-synaptically, with a reduction in acetylcholine (ACh) release due to local anesthetic-like activity on the nerve terminal, alteration or impairment of calcium flux into the nerve terminal or a hemicholinium effect; post-synaptically, with antibody blockade of ACh receptors, curare-like effects or potentiation of depolarizing or non-depolarizing neuromuscular blocking agents; or, in varying degrees, both. Each of these pharmacological interactions may result in any of the clinical situations described above. Since the publication of the early summaries of Barrons, Kaeser and Howard describing disorders of neuromuscular transmission occurring as the result of adverse drug reactions many more reports have surfaced adding to the list of potentially dangerous drugs (Barrons RW, 1977; Kaeser, HE, 1984; Howard JF, 1990). An up-to-date list of these potential drug-disorder interactions is maintained on the web site of the Myasthenia Gravis Foundation of America. Unfortunately, much of the literature is anecdotal and there are only a few comprehensive in vitro studies of drug effects on neuromuscular transmission in animal or human nerve-muscle preparations. The potential adverse effects of these medications must be taken into consideration when deciding which drugs to use in treating patients who have disorders of synaptic transmission.

With the possible exceptions of D-penicillamine, α-interferon and botulinum toxin, there are no drugs that are absolutely contraindicated in patients with disorders of neuromuscular transmission such as MG. There are, however, numerous drugs that interfere with neuromuscular transmission and will make the weakness of these patients worse or prolong the duration of neuromuscular block in patients receiving muscle relaxants. Drug-induced disturbances of synaptic transmission resemble MG with varying degrees of ptosis, ocular, facial, bulbar, respiratory and generalized muscle weakness. Treatment includes discontinuation of the offending drug and when necessary reversing the neuromuscular block with intravenous infusions of calcium, potassium or cholinesterase inhibitors. In rare instances, these drugs may induce an autoimmune form of MG (D-penicillamine and interferon alpha). In these situations, the treating physician must utilize therapies that are typically used for other forms of autoimmune MG.

While it is most desirable to avoid drugs that may adversely affect neuromuscular transmission, in certain instances they must be used for the management of other illness. In such situations a thorough knowledge of the deleterious side effects can minimize their potential danger. If at all possible it is wise to use the drug within a class of drugs that has been shown to have the least effect on neuromuscular transmission. Unfortunately, studies, which allow such comparisons, are quite few.

The most frequently encountered problems are the effects of antibiotics (aminoglycoside and macrolides) and ß-adrenergic

blocking agents acutely worsening the strength of patients with MG.

11.1.1 Antibiotics

The aminoglycoside antibiotics may produce neuromuscular weakness irrespective of their route of administration (Pittinger C, 1972). These drugs have pre- and post-synaptic actions; many have elements of both. Neuromuscular toxicity data exist for several of the antibiotics including amikacin, gentamicin, kanamycin, neomycin, netilmicin, streptomycin, and tobramycin (Caputy A, 1981). Of the group neomycin is the most toxic; tobramycin the least. Clinically, gentamicin, kanamycin, neomycin, tobramycin, and streptomycin have been implicated in producing muscle weakness in non-myasthenic patients (Kaeser, HE, 1984).

Neuromuscular blockade is not limited to the aminoglycoside antibiotics. Myasthenic patients given the macrolides, erythromycin or azithromycin, will report a mild exacerbation of their weakness (Snavely SR, 1984; Cadisch R, 1996. The newly recognized ketolide, telithromycin, has produced abrupt and severe worsening in MG or unmasked previously undiagnosed MG [author's observation] (Perrot, X, 2006). This has prompted a specific FDA-mandated warning about its use in patients with MG in the package insert of the drug.

The polypeptide and monobasic amino-acid antibiotics, penicillins, sulfonamides, tetracyclines, and fluroquinolones may cause transient worsening of myasthenic weakness, potentiate the weakness of neuromuscular blocking agents, or have theoretical reasons for blocking synaptic transmission (Roquer J, 1996; Sieb JP, 1998). Lincomycin and clindamycin can cause neuromuscular blocking which is not readily reversible with cholinesterase inhibitors (Samuelson RJ, 1975; Fogdall RP, 1974). Polymyxin B, colistimethate, and colistin are also reported to produce neuromuscular weakness particularly in patients with renal disease or when used in combination with other antibiotics or neuromuscular blocking agents (Pittinger C, 1972; McQuillen MP, 1975). These drugs, ampicillin, the tetracycline analogs, oxytetracycline and rolitetracycline, and more recently, ciprofloxacin exacerbate MG, although the mechanism for each medication is not fully understood.

11.1.2 Cardiovascular Drugs

Many cardiovascular drugs are implicated in adversely affecting the strength of patients with MG and LES, and they (along with the antibiotics) account for the majority of adverse drug reactions in patients with neuromuscular disorders. Beta-adrenergic blockers may cause exacerbation of MG, or their use may coincide with the onset of myasthenic manifestations (Howard JF, 1987, 1990). Even those drugs instilled topically on the cornea are capable of producing such weakness (Coppeto JR, 1984; Verkijk A, 1985). Atenolol, labetolol, metoprolol, nadolol, propranolol, and timolol cause a dose-dependent reduction in the efficacy of neuromuscular transmission in normal rat skeletal muscle and human myasthenic intercostal muscle biopsies (Howard JF, 1987). Different ß-blockers have reproducibly different pre- and postsynaptic effects on neuromuscular transmission. Of the group, propra-

nolol is most effective in blocking neuromuscular transmission and atenolol the least.

The effects of calcium channel blockers on skeletal muscle are not understood, and studies have provided conflicting information. Some demonstrated neuromuscular blockade with postsynaptic curare-like effects, presynaptic inhibition of ACh release, and both pre- and postsynaptic effects (Bikhazi GB, 1982; Van der Kloot W, 1975; Ribera AB, 1989). One patient with moderately severe, generalized MG developed acute respiratory failure within minutes following verapamil initiation (author's observations). Low doses of verapamil and its timed-release preparation have been used successfully for the treatment of hypertension in patients with MG receiving cyclosporine (author's observations).

Procainamide may produce acute worsening of strength in patients with MG (Kornfeld, P, 1976). The rapid onset of neuromuscular block and the rapid resolution of symptoms following discontinuation of the drug suggest the drug has a direct toxic effect on synaptic transmission, rather than the induction of an autoimmune response against the neuromuscular junction. The postulated mechanism of action is primarily at the presynaptic membrane with impaired formation of ACh or its release, although it is known to have postsynaptic blocking effects as well. Two case reports suggest that the antiarrhythmic P-glycoprotein inhibitor, propafenone, may cause acute exacerbations of myasthenic weakness (Lecky BR, 1991; Fierro B, 1987). Like the effects of procainamide, the rapid onset of worsening and resolution following the discontinuation

of the drug implicates a direct toxic effect on neuromuscular transmission.

The earliest report of quinidine (the steroisomer of quinine) administration aggravating MG was by Weisman (1949). There are several reports of the unmasking of previously unrecognized MG following treatment with quinidine (Shy ME, 1985; Stoffer SS, 1980; Miller RD, 1968). The neuromuscular block is both presynaptic; impairing either the formation or release of ACh or, in larger doses, postsynaptic with a curare-like action. It has been claimed the ingestion of small amounts of quinine, for example in a gin and tonic, may acutely worsen weakness a myasthenic patient, although this cannot be substantiated with objective reports.

11.1.3 Rheumatologic Drugs

d-Penicillamine (d-P) is used in the treatment of rheumatoid arthritis (RA), Wilson's disease, and cystinuria. A number of autoimmune diseases occur in patients receiving d-P of which MG is most frequent. The MG induced by d-P is usually mild and may be restricted to the ocular muscles. In many patients the symptoms are not recognized, and it may be difficult to demonstrate mild weakness of the limbs in the presence of severe arthritis. It is unlikely that d-P has a direct effect on neuromuscular transmission as MG begins after prolonged d-P therapy in most patients and has a relatively low incidence in patients receiving d-P for Wilson's disease compared with those receiving it for RA. It is more likely that d-P induces MG by stimulating or enhancing an immunological reaction against the neuromuscular junction (Masters CL, 1977). When MG begins while the patient is receiving d-P, it remits in 70% of patients within 1 year after the discontinuation of the drug (Albers, J, 1981). In a few patients the MG persists after d-P is discontinued, implying that a subclinical myasthenic state existed prior to the initiation of the d-P (author's observations).

11.1.4 Interferon Alpha

Generalized MG may occur after starting interferon alpha therapy for leukemia, during interferon alpha-2b treatment for malignancy, and during treatment for chronic active hepatitis C (Perez A, 1995; Batocchi AP, 1995; Lensch E, 1996). Myasthenic crisis may even develop with inter- feron alpha therapy (Konishi, T, 1996). The mechanism of interferon-induced MG is not known. Such studies suggest that the expression of interferon gamma at the motor endplates provoked an autoimmune humoral response, similar to that which occurs in human MG (Gu, D, 1995).

11.2 Drug-Drug Interactions

The pharmacist must be aware of the numerous drug-drug interactions that may impact on the well being of the myasthenic patient. However, significant errors do exist in the standard pharmacopeias for which the pharmacist must be aware. For example, a search for prednisone
and pyridostigmine will find a warning that the concurrent use of these two drugs is contraindicated because they will produce an acute exacerbation of myasthenic muscle weakness.

Modern usage finds this to be untrue. It is likely that this erroneous statement was due to the unrecognized steroid-induced exacerbation of muscle weakness that may occur with steroid initiation.

Cyclosporine, an immune modulating drug that selectively inhibits T-cell function has multiple interactions with other drugs. Some of the effects are to increase the level of the active metabolite and with others to reduce it. The result is that certain drugs must be used cautiously to prevent either inadequate cyclosporine effect or drug toxicity. An increase in serum concentration can also be seen with foodstuffs, e.g. grapefruit. Other drug-drug interactions may produce adverse reactions, e.g. worsening renal function with concurrent use of non-steroidal anti-inflammatory agents.

11.3 Final Considerations

Numerous other drugs may interfere with neuromuscular transmission. Many local anesthetics, certain anticonvulsants, magnesium, iodinated contrast dyes and of course, the neuromuscular blocking agents used by anesthesiology during surgery are included in this list. Newly reported adverse drug-disorder interactions are reported frequently. It is beyond the scope of this section to discuss them all in detail and the reader is referred to a more comprehensive review of the topic or to the web address of MG Foundation of America as noted earlier.

In each instance, the pharmacist must have a thorough knowledge of the patient's problem list and freely utilize pharmacological databases to minimize either a significant drug interaction that will alter the pharmacokinetics of the drug or result in an adverse event harmful to the patient. Dialog with the treating physician will be most helpful.

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Myasthenia Gravis Foundation of America

The Myasthenia Gravis Foundation of America (MGFA) is the only national volunteer health agency dedicated solely to the fight against myasthenia gravis.

Jane Ellsworth founded the Myasthenia Gravis Foundation of America, Inc. in 1952, when her teenage daughter, Pat, was diagnosed with MG. Finding little information available, Jane established the MGFA to create a foundation whose mission was to have "A World without MG". This newly formed foundation provided patients and families with the information and support needed to understand and cope with MG. Until a cure is found, the MGFA will continue Jane Ellsworth's efforts to help patients and their families manage the difficulties of living with MG.

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Appendices

Appendix 2.1 Quantified Myasthenia Gravis (QMG) Score

Test item/Grade	None/0	Mild/1	Moderate/2	Severe/3	Score
Double vision on lateral gaze right or left (circle one), seconds	61	11-60	1-10	Spontaneous	
Ptosis (upward gaze), seconds	61	11-60	1-10	Spontaneous	
Facial muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Complete, without resistance	
Swallowing 4 oz. water (1/2 cup)	Normal	Minimal coughing or throat clearing	Severe coughing/ choking or nasal regurgitation	Cannot swallow (test not attempted)	
Speech after counting aloud from 1 to 50 (onset of dysarthria)	None at 50	Dysarthria at 30–49	Dysarthria at 10-29	Dysarthria at 9	
Right arm outstretched (90 deg sitting), seconds	240	90-239	10-89	0-9	
Left arm outstretched (90 deg sitting), seconds	240	90-239	10-89	0-9	
Vital capacity, % predicted	80	65-79	50-64	<50	
Rt-hand grip, kgW					
Men	45	15-44	5-14	0-4	
Women	30	10-29	5-9	0-4	
Lt-hand grip, kgW					
Men	35	15-34	5-14	0-4	
Women	25	10-24	5-9	0-4	
Head lifted (45 deg supine), seconds	120	30-119	1-29	0	
Right leg outstretched (45 deg supine), seconds	100	31-99	1-30	0	
Left leg outstretched (45 deg supine), seconds	100	31-99	1-30	0	

Appendix 2.2 MGFA Postintervention Status

Complete Stable Remission (CSR)	The patient has had no symptoms or signs of MG for at least 1 year and has received no therapy for MG during that time. There is no weakness of any muscle on careful examination by someone skilled in the evaluation of neuromuscular disease. Isolated weakness of eyelid closure is accepted.
Pharmacologic Remission (PR)	The same criteria as for CSR except that the patient continues to take some form of therapy for MG. Patients taking cholinesterase inhibitors are excluded from this category because their use suggests the presence of weakness.
Minimal Manifestations (MM)	The patient has no symptoms of functional limitations from MG but has some weakness on examination of some muscles. This class recognizes that some patients who otherwise meet the definition of CSR or PR do have weakness that is only detectable by careful examination.
MM-0	The patient has received no MG treatment for at least 1 year.
MM-1	The patient continues to receive some form of immunosuppression but no cholinesterase inhibitors or other symptomatic therapy.
MM-2	The patient has received only low-dose cholinesterase inhibitors (<120 mg pyridostigmine/day) for at least 1 year.
MM-3	The patient has received cholinesterase inhibitors or other symptomatic therapy and some form of immunosuppression during the past year.
Change in Status	
Improved (I)	A substantial decrease in pretreatment clinical manifestations or a sustained substantial reduction in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific decrease in QMG score.
Unchanged (U)	No substantial change in pretreatment clinical manifestations or reduction in MG medications as defined in the protocol. In prospective studies, this should be defined in terms of a maximum change in QMG score.
Worse (W)	A substantial increase in pretreatment clinical manifestations or a substantial increase in MG medications as defined in the protocol. In prospective studies, this should be defined as a specific increase in QMG score.
Exacerbation (E)	Patients who have fulfilled criteria of CSR, PR, or MM but subsequently developed clinical findings greater than permitted by these criteria.
Died of MG (D of MG)	Patients who died of MG, of complications of MG therapy, or within 30 days after thymectomy. List the cause (see Morbidity and Mortality table).

Appendix 2.3: MGFA Therapy Status

NT	No therapy
SPT	Status post-thymectomy (record type of resection)
CH	Cholinesterase inhibitors
PR	Prednisone
IM	Immunosuppression therapy other than prednisone (define)
PE(a)	Plasma exchange therapy, acute (for exacerbations or preoperatively)
PE(c)	Plasma exchange therapy, chronic (used on a regular basis)
IG(a)	IGIv therapy, acute (for exacerbations or preoperatively)
IG(c)	IGIv therapy, chronic (used on a regular basis)
OT	Other forms of therapy (define)

Appendix 2.4: Guidelines for the Performance of an Edrophonium Test

I. Edrophonium (Tensilon®, Reversol®, Enlon®) is a short-acting cholinesterase inhibitor compound whose action is to inhibit or inactivate acetylcholinesterase at sites of cholinergic transmission in skeletal and smooth muscle, autonomic glands and the central nervous system.

Its primary use is to aid in the diagnosis of myasthenia gravis (MG) and to assist in the monitoring of MG patients being treated with longer-acting cholinesterase inhibitor compounds.

In both situations, the drug is given intravenously (IV), directly into the vein or via a heparin lock whose tubing is less than 5 cm (IV tubing is NOT acceptable because of possible drug binding to the plastic and the inability to accurately determine the onset of dose effect, dose given, etc.). It is highly recommended that a l-cc TB syringe with a 27 g. needle be used for accurate dose delivery (10 mg/ml) and patient comfort.

II. As a **DIAGNOSTIC TEST**

- Explain to the patient:
  - You will administer two drugs to determine if there is improvement in strength.
  - They may experience certain side effects

(warmth, flushing, tearing, abdominal “rumblings”, muscle twitching) which will pass quickly, but if too severe, they will be treated with a third medication.

- Examine and note the strength of the patient. Limit your self to those muscle groups, which can be easily and quickly tested (lids, ocular motility, neck flexors, upper extremity…).

- With a nurse or an assistant in attendance, administer in a “double-blind” fashion, placebo saline first edrophonium IV:

    - label each syringe “A” (with placebo saline) and “B” (with edrophonium). Do not mention the codes in front of the patient.

    - Initially administer from syringe “A” 2 mg (0.2 ml) IV and wait for 45 seconds before proceeding, observing for any untoward or beneficial effects.

        - If weakness should occur, discontinue the test.
        - If improvement occurs, discontinue the test as it is “positive”

    - If this does not occur after a 45 to 60 second wait, slowly infuse 3 mg (0.3 ml) of drug over 20 to 30 seconds.

        - If weakness occurs, discontinue the test
        - If improvement occurs, discontinue the test as it is “positive”

    - If nothing occurs, after a 45 to 60 second wait, slowly infuse 5 mg (0.5 ml) of edrophonium over 20 to 30 seconds

        - If weakness occurs, discontinue the test
        - If improvement occurs, discontinue the test as it is “positive”

    - If nothing occurs, after a 45 to 60 second proceed with syringe “B”

- In a serial fashion, examine the same motor groups previously tested and record the degree of change.

- Should the patient experience moderate or severe muscarinic side effects, a small amount of atropine (0.1-0.4 mg. IV) will promptly relieve these symptoms. On occasion, it may be necessary to administer this having given the patient placebo saline to insure that the patient is unaware of the situation. In such instances a minimal amount may be administered.

- After a wait of 5 to 10 minutes, repeat the procedures in Sections II.3 for syringe “B” containing active drug, edrophonium.

- As outlined above, administer 2 mg. (0.2 ml) edrophonium IV, watching particularly for acute cholinergic weakness or muscarinic side effects.
    - If weakness should occur, discontinue the test.
    - If improvement occurs, discontinue the test as it is "positive"
- If this does not occur after a 45 to 60 second wait, slowly infuse 3 mg (0.3 ml) of edrophonium over 20 to 30 seconds.
    - If weakness occurs, discontinue the test as it is positive with cholinergic excess.
    - If improvement occurs, discontinue the test as it is "positive"
- If nothing occurs, after a 45 to 60 second wait, slowly infuse 5 mg (0.5 ml) of edrophonium over 20 to 30 seconds
    - If weakness occurs, discontinue the test as it is positive with cholinergic excess.
    - If improvement occurs, discontinue the test as it is "positive"
- If nothing occurs, after a 45 to 60 second wait either the patient does not have a disorder of neuromuscular transmission or, if suspicions are high, arrange for a Neostigmine Test (see below)

- Record your results similar to the following example:

(date, time)
Edrophonium Test 2/8 mg. IV performed

	PRE	***"A"***	***"B"***
Ptosis ½ limbus	None	½ limbus	
Masseter	4.0	5.0	4.0
Neck Flexor	3.5	4.5	3.5
Deltoid	3.0	5.0	3.0
etc.			

Label "A" and "B" and note which is placebo and active drug

If there has been no response to edrophonium, but one still strongly suspects the diagnosis of MG, then proceed with a NEOSTIGMINE TEST.

- obtain a baseline examination
- administer 0.2-0.4 mg. atropine S.C.
- administer 0.5-1.0 mg. Neostigmine methylsulfate IM.
- perform serial examination every 30 minutes for 4 hours (same examiner throughout).
- record your results as in previous example but with headings of:

PRE	0.5	1.0	1.5	2.0 …	4.0 HOURS
ptosis					
masseter					
etc.					

III. As a **MANAGEMENT TOOL**

- Explain to the patient the methodology of the test and possible side effects as outlined in Section II. "Double-blind" testing is usually not necessary.
- Examine and note the strength of the patient, paying particular attention to the motor groups you are most interested in. NEVER disregard the bulbar and respiratory muscles.
- As outlined in Section II, administer 2 mg. (0.2 ml) edrophonium IV, watching particularly for acute cholinergic weakness or muscarinic side effects.
    - o If weakness should occur, discontinue the test.
    - o If this does not occur after a 45 to 60 second wait, slowly infuse 3 mg (0.3 ml) of edrophonium over 20 to 30 seconds.
        - If weakness occurs, discontinue the test as it is positive with cholinergic excess.
        - If improvement occurs, discontinue the test as it is "positive"
        - If nothing occurs, after a 45 to 60 second wait, slowly infuse 5 mg (0.5 ml) of edrophonium over 20 to 30 seconds
            - o If weakness occurs, discontinue the test as it is positive with cholinergic excess.
            - o If improvement occurs, discontinue the test as it is "positive"
            - o If nothing occurs, after a 45 to 60 second wait either the patient does not have a disorder of neuromuscular transmission or, if suspicions are high, arrange for a Neostigmine Test (see above)
- Examine the selected motor groups in a serial fashion as described in Section II.4.
- Atropine may be used, as in Section II.5, for muscarinic side effects.
    - o Remember that atropine will NOT reverse the weakness of cholinergic toxicity.

- Record your results as shown below:

(date, time) Edrophonium Test 2/8 mg. IV performed		
	PRE	***POST(2/8 mg. IV)***
Ptosis 1/2 limbus	3/4 pupil	
masseter	4.0	4.5
neck flexor	3.5	4.5
deltoid	3.0	2.5

a) It is critical that the procedure have the date, time, dose and the time after last dose of cholinesterase inhibitors; only in this way can an outside viewer interpret the results of this test.

IV. **CLINICAL PEARLS**

- There is no absolute cookbook approach to edrophonium testing and variations will be necessary depending upon the situation.
- Muscle strength of a normal person will not change, although he may experience muscarinic side effects and occasionally have fasciculations.
- Extravasated edrophonium (and neostigmine) will burn.
- Atropine will not reverse cholinergic weakness.
- The timing of the test (drug peak or trough) depends upon the information you are trying to obtain.
- Have an extra pair of hands available. This test may precipitate acute cholinergic weakness or marked bronchorrhea which may be **LIFE-THREATENING**! Suctioning equipment should be available in the room.
- Most common result is a differential response; some muscles improve, others do not change and still others worsen. Clinical interpretation of this must be based upon the muscle groups you are most interested in; at all times, bulbar and respiratory groups have priority.
- There is no such thing as a true “double blind” test because of the associated side effects of the drug. However, the unaware patient will not realize this. Therefore always administer placebo saline first to see if there is a placebo response.

V. **OTHER**

- The edrophonium test is a billable procedure.
- Appropriate documentation is mandatory.
- Use CPT Code 95857

Appendix 2.5 Sample Medication Advisory Form for the Medical Record

THIS PATIENT HAS MYASTHENIA GRAVIS or LAMBERT-EATON SYNDROME

USE THESE DRUGS WITH CAUTION

1. Antibiotics of the Following Classes
    a. Aminoglycosides (end in "**mycin**","**micin**" e.g. neomycin, tobramycin, gentamicin)
    b. Fluoroquinolones (end in "**acin**" e.g. levofloxacin [Levaquin], ciprofloxacin)
    c. Flagyl (metronidazole)
    d. Ketolides (e.g. Telithromycin)
    e. Macrolides (e.g. erythromycin, azithromycin [Zithromax], clarithromycin)
2. BetaBlockers(oral,parenteralandophthalmic preparations)
    a. (end in "**olol**" e.g. atenolol, labetalol, metoprolol, propranolol, sotalol, timolol, etc)
3. Calcium Channel Blockers(end in"**ipine**"e.g. amlodipine [Norvasc], nicardipine, nifedipine [Procardia], felodipine [Plendil])
4. Corticosteroids & ACTH
5. Interferons
6. Magnesium
7. Narcotic analgesics (if there is respiratory compromise; e.g. Demerol, morphine)
8. Phenothiazines(end in "**zine**" e.g. Compazine, chlorpromazine [Thorazine], fluphenazine [Prolixin], perphenazine [Trilafon], Sparine)
9. RespiratoryDepressants
10. Sedatives & Hypnotics

THESE DRUGS SHOULD NOT BE USED IN PATIENTS WITH MYASTHENIA GRAVIS WITHOUT PRIOR DISCUSSION WITH A NEUROMUSCULAR SPECIALIST

1. Botulinum toxin
2. D-Penicillamine

NURSES — TRIPLE CHECK BEFORE GIVING THE FOLLOWING DUE TO THE HIGH PROBABILITY OF PROLONGED WEAKNESS OR MG CRISIS

1. Neuromuscular blocking agents (both depolarizing and non-depolarizing)
    a. Succinylcholine-like
    b. Curare-like
2. Quinidine
3. Quinine

NOTE: This is a **small, limited list** of potentially dangerous drugs for patients with disease of neuromuscular transmission (Myasthenia Gravis, LEMS). Up to date information regarding the potential for drug-induced exacerbation of myasthenic patients may be found at the Myasthenia Gravis Foundation (MGFA) website, http://www.myasthenia.org/docs/MGFA_MedicationsandMG.pdf

The decision to use a potentially dangerous drug must be made on the basis of the clinical decision, urgency of need and lack of alternative agents.

Appendix 3.1 Sample Nursing Care Plans for the MG Patient

Nursing

PATIENT CARE PLAN

Initiated: Date: _____ **Time:** _____ **R.N.** _____

Patient Care Plan for: **Myasthenia Gravis**

Problem Activated Date/ Time Signature	Problem Resolved Date/ Time Signature	Focus/ Problem	Outcome - The Patient will:	Applicable Interventions/Plan • *Document Implementation of protocol in PCR/Flowsheet* • *Document Outcomes in Progress Notes*
		1. Alteration in respiratory function related to: – weakness of intercostal muscles – weakness of diaphragm	Maintain a patent airway, as evidenced by –unlabored respirations – adequate air exchange – effective spontaneous cough	1. Assess and document respiratory status, rate, rhythm and breath sounds at time of admission, then every 4 hours x 24 hours then every shift. 2. Obtain baseline Forced Vital Capacity (FVC) (normal > 60 mg/kg) and Negative Inspiratory Force (NIF) (>70cm$H_2$0) and continue to monitor as ordered and record on MG checklist. 3. Notify MD for any respiratory abnormalities or change in FVC and/or NIF from baseline value or NIF < 30, FVC <1.5L. (Values of FVC < 1.0L <15mL/ kg body weight /NIF <20 cm H_2O are indications for mechanical ventilation.) 4. Determine at time of admission when cholinesterase inhibitor medications were last taken. 5. Place cholinesterase inhibitor drug schedule at head of bed with dose and time to be administered 6. Administer cholinesterase inhibitor drugs EXACTLY on time. 7. Implement Oxygen Therapy in Non-Ventilated Patients Protocol.

Appendix 3.1 Sample Nursing Care Plans for the MG Patient

continued from previous page

Problem Activated Date/ Time Signature	Problem Resolved Date/ Time Signature	Focus/ Problem	Outcome - The Patient will:	Applicable Interventions/Plan • *Document Implementation of protocol in PCR/Flowsheet* • *Document Outcomes in Progress Notes*
				8. Suction if patient unable to manage secretions. 9. Teach patient/caregiver how to use oral suction. *10. Keep Atropine and Tensilon on unit for emergency use. 11. Assess gag and cough reflexes upon admission and as ordered. 12. Post "Myasthenic Precautions" sign (available on unit) on front of chart. 13. If facial weakness – obtain NIF/FVC per face mask. 14. Assess quality of voice – notify MD of changes from baseline.
		2. Self-care deficit related to europhysiologic function	Within 24 hours of admission, demonstrate energy conservation techniques. Independently perform ADLs within limitations of weakness.	1. Assess and document ability to do own ADLs on admission and daily. 2. Assess muscle strength q8h according to myasthenia record. 3. Notify MD for deterioration in muscle strength. 4. Assist patient with ADLs and allow patient to assist within limitations. 5. Provide rest period before and after ADL activities. 6. Teach patient to use energy conservation techniques. *7. Request P.T. Consult. *8. Request O.T. Consult.

Appendix 3.1 Sample Nursing Care Plans for the MG Patient

continued from previous page

Problem Activated Date/ Time Signature	Problem Resolved Date/ Time Signature	Focus/ Problem	Outcome - The Patient will:	Applicable Interventions/Plan • *Document Implementation of protocol in PCR/Flowsheet* • *Document Outcomes in Progress Notes*
		3. Alteration in nutrition related to: – dysphagia – difficulty chewing	Maintain nutrition by: - eating > 75% of diet	1. Assess baseline swallowing and gag using **Myasthenic Check Record.** 2. Consult dietitian. 3. Monitor food intake by documenting percentage of food eaten. 4. Encourage 30 minute rest periods before meals. 5. Encourage taking small bites, chewing well and frequent swallowing. 6. Encourage small frequent meals. 7. Keep fluids at bedside and encourage frequent small sips. 8. Request Speech Therapy Consultation for dysphagia. 9. Maintain Aspiration Precautions.
		4. Potential for injury related to: –muscle weakness –immobility –neurological deficits	Sustain no injuries due to falls. Remain free of skin breakdown throughout hospitalization	1. Implement Falls Prevention [Adult] Protocol. 2. Implement Skin Integrity [Adult] Protocol. 3. Implement Neurological Assessment [Adult] Protocol. 4. Maintain Aspiration Precautions. 5. Implement PIV protocol 6. Provide alternative nurse call system for increased weakness

Appendix 3.1 Sample Nursing Care Plans for the MG Patient

continued from previous page

Problem Activated Date/ Time Signature	Problem Resolved Date/ Time Signature		Focus/ Problem	Outcome - The Patient will:	Applicable Interventions/Plan • *Document Implementation of protocol in PCR/Flowsheet* • *Document Outcomes in Progress Notes*
		5.	Fear/Anxiety related to sequelae of disease.	Identify fears and concerns related to the disease process. Verbalize effective coping strategies within limitation of disease within 24 hours of discharge.	1. Encourage patient to verbalize feelings. 2. Implement Spiritual Distress protocol. 3. Facilitate patient and family conference to discuss treatment plan. 4. Provide patient/caregiver with information regarding support group
		6.	Knowledge deficit related to: –disease process –medications –treatments –home care management	Verbalize understanding of: – drug regimen – medication side effects – conditions that will exacerbate the disease – cholinergic versus myasthenic crisis – home care management – reasons for and goals of medical management	1. Assess and document any barriers to learning and readiness for learning. 2. Document topics taught and patient/caregiver response to teaching, level of understanding and any further learning needs. 3. Consult Social Work/Continuity of Care for discharge planning needs.

Reference:
Hickey, J. (2003). The Clinical Pracitce of Neurological and Neurosurgical Nursing. 5th Ed. Philadelphia, PA. Lippincott Williams & Wilkins.
Kaminski. H. (Ed.).(2003) Myasthenia Gravis and Related Disorders. Totowa, NJ. Humana Press.

Appendix 3.2 Nursing Care Plan for the Myasthenic Patient Taking Cholinesterase Inhibitors

Nursing Diagnosis	Patient Outcome	Intervention
Changes in Bowel Pattern – Diarrhea	The patient will have a decrease in episodes of diarrhea. Fluid and electrolyte balance will be maintained. Early detection of changes from non therapeutic levels of medication will be assessed and reported for proper intervention.	1. Maintain record of intake and output and number of stools 2. Monitor electrolyte studies 3. Increase fluid intake. (Note: Carefully monitor Na and water retention in patients taking corticosteroids) 4. Advance diet from liquid to bland to regular diet as tolerated. 5. Instruct the patient to avoid foods such as fresh fruit, salads, or spicy or fried foods that may aggravate diarrhea. 6. Assess muscle strength to determine changes related to overdosage/ under dosage of cholinesterase inhibitor medications. 7. Instruct the patient to consult physician for medications to control diarrhea.

Appendix 3.3 Nursing Care Plan for the Myasthenic Patient Taking Corticosteroids

Nursing Diagnosis	Patient Outcome	Intervention
Alteration in Fluid Balance Related to Na and H_2O Retention	The patient will decrease the degree of water retention while on steroid medication	Maintain record of intake and output Daily weights Instruct patient on ways to decrease salt intake: – No added salt to food preparation – No added salt to food at meal time – Avoid salted snacks: Read food labels for sodium content Avoid canned foods or frozen foods that add salt to food preparation
Electrolyte Imbalance Related to Potassium Loss	Potassium levels will be maintained in a therapeutic range	Monitor lab values and vital signs, and characteristics of pulse Assess changes in muscle strength Assist patient to include foods high in potassium, such as citrus fruits, green vegetables, meats, whole grain foods and fish
Weight Gain Related to Increased Appetite and Water Retention	The patient will maintain a normal body weight	Instruct patient on principles of good nutrition Instruct patients to avoid fad diets and to consult a physician before starting a weight loss program Advise patient that fluctuations in appetite are a normal effect of steroid medications that require a conscious effort to control Provide emotional support when changes in body image occur from weight gain from steroids

Appendix 3.4 Nursing Care Plan for the Myasthenic Patient With Feeding Difficulties

Nursing Diagnosis	Patient Outcome	Intervention
Difficulty chewing	The patient will be able to achieve nutritional intake of food to sustain life	Instruct patient on principles of good dental hygiene Instruct patient to take small portions of food into the mouth. Instruct patient to take rests while chewing and in between bites to restore strength. Serve meals at times of maximum strength (usually in the earlier part of the day and 1/2 hour after cholinesterase inhibitor medications). Serve larger meal in the morning and smaller meals in the evening. Review food preparation techniques so that food is easier to consume because of softer consistencies. Review principles of nutrition and basic food groups so that the patient can select food that provides a balanced diet.
Difficulty swallowing with the potential for episodes of choking	The patient will chew and swallow food with minimal problems The patient will take in food without experiencing coughing or choking	Apply principles of good nutrition in food selection. Place the patient in an upright position with head tilted slightly forward for optimal positioning for swallowing. Provide liquids in small amounts to facilitate swallowing. Provide meals at optimal strength times. (after medication, earlier in the day). If swallowing only slightly impaired, instruct patient to lean forward, take a small breath through the nose and cough forcefully to push the irritating substance out of the throat If choking occurs, apply emergency principles as outlined by the American Heart Association to include the Heimlich maneuver

Appendix 3.5 Nursing Care Plan for the Psychosocial Aspects of MG

Nursing Diagnosis	Patient Outcome	Intervention
Potentially dysfunctional self concepts	Positive self esteem, body image & personal identity	Encourage patients to verbalize the meaning of the illness/loss (i.e., "How do you feel about what is happening to you?") Listen attentively and compassionately. Since appearances may greatly alter and weakness may leave patients unable to take care of grooming needs, help them to look their best. Be honest about realities of the illness; encourage patients to seek help if denial becomes detrimental. Facilitate acceptance; help patients set realistic, short-term goals so that success may be achieved. Encourage patients to do the things that they are capable of doing. Share hopeful aspects of the disease with patients and family. Recognize that the family too will be experiencing grief for the loss of the way the patient "used to be."

Appendix 3.5 Nursing Care Plan for the Psychosocial Aspects of MG

continued from previous page

Nursing Diagnosis	Patient Outcome	Intervention
Ineffective Coping Mechanisms	Identify new coping mechanisms	Help patients to identify how they coped with adversity in the past
Altered role performance	Adjust to new role changes	Determine what their usual coping mechanisms are, and how they can best be used to cope with the MG. Assist patients in identifying factors in their environment that have the potential to undermine positive adaptation. Involve patients in the planning and decision making regarding care. Give patients and family information regarding the disease, medications, emergency measures, and precautions for living with MG after discharge from the acute care setting. Explore patient role changes so that they will be less threatening Supply information on local MG chapter. Relationships can be formed with others with the disease and be a great source of strength to patients and family
Anxiety related to disease process and lifestyle alterations	Patient and significant others will express causes of anxiety	Active Listening Refer if necessary for counseling or therapy to deal with anxiety
Fear of death: patient family and friends	Patient, family and friends will set realistic goals related to the causes of anxiety	Active Listening

Appendix 7.1: Testing Procedure for Hand-Held Dynamometry

Appendix 7.2 lists the test position for each muscle group. All tests are conducted with the patient supine except for knee flexion and extension which are tested with the patient in sitting. Each muscle group is tested in a gravity eliminated position and the shaft of the dynamometer is held perpendicular to the tested limb segment. Patients are stabilized by another person during knee flexion and extension and shoulder extension trials. See associated figures for a visual reference.

At least one practice is given to the patients to give them the feel of pushing against the dynamometer. Patients are taken through each desired movement passively by the tester. The patient then performs the movement actively until the movement is performed correctly. Make tests are employed as the patients are asked to build their force gradually to a maximum voluntary contraction over a two second period. Each trial lasts 7.0 seconds during which the tester holds the dynamometer still and perpendicular to the limb segment. A rest period lasting one to two minutes is provided before a second measure was taken. Peak force values are recorded for each trial from the digital readout on the dynamometer.

Appendix 7.2 Subject Position, Placement of Dynamometer, and Location of Stabilization Provided for each Tested Muscle Group.

MUSCLE GROUP	SUBJECT POSITION	DYNAMOMETER PLACEMENT	STABILIZATION OF SUBJECT
Shoulder Flexors	Shoulder flexed 90°; elbow extended	Just proximal to epicondyles of humerus	Proximal arm
Shoulder Extensors	Shoulder flexed 90°; elbow extended	Just proximal to epicondyles of humerus	Assistant stabilized at superior aspect of shoulder
Shoulder Abductors	Shoulder abducted 45°; elbow extended	Just proximal to lateral epicondyle of humerus	Superior aspect of shoulder
Shoulder Lateral Rotators	Shoulder abducted 45°; elbow at 90°	Just proximal to styloid processes	Elbow
Shoulder Medial Rotators	Shoulder abducted 45°; elbow at 90°	Just proximal to styloid processes	Elbow
Elbow Flexors	Shoulder at neutral; elbow flexed 90°; forearm supinated	Just proximal to styloid processes	Superior aspect of shoulder
Elbow Extensors	Shoulder at neutral; elbow flexed 90°; forearm in neutral	Just proximal to styloid processes	Anterior aspect of shoulder
Wrist Extensors	Shoulder at neutral; elbow flexed 90°; wrist at neutral; fingers relaxed	Just proximal to metacarpophalangeal joints	Forearm maintained in gravity-eliminated position
Hip Flexors	Hip flexed 90°; knee relaxed; contralateral limb in neutral	At femoral condyles	Thigh maintained in gravity-eliminated position
Hip Abductors	Both lower limbs in neutral	At lateral femoral condyle	Contralateral lower limb held in neutral
Knee Flexors	Hips and knees flexed 90°; hands resting in lap	Just proximal to malleoli	Assistant stabilized at shoulders
Knee Extensors	Hips and knees flexed 90°; hands resting in lap	Just proximal to malleoli	Assistant stabilized at shoulders
Ankle Dorsiflexors	Hip, knee, and ankle at 0°	Just proximal to metatarsophalangeal joints	Knee maintained in full extension; leg supported with foot off table

Appendix 7.3 Sample Hand Held Dynamometry Scoring Sheet

UNC HOSPITALS
Chapel Hill, North Carolina
DEPARTMENT OF PHYSICAL THERAPY
DYNAMOMETRY RECORDING SHEET

Notes: _____

	Test 1 Date _____		Test 2 Date _____		Test 3 Date _____	
NECK	Left	Right	Left	Right	Left	Right
FLEXION						
EXTENSION						
SHOULDER	Left	Right	Left	Right	Left	Right
FLEXION						
EXTENSION						
ABDUCTION						
ADDUCTION						
EXT ROTATION						
INT ROTATION						
ELBOW	Left	Right	Left	Right	Left	Right
FLEXION						
EXTENSION						
WRIST	Left	Right	Left	Right	Left	Right
FLEXION						
EXTENSION						
UPPER LIMB MEAN						
HIP	Left	Right	Left	Right	Left	Right
FLEXION						
EXTENSION						
ABDUCTION						
ADDUCTION						
KNEE	Left	Right	Left	Right	Left	Right
FLEXION						
EXTENSION						
ANKLE	Left	Right	Left	Right	Left	Right
DORSIFLEXION						
PLANTAR FLEX						
LOWER LIMB MEAN						

Comments/Summary: _____
_____, PT Physical Therapist

Appendix 10.1 Patient/Provider Handout for the Dental Patient

DENTAL CARE FOR PATIENTS WITH MYASTHENIA GRAVIS

INFORMATION FOR THE PATIENT AND THE PATIENT'S DENTIST.

Maintaining good oral health is important to overall health. Regular oral hygiene performed at home with tooth brushing and daily flossing between the teeth is essential for plaque control and the prevention of both gum disease and tooth decay. Regular dental visits for professional cleaning and exams are important to maintaining a healthy dentition. If your myasthenia is under good control you should be able to receive regular dental care at the general dentist's office in your community.

The following are suggestions and information for you and your dentist to allow you both to enjoy a safe and pleasant dental experience.

ORAL/FACIAL FINDINGS that might be noticed in association with myasthenia gravis:

1. **Tongue**: Lipomatous atrophy of the tongue may result in a furrowed and flaccid clinical appearance. In severe cases, it can result in a triple longitudinal furrowing of the tongue.

2. **Mouth Drop**: Lack of muscle strength in the masseter muscle, especially following a sustained chewing effort, may cause the mouth to hang open, unless the mandible (lower jaw) is held shut by hand.

3. **Chewing/Swallowing**: Lack of strength in the muscles of mastication can inhibit proper mastication of food. Eating can be further inhibited by dysphagia (difficulty swallowing), when the tongue and other muscles used for swallowing are involved and by abnormal passage of food or liquids from the nasopharynx into the nasal cavity, when the palatal and pharyngeal muscles are affected.

Consequences:

a. poor nutrition
b. dehydration
c. hypokalemia

To prevent/improve:

a. take cholinesterase inhibitor medication 1 hr before meal
b. allow ½ hr rest period before meals and frequent rests while eating
c. eat your main meal in the morning when muscles are stronger
d. consume soft foods in small portions

DENTAL CARE FOR PATIENTS WITH MYASTHENIA GRAVIS

INFORMATION FOR THE PATIENT AND THE PATIENT'S DENTIST.

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DENTAL MANAGEMENT CONSIDERATIONS:

1. <u>Preventing and managing myasthenic weakness or crisis</u>.

a. Short duration, morning appointments
– reduce stress
– minimize fatigue
– take advantage of typically greater muscle strength in AM

b. Schedule appointment approx. 1-2 hrs following pyridostigmine intake or if your physician allows, modify your pyridostigmine schedule to allow drug intake approx. 1 hr prior to dental appt. to maximally benefit from the drug's peak effect.

c. Tell your dentist how frequently you have weakness and what muscles are usually involved.

– if your MG is stable, with limited or mild neuromuscular involvement, you can be safely treated in a private dental office

– if you have frequent exacerbations, or significant oropharyngeal, respiratory, or generalized weakness you may receive dental care most safely in a facility with emergency intubation and respiratory support capabilities, such as a hospital or Oral Surgeon's office. Ask your dentist about his emergency equipment.

– if you are anticipating significant oral surgery (wisdom tooth extractions, multiple tooth extractions) and you have frequent severe crises, your physician may recommend PLEX therapy before your oral surgery.

d. If an exacerbation is precipitated, you should be evaluated for severity of neuromuscular involvement by your neurologist, if possible. This may involve an intravenous injection of edrophonium.

e. If respiratory collapse occurs, an open airway and adequate respiratory exchange must be established. Ask your dentist if he and his staff are trained in and prepared to do basic life support (CPR) until the ambulance arrives, if needed. Dental suction devices can be used to suction secretions and debris from the oropharynx to prevent aspiration and mechanical blockage of the airway. Manual retraction of the weakened tongue may prevent obstruction of the airway.

DENTAL CARE FOR PATIENTS WITH MYASTHENIA GRAVIS
INFORMATION FOR THE PATIENT AND THE PATIENT'S DENTIST.

continued from previous page

2. <u>Avoiding harmful drug interactions.</u>

Common drugs used in dentistry with potential complications for MG patients

General comments concerning local anesthetics:

1. Care should be observed in avoiding intravascular injection of local anesthetic.

2. Use of a vasoconstrictor, such as 1:100,000 epinephrine in combination with lidocaine is beneficial in maximizing anesthesia efficacy at the oral site, while minimizing total anesthetic dose.

3. The periodontal ligament injection and intrapulpal injection techniques should be considered if the dental procedure warrants their use.

4. Nitrous oxide/oxygen sedation may be helpful in allaying apprehension.

5. Intravenous sedation techniques and narcotic analgesics should be used with caution to avoid respiratory depression.

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3. Monitoring oral side effects/drug interactions of drugs/ therapies used to treat MG.

A. **Cyclosporine**:

1. May cause gingival hyperplasia (fibrous gum overgrowth) which may begin as early as the first month of drug use and seems to be dependent upon the presence of dental plaque or other local irritants, individual susceptibility and the dose of cyclosporine used.

2. Interacts with medications your dentist might prescribe:
   a. nephrotoxic interaction: gentamicin, vancomycin, ketoconazole and the nonsteroidal anti-inflammatory drugs (NSAIDS) e.g. ibuprofen.
   b. Cyclosporine levels increase to possibly toxic levels: erythromycin, ketoconazole, fluconazole and itraconazole.

B. **Azathioprine (Imuran®)**:

1. Suppresses immune system.
   a. may predispose to oral/wound infection
   b. may delay wound healing
   Consider need for antibiotic after oral surgery.

C. **Prednisone:**

1. Suppresses immune system.
   a. may predispose to oral/wound infection
   b. may delay wound healing
   Consider need for antibiotic after oral surgery.

2. May cause adrenal suppression, depending on dose taken.

Discuss with your physician and dentist whether you need to increase your steroid dose before stressful or complicated dental procedures (e.g. multiple extractions or general anesthesia). Generally no supplemental dose is needed for routine dental treatment.

D. **Pyridostigmine (Mestinon®, Regonol®):**

1. May cause your saliva flow to increase.
   a. You can use a low speed saliza ejector to collect the saliva during dental treatment.
   b. Your dentist can use high speed evacuation/suction to collect debris and saliva in your mouth during treatment.
   c. When having restorations (fillings) done, a rubber dam can be used to isolate your teeth and keep the dentist's water and restorative materials from getting near your throat. The dental treatment that requires a dry mouth and cannot be done using rubber dam isolation is making an impression for a crown or bridge prosthesis. If you are having this done you may need to ask for an appointment at a time when you haven't just taken your dose of pyridostigmine.

E. **Plasma Exchange:**

1. If your exchange protocol involves the use of anticoagulants (blood thinners), including heparin, dental treatment should be arranged for a non-exchange day in the treatment sequence.

DENTAL CARE FOR PATIENTS WITH MYASTHENIA GRAVIS

INFORMATION FOR THE PATIENT AND THE PATIENT'S DENTIST.

continued from previous page

4. <u>Modifying dental treatment to accommodate altered muscle strength.</u>

A. Oral hygiene aids:

1. Electric toothbrush
2. Manual toothbrush with modified handle for ease of grasp

B. Mouth prop, rubber dam isolation and saliva ejector use during dental treatment:

1. Mouth props prevents muscle strain of having to hold the mouth open during treatment
2. Rubber dam isolation prevents worries about choking. By keeping dental materials and water spray out of the throat
3. Saliva ejector suction tubing may be held and controlled by the patient to help avoid drooling and choking on saliva during procedures

C. Dental chair position:

1. Dental treatment is usually done in a reclining position. Let your dentist know if you are so far back that you feel like your throat is closing off.

D. Scheduled rest periods:

1. Let your dentist know if you will need frequent rest breaks during treatment.

E. Compromised ability to manage complete dentures:

1. Inability of the flaccid muscles to assist in retaining the lower denture and to maintain a peripheral seal for the upper denture.
2. Overextended and overcontoured maxillary dentures with thick flanges that impinge upon muscle and frenal attachments can lead to muscle fatigue and altered salivation.
3. Ill-fitting dentures may exacerbate symptoms of difficulty in closing the mouth, tongue fatigue, a tight upper lip, dry mouth, impaired phonation, dysphagia and masticatory problems.

Final Words of Wisdom:

Good preventive dental care (your good oral hygiene efforts at home and 6 month dental recall/professional cleaning visits) will help to prevent dental problems, oral infections and avoid the need for emergency dental care which is by its nature stressful.