Update for nurse anesthetists

Etiology, mechanisms, and anesthesia implications of autoimmune myasthenia gravis

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Myasthenia gravis (MG) is the prototypical neurological autoimmune disease. It is characterized by muscle weakness that progressively worsens on repetition but improves with rest. Muscle weakness and fatigability arise from defective or decreased acetylcholine receptors at the neuromuscular junctions, where nerve signals from spinal motor neurons that innervate muscles cannot effectively induce muscle contraction. Several mechanisms of pathogenesis lead to the MG syndrome. The most prevalent cause of MG is an autoimmune disorder in which the patient produces antibodies that attack the nicotinic acetylcholine receptor at the neuromuscular junction. Anesthesia management of the patient with MG is challenging and requires specific management; however, safe and successful outcomes are achievable. This course emphasizes the autoimmune neuromuscular defect in MG, current treatments for this syndrome, contraindications of certain anesthetic drugs in this condition, and anesthetic management of a patient with MG in the operating room environment.

Key words: Acetylcholine receptor, autoimmune disease, myasthenia gravis, receptor, neuromuscular junction.

Objectives
At the conclusion of this course, the reader should be able to:
1. Discuss the pathologic processes related to the neuromuscular junction in autoimmune myasthenia gravis.
2. Identify the cellular autoimmune events occurring in myasthenia gravis.
3. Describe the various modalities used in the treatment of myasthenia gravis.
4. Identify the pharmacologic agents that reduce neuromuscular transmission in patients with myasthenia gravis and should be avoided in the perioperative period.
5. Discuss the prudent delivery of anesthesia and the anesthetic plan for patients with myasthenia gravis.

Introduction
Myasthenia gravis (MG) is the prototypical neurological autoimmune disease. Willis first described the malady in 1672, but it was not until 1895 that Jolly used the name, myasthenia gravis. Jolly described a condition of 2 boys who exhibited muscle weakness that progressively worsened on repetition but improved with rest. Muscle weakness and fatigability arise from defective or decreased acetylcholine receptors (AChRs) at the neuromuscular junctions (NMJs), where nerve signals from spinal motor neurons that innervate muscles cannot effectively induce muscle contraction.

Various mechanisms of pathogenesis lead to the MG syndrome. Congenital myasthenias are caused by a variety of genetic defects (eg, ion channels or subunits of AChR mutations) of the presynaptic or postsynaptic machinery of the NMJ. Lambert-Eaton myasthenic syn-
drome frequently is associated with neoplasms and involves a dysregulation of presynaptic acetylcholine (ACH) release. It seems that the presynaptic defect involves an alteration in calcium channels and, consequently, decreased release of acetylcholine into the synapse.\textsuperscript{3,4} The most common cause of MG is an autoimmune disorder in which the patient produces antibodies that attack the nicotinic acetylcholine receptor at the NMJ.\textsuperscript{5} This article emphasizes the autoimmune neuromuscular defect in MG, current therapy for this syndrome, contraindications of certain anesthetic drugs in this condition, and anesthetic management of a patient with MG in the operating room environment.

**History and review of the literature**

- **Autoimmune neuromuscular MG.** The hallmark features of autoimmune MG are fatigue, increasing weakness with repetitive motion, and a higher incidence in women.\textsuperscript{6} Characteristics and symptoms of MG reflect the dysfunctional AChR at the NMJ, including generalized weakness in 85\% of patients and limited weakness of ocular muscles in 15\% of patients with ocular MG.\textsuperscript{7} While ocular MG is less prevalent, ocular muscle problems, such as ptosis or diplopia, usually are the initial complaint, with subsequent progression to the generalized disease.\textsuperscript{8} Patients with generalized MG complain of dysphagia, dysphonia, proximal limb muscle weakness, and even exacerbation to dyspnea or ventilatory failure (myasthenic crisis).\textsuperscript{9} In 85\% to 95\% of patients with MG, a thymic abnormality, such as thymoma or thymic hyperplasia, may be responsible for secretion of AChR antibodies.\textsuperscript{10}

Diagnosis testing for MG includes pharmacologic, electrophysiologic, and laboratory testing. Edrophonium, an anticholinesterase (anti-AChE), is administered to inhibit the enzyme that degrades ACh; therefore, more ACh remains at the synapse. The patient with MG (Figure 1) usually demonstrates a temporary reversal of muscle weakness with edrophonium.\textsuperscript{11} Nerve conduction tests, such as repetitive nerve stimulation, also are performed to verify the MG diagnosis. Motor response is monitored after the nerve is stimulated repetitively at the rate of 2 Hz, and the patient with MG usually exhibits a gradual decrease in amplitude.\textsuperscript{12} In addition, serum AChR antibodies are assayed to confirm the diagnosis; results for 90\% to 95\% of patients with MG are positive.\textsuperscript{10} The positive results from these testing modalities point to a defect in the NMJ in the patient with MG.

- **The neuromuscular junction.** Proper functioning of the NMJ is required for impulse propagation and muscle contraction. The NMJ is a complex structure, composed of the motor nerve terminal, postsynaptic muscle surface, and specialized basal lamina (Figure 2).

Nerve terminal endings are located presynaptically in the primary synaptic clefts at the synapse. The muscle surface area, postsynaptically, is enlarged by invaginations of the plasma membrane into secondary synaptic folds. The AChRs are located primarily at the distal extents of the folds, in closer apposition to the nerve terminals.\textsuperscript{6} There is continual AChR turnover, in which old receptors are internalized and degraded, and new receptors are synthesized and inserted into the synaptic folds.\textsuperscript{6} Skeletal muscle sodium channels are located in the depths of the folds, and AChE, the enzyme that hydrolyzes ACh, is located at the basal lamina of the secondary synaptic fold.\textsuperscript{6}

The generation of a muscle action potential and, ultimately, muscle contraction begins with the depolarization of the presynaptic nerve terminal. This leads to calcium influx via channels and calcium-dependent fusion of synaptic vesicles with presynaptic nerve terminal membrane in the nerve boutons. Fusion allows the release of ACh into the synapse, where the neurotransmitter then can diffuse across the synaptic cleft and bind to AChRs. If a large enough quantity of ACh is released, a muscle endplate potential is reached, resulting in postsynaptic depolarization and muscle contraction. ACh is removed by AChE hydrolysis and by diffusion.\textsuperscript{6}

Adult human AChR (Figure 3) is part of a superfamily of neurotransmitter-gated ion channels, and its pentameric (5-subunit) structure includes 2 α and 1 each of the β, δ, and ε subunits. Fetal AChR is similar, except a γ subunit is substituted for the ε subunit.\textsuperscript{13,14} The fetal AChR is retained in adult thymic myoid cells\textsuperscript{13} and adult ocular muscle fibers.\textsuperscript{16} The adult AChR subunits (see Figure 3) are believed to be arranged around a central ion channel in the following
order: \(\alpha_1\epsilon\alpha_1\delta\beta_1\). The ACh binding sites are formed at the union of the \(\alpha_1\) and \(\epsilon\) and the \(\alpha_1\) and \(\delta\) subunits. Both binding sites must be occupied by an agonist (ACh) for the ion channel to open. The binding of ACh to both sites results in a conformational change in the AChR and channel opening. Conversely, if an antagonist (e.g., vecuronium) binds one site, channel opening is prevented.

- **Autoimmune pathology.** A region located on the extracellular tip of the \(\alpha_1\) subunits has been described as the main immunogenic region. Since the main immunogenic regions are located at the outer (extracellular) portion of the AChR, they are easily recognized by antibodies. A single antibody is unable to cross-link 2 \(\alpha_1\) subunits but easily cross-links (Figure 4) 2 adjacent AChRs. These properties and characteristics of the main immunogenic region facilitate the pathogenic mechanisms involved in the autoimmune response to AChRs.

The evidence that links AChR antibodies as the causative factor in MG includes the following: (1) Of patients with MG symptoms, 85% have these antibodies. (2) Immunoglobulin G (IgG) has been found at the neuromuscular endplate. (3) Plasmapheresis to reduce circulating antibodies provides temporary symptomatic relief. (4) Healthy animals injected with antibodies against AChR produce MG signs. There also is the possibility that the antibodies bind to or near the ligand-binding site. Antibodies also can cross-link AChRs resulting in internalization, increased degrade-
tion rate, and a decrease in AChR density at the end-plate. This increase in AChR degradation correlates well with clinical manifestations of MG. Moreover, complement-mediated destruction of the NMJ occurs as a result of AChR antibodies. Antibodies bind to the C9 component of complement (part of the immune system involved in cell destruction), triggering an inflammatory cell response, endplate membrane degradation, and destruction of junctional folds that harbor AChR-abundant membranes (Figure 5). This inevitably would reduce the membrane surface available for AChR insertion. Therefore, the autoimmune response in MG affects many components of the machinery at the postsynaptic membrane, resulting in altered depolarization of muscle tissue.

Morphological studies of the NMJ in MG demonstrate the following postsynaptic anomalies (Figure 6): decreased quantity of AChR, widened and decreased machinery of the postsynaptic fold, and increased gap between presynaptic and postsynaptic membranes. Therefore, the primary pathologic mechanism of MG is a reduction in AChRs and, thus, a reduction in the end-plate potential that is not strong enough to reach threshold potential, depolarization of muscle membrane, and resultant muscle contraction. If this transmission failure occurs at many junctions, the strength of the muscle contraction is reduced and the patient becomes weak. Normally, only 25% to 30% of AChRs are necessary for neuromuscular transmission. The remaining 70% to 75% of receptors represent a “safety margin.” In MG, there is a decrease in the number of functional AChR and a decrease in the safety margin.

- **Cellular autoimmunity mechanisms.** The precipitating events that cause MG are not completely understood, but evidence implicates the thymus, as altered thymic function has a 90% prevalence in this disease. For example, thymoma or hyperplasia of the thymus occurs in high frequency in patients with MG, T and B cells have an active role in antibody formation, myoid cells of the thymus gland have the same type of surface as AChR, and thymectomies usually are beneficial for patients with MG. There seem to be different trigger mechanisms of autoimmunity for the various forms of MG. The patient with rheumatoid arthritis may trigger an MG syndrome by taking penicillamine, which is believed to react covalently with AChRs, producing new antigenic sites. This MG condition is reversible with the termination of penicillamine. A paraneoplastic immune response may account for the 12% of patients with MG who have a thymoma, for they have different HLA marker frequencies than do other patients with MG. This indicates a probable difference in immune system genetic background. They have not only high levels of AChR antibodies, but also antibodies to several muscle proteins in the interior of the cells. In most MG cases, the immunogen is likely the native muscle AChR or a closely related protein. The fetal type (γ subunit) has been implicated as the immunogen, as selective reaction with fetal AChRs has been reported with antibodies from patients with MG.

- **Molecular mimicry by microbes.** Also has been suggested to be responsible for the autoimmune response in MG, in which bacterial or viral proteins initiate the immune response, then reaction with the AChR leads to epitope (antigenic determinant) spreading. In addition, both bacteria and viruses can express superantigens that nonspecifically activate many T and B cells. Although the B cells synthesize the autoantibodies to AChR, there is evidence for a T-cell role in autoimmunity, as T cells from patients with MG seem to respond to AChR stimulation and aid in the production of AChR antibodies. Another T-cell role in MG is polyclonal and heterogeneous and recognized different epitopes on the AChR.

**State of the art**

- **Treatment of MG.** Treatment modalities usually reflect the rate of progression, severity, and weakness
distribution of the patient. Age, sex, and the presence of concomitant diseases also influence long-term therapy decisions. In general, the treatment for MG consists of 5 modalities: anticholinesterase drugs, immunosuppressants, thymectomy, plasmapheresis, and intravenous immunoglobulins (IgG).

Anticholinesterases usually are the initial therapy and provide symptomatic improvement in muscular strength, as they inhibit the enzyme that degrades ACh. This allows ACh to remain longer at the NMJ, increasing the probability for ACh binding to AChRs.

Immunosuppressant drugs (eg, corticosteroids, azathioprine, and cyclosporine) are administered to decrease the immune response and modulate mechanisms in cellular immunity. Since thymic abnormalities (hyperplastic changes and neoplasias) are prevalent and evidence suggests they are intricately involved in many forms of MG, surgical thymectomies are also performed. As mentioned previously, it is hypothesized that autoreactive T cells are activated in the thymus. Studies indicate that thymectomies decrease T-cell reactivity against disease-specific antigens and provide symptomatic relief. In addition, if the source of the immunogen is thymic myoid cells, their elimination may decrease the immune response as a possible reservoir of AChR antibody-producing B cells may be removed with this operation.

Plasmapheresis usually is used as a short-term treatment in patients with extreme weakness. This treatment is believed to remove circulating AChR antibodies and immune complexes, often resulting in rapid improvement, which lasts 6 to 8 weeks.

In addition to plasmapheresis, intravenous immunoglobulins (IgG) have been used in the extremely weakened patient with acute MG. The mechanism by which IgG improves MG symptoms is unclear but is speculated to involve the interaction between autoantibodies and anti-idiotypic (nonspecific) antibodies in
IgG preparations. Future treatment modalities are being considered with a more cell-directed approach, such as monoclonal antibodies directed against helper T cells and administration of immunotoxins that would destroy B cells specific for AChRs.

- **Anesthesia pharmacology contraindications.** The hallmark symptom of muscle weakness, especially after repetitive stimuli, can lead to dangerous and life-threatening situations for the patient with MG. One such environment or condition is surgery (often an elective thymectomy) and, more important, the administration of anesthesia during the surgical procedure. MG is a condition of particular interest to anesthesia as it involves the NMJ, the site of action of many commonly used anesthetic drugs. There are many pharmacologic agents used in anesthesia that can lead to devastating consequences and even precipitate a myasthenic crisis in the patient with MG.

- **Muscle relaxants.** The response of the patient with MG to muscle relaxants is difficult to predict, and administration of these drugs should be monitored closely with a peripheral nerve stimulator. The drugs that are used to treat MG (anticholinesterases) have an effect on the response to muscle relaxants. For example, the anticholinesterase, pyridostigmine, not only inhibits the AChE enzyme, but also decreases plasma cholinesterase activity. Plasma cholinesterase is responsible for degrading succinylcholine, a depolarizing neuromuscular blocker, and ester-type local anesthetics. In addition, patients with MG treated with pyridostigmine show a marked resistance to succinylcholine, which causes depolarization of muscle endplates, and this is thought to be the result of the reduced number of AChRs at the NMJ. Thus, there may be prolonged effects of anesthetic drugs from these medications. Conversely, patients with MG are extremely sensitive to nondepolarizing muscle relaxants (eg, curare). Studies demonstrate the increased sensitivity to various nondepolarizing muscle relaxants (competitive antagonists) such as atracurium and vecuronium. However, the use of short- and intermediate-acting muscle relaxants is acceptable with judicious titration and peripheral nerve monitoring, with the ability to reverse their effects at the end of surgery. In addition, the use of these shorter-acting muscle relaxants may avoid the need for reversal with anti-AChE, which can trigger a cholinergic crisis. A cholinergic crisis is characterized by muscle weakness and respiratory insufficiency similar to that seen with MG. It is precipitated by an excess of the anti-AChE agent.

- **Miscellaneous drugs.** Certain antibiotics have been reported to reduce neuromuscular transmission in patients with MG and should be avoided during the perioperative period. Aminoglycosides (streptomycin, kanamycin, gentamicin, neomycin, amikacin, erythromycin, and polymyxin B sulfate) have all been implicated in this action. It seems that calcium gluconate is effective in reversing this aminoglycoside-induced muscle weakness, whereas calcium chloride partially antagonizes the neuromuscular block produced by polymyxin B. In addition, 2 cases have been reported involving ciprofloxacin and increased neuromuscular blockade. There are several cardiovascular drugs that also have demonstrated worsening of MG and should be given with caution or avoided. Propranolol seems to potentiate MG, and β-blockers seems to also potentiate MG because of their depressant effects on the NMJ. and antiepileptic drugs, especially phenytoin, can decrease muscle strength. These medications should be avoided whenever possible.

### Current practice of anesthesia in MG

- **Preoperative care.** An MG severity classification system by Osseman and Genkins (Table) has been described: I, ocular signs and symptoms only; IIA, generalized mild muscle weakness; IIB generalized moderate weakness and/or bulbar dysfunction; III, acute fulminating manifestations and/or respiratory dysfunction; and IV, late, severe, generalized MG. This grading system can be useful as an indication for perioperative complications.

There is approximately a 10% incidence of other autoimmune diseases that occur concomitantly with MG, including hypothyroidism (10% occurrence), rheumatoid arthritis, systemic lupus erythematosus, and pernicious anemia. It is important to optimize these conditions before elective surgery for the patient with MG. This includes optimizing a euthyroid state, evaluating cervical spine involvement in the patient with rheumatoid arthritis, and relief or lessening of systemic lupus erythematosus manifestations.

The respiratory status of the patient should be evaluated with spirometry, as MG affects both the inspiratory and expiratory muscles. Pulmonary function

### Table. Myasthenia gravis severity classification system by Osseman and Genkins

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<tr>
<th>Classification</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>I</td>
<td>Ocular signs and symptoms</td>
</tr>
<tr>
<td>IIA</td>
<td>Generalized mild muscle weakness</td>
</tr>
<tr>
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<td>Late, severe, generalized myasthenia gravis</td>
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tests show low vital capacity, normal total lung capacity, normal or elevated residual volume, and decreased maximal inspiratory and expiratory pressures. However, patients with MG maintain a normal response to carbon dioxide and an intact ventilatory drive. About 15% of patients with MG have thymomas that, if they become large enough, can cause airway collapse and occlusion at the induction of general anesthesia. These patients should undergo chest computed tomography and flow volume spirometry to evaluate the severity of this mediastinal mass and the potential for tracheal occlusion.

A thorough cardiac assessment should be conducted, especially for conduction defects, ST and T wave changes, and arrhythmias (bradycardia, ventricular premature contractions, atrial fibrillation) that are observed in patients with MG. Significant arrhythmias should be evaluated and treated by a cardiologist before surgery. A small percentage of patients with MG are reported to have myocarditis, which may be related to MG or to an associated autoimmune disorder. These patients demonstrate impaired left ventricular filling that usually is reversed by an anticholinesterase. When symptoms of impaired cardiac function are discovered, referral to cardiology for further evaluation (eg, echocardiography) and optimization should be performed.

As a result of the weakened muscularature of the oropharynx, the patient with MG is at high risk for pulmonary aspiration of gastric contents. Therefore, it is prudent to prophylactically administer sodium citrate to neutralize gastric acids, a gastrointestinal prokinetic medication (eg, metoclopramide) to increase gastric motility, and a histamine (H2) blocker to decrease gastric acid production.

Preoperative management goals include optimization of anticholinesterase therapy, weaning of corticosteroids to the lowest possible dose, and, if needed, plasmapheresis to prepare the patient for surgery. Plasmapheresis is recommended for patients with MG with a vital capacity of less than 2 L and leads to temporary remission in 45% of cases. However, caution needs to be taken in administering drugs metabolized by plasma cholinesterases, such as succinylcholine and mivacurium, as their action may be prolonged.

• Premedication. There are varying regimens for the administration of anticholinesterase (anti-AChE) drugs to the patient with MG. One regimen suggests administering one half the usual morning dose for patients with class I or II MG and the full dose for more severe cases. Other anesthesiologists withhold anti-AChE drugs on the morning of surgery in order to decrease the dose of muscle relaxant needed.

Preoperative sedation with opioids and anxiolytics should be used judiciously, as patients with MG have very little respiratory reserve. There also is a high likelihood of a need for postoperative ventilatory support; therefore, the patient should be counseled for the possibility of endotracheal tube intubation and ventilatory support following surgery. The following preoperative criteria correlate with the need for postoperative ventilatory support in the patient undergoing thymectomy: (1) disease duration greater than 6 years, (2) presence of chronic obstructive pulmonary disease, (3) pyridostigmine dose greater than 750 mg per day during the 48 hours before surgery, and (4) preoperative vital capacity less than 2.9 L.

The anesthetic plan or management of the myasthenic patient should be individualized according to the severity of the disease and the nature of the surgical procedure. Whenever possible, regional or local anesthesia should be used rather than general anesthesia. However, the amount of local anesthetic may need to be reduced, especially ester local anesthetics in a patient receiving anticholinesterase drugs, since ester local anesthetics are degraded by plasma cholinesterases. Furthermore, the level of block for spinal or epidural anesthesia must be controlled closely to prevent a high thoracic block that could weaken accessory respiratory muscles, resulting in dyspnea or acute respiratory failure. In addition, a combined technique of general anesthesia and regional anesthesia (epidural block) can provide excellent muscle relaxation without the use of neuromuscular blockers. This has been demonstrated in laparoscopic surgery with immediate tracheal extubation postoperatively.

• Intraoperative care. Standard monitoring should be used for every patient with MG undergoing surgery: temperature, electrocardiogram, blood pressure, pulse oximetry, in-line carbon dioxide, and ventilation rate, and an arterial line should be inserted for obtaining samples for blood gas analysis that can guide the timing of extubation. In addition, for a large thymoma case, central venous access should be obtained, as the potential for blood loss is increased.

Induction of anesthesia with a short-acting intravenous agent is appropriate for the patient with MG; however, one should anticipate an exaggerated respiratory depressant effect. The intubation of the trachea usually requires the use of muscle relaxation in the patient without MG; however, this may be accomplished without muscle relaxation by exploiting the existing weakness and the relaxing effects of volatile gas anesthetics on skeletal muscle. As an alternative, lower doses of muscle relaxants may be used prudently.

The maintenance of anesthetic depth for surgery often is achieved by the use of nitrous oxide and a volatile anesthetic gas. The muscle-relaxing properties
associated with volatile anesthetic gases usually reduce or even eliminate the dose of muscle relaxants needed, as neuromuscular transmission is reduced by about 50%. In addition, anesthetic gases dissipate at the end of surgery, which allows for the evaluation of skeletal muscle strength during the early postoperative period. If a muscle relaxant is required, a short- or intermediate-acting nondepolarizing muscle relaxant, such as mivacurium or vecuronium, is used with one half to two thirds the normal dose administered. Careful monitoring with a peripheral nerve stimulator should be conducted. Opioids are used with caution due to their ventilatory depressant effects. Intravenous general anesthesia with propofol also has been used successfully; it provides easy control of depth and quick recovery and avoids consequences at the NMJ.

**Postoperative care.** Postoperatively, the endotracheal tube often is left in place until demonstration of adequate levels of ventilation are observed. Good indications of the need for postoperative ventilatory support are the aforementioned preoperative criteria. Gracey et al describe recent surgery (especially thymectomy) as the most common reason for respiratory failure. Criteriathe patient's respiratory rates should be less than 30 per minute and vital capacity more than 10 mL/kg; arterial blood gases should reflect a PaO2 of more than 90 mm Hg, a PaCO2 of less than 50 mm Hg, and pH more than 7.30. Another reason the patient with MG may have respiratory difficulty postoperatively is bilateral vocal cord abductor weakness (stridor), and this should be evaluated.

Postoperative analgesia can be achieved by cautious administration of oral or parenteral opioid analgesics or by using regional anesthesia techniques. With opioid administration, it is imperative to monitor the respiratory status of the patient with MG, as ventilatory reserve is decreased and the patient is more prone to respiratory depression. As an alternative, epidural narcotics provide excellent postoperative analgesia for the patient with MG with a much lower incidence of respiratory depression.

Furthermore, the reintroduction of the patient's preoperative medications in the early postoperative period is very important, especially the anticholinesterases. Preoperative medications must be continued as soon as possible, especially since the improvement of MG symptoms is delayed after a thymectomy. Efforts to optimize preoperative respiratory function and postoperative pain control are effective in decreasing postoperative complications. It also is extremely important to avoid drugs known to increase the muscle weakness of MG.

**Summary**

Myasthenia gravis most commonly is an acquired autoimmune disease that is exemplified by production of AChR antibodies. Decreased AChR numbers at the NMJ are manifested as a decreased amplitude of endplate potential, which is represented clinically as muscle weakness. The AChR antibodies are present in 80% to 90% of cases and are produced by B cells in a T cell–dependent manner, and a pathologic thymus is implicated to have an important role in MG genesis and progression. IgG and complement components are deposited on the postsynaptic membrane, and destructive mechanisms may consist of increased degradation of AChRs, cross-linking of AChRs, and blockage of AChRs. Since the NMJ involves the site of action of many commonly used anesthetic drugs, anesthesia providers must understand the pathophysiology of MG, be cognizant of the many drug interactions that can be detrimental to the myasthenic patient, and administer anesthetics that would most benefit the patient with MG.

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