Anesthesia for the patient with myasthenia gravis

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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder characterized by fatigable weakness of skeletal muscles. Weakness results from an antibody-mediated immunologic attack directed at acetylcholine receptors (or receptor-associated proteins) in the postsynaptic membrane of the neuromuscular junction.

Anesthetic concerns for patients with MG include the interactions among the disease, the disease treatment, and the medications used for anesthesia, particularly neuromuscular blocking agents (NMBAs). Patients with MG are unpredictably sensitive to nondepolarizing NMBAs and are resistant to succinylcholine, a depolarizing NMBA.

Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder of the neuromuscular junction, with antibodies directed against the presynaptic voltage-gated calcium channels. It is often associated with an underlying malignancy, most commonly small cell lung cancer, though it is also associated with other autoimmune processes. Patients with LEMS are very sensitive to both depolarizing and nondepolarizing NMBAs.

This topic will discuss the anesthetic management of patients with MG and LEMS. Diagnosis, clinical manifestations, and management of MG and LEMS are discussed in detail separately.

- (See "Diagnosis of myasthenia gravis".)
- (See "Clinical manifestations of myasthenia gravis".)

- (See "Overview of the treatment of myasthenia gravis".)
- (See "Lambert-Eaton myasthenic syndrome: Clinical features and diagnosis".)
- (See "Lambert-Eaton myasthenic syndrome: Treatment and prognosis".)

PREOPERATIVE EVALUATION

Preoperative preparation for elective surgery for patients with MG should be coordinated with the patient's neurologist. Elective surgery should be performed during a stable phase of the disease, when the patient requires minimal immunomodulatory medication or glucocorticoids, to minimize the chance of postoperative myasthenic crisis. In addition to routine preoperative evaluation, assessment of patients with MG should focus on bulbar and respiratory symptoms, as well as prior history of exacerbations or myasthenic crisis. Surgery should be scheduled as early in the day as possible, when the patient is strongest [1].

History — Patients with MG should be evaluated preoperatively for the following:

- Bulbar symptoms (eg, dysphagia, dysarthria, nasal speech, or low-intensity speech), which may predispose to aspiration
- History of myasthenic crisis and need for endotracheal intubation
- Respiratory muscle weakness, shortness of breath, and dyspnea
- MG therapy
- Associated diseases, including other autoimmune diseases (eg, thyroiditis, rheumatoid arthritis, systemic lupus erythematosus)

Patients having thymectomy for thymic mass may be at risk for airway compromise with induction of anesthesia. Imaging studies (eg, chest computed tomography) should be reviewed. (See "Anesthesia for patients with an anterior mediastinal mass".)

Prediction of postoperative myasthenic crisis

Risk factors — A number of authors have attempted to define risk factors for postoperative myasthenic crisis. Retrospective studies including patients with MG who underwent transsternal thymectomy or videoscopic thymectomy using a variety of anesthetic strategies have reported associations between a number of preoperative factors and the need for postoperative ventilation. These include:

- Vital capacity <2 to 2.9 L [2-4]

- Duration of MG (greater than six years) [3]
- Pyridostigmine dose >750 mg/day [3]
- History of chronic pulmonary disease [3]
- Preoperative bulbar symptoms [5-8]
- History of myasthenic crisis [5,8]
- Intraoperative blood loss >1000 mL [5]
- Serum antiacetylcholine receptor antibody >100 nmol/mL [5]
- More pronounced decremental response (18 to 20 percent) on low-frequency repetitive nerve stimulation [4].

Preoperative pulmonary evaluation — In consultation with the patient's neurologist, pulmonary function testing (PFT) may be performed for patients with MG who will receive general anesthesia with the use of neuromuscular blocking agents (NMBAs) to assess optimization, to help establish a baseline for extubation, and to help plan for the level of postoperative care.

The available literature is insufficient to determine the level of preoperative pulmonary dysfunction that would predict the need for postoperative ventilation or the risk of myasthenic crisis for a specific surgical procedure. A retrospective review of patients who underwent video-assisted thoracoscopic thymectomy reported no difference in the need for intensive care unit admission for patients with a preoperative vital capacity <2 L compared with those with vital capacity >2 L [8], although previous studies had found an association [2,3]. A retrospective review of patients with MG who underwent videoscopic thymectomy found that patients who had myasthenic crisis after surgery had lower forced vital capacity (FVC) than those who did not (2.1 versus 3.0 L) [4].

Myasthenia gravis treatments — Patients with MG are treated with one or more medical therapies: symptomatic treatment (ie, anticholinesterase agents), chronic immunomodulating treatments (ie, glucocorticoids and other immunosuppressive medication), and rapid immunomodulating treatments for symptom exacerbations (ie, plasmapheresis and intravenous immune globulin [IVIG]). These therapies are discussed separately. (See "Overview of the treatment of myasthenia gravis", section on 'Overview of therapies'.)

Anticholinesterase agents — We suggest continuing anticholinesterase agents (ie, pyridostigmine or neostigmine) up to and including the morning of surgery, recognizing that the response to both depolarizing and nondepolarizing NMBAs may be modified by these medications. In addition, the response to NMBA reversal agents may be unpredictable or insufficient. Patients with MG who are maintained on

anticholinesterases can be quite sensitive to discontinuation of the medication, with development of respiratory and bulbar weakness if medication is withheld. (See 'Neuromuscular blocking agents' below.)

A study of 14 patients with MG scheduled to undergo thymectomy randomly assigned patients to receive their usual dose of pyridostigmine on the morning of surgery or to discontinue the medication after the last dose the night prior to surgery. Three of seven (43 percent) patients who did not receive pyridostigmine on the morning of surgery complained of respiratory discomfort while waiting for surgery (including two who required rescue IV neostigmine preoperatively), compared with none of the patients who received their usual medication. The study reported resistance to and delayed onset of block with vecuronium administration in patients who took their morning dose of pyridostigmine, but full reversal of neuromuscular block was accomplished in all patients [9].

Pyridostigmine, the most commonly used anticholinesterase for MG, has a rapid onset of action (15 to 30 minutes), with peak action at approximately two hours, and its effects last for three to four hours, sometimes longer. The timing and dose of medication is individualized based on the patient's symptoms. The starting dose is often 30 mg orally (per os [PO]), with the dose then titrated to effect. If IV dosing is necessary in the perioperative period, the IV dose is approximately one-thirtieth the oral dose (ie, 1 mg IV is equivalent to 30 mg PO).

Glucocorticoids — Patients whose treatment for MG includes glucocorticoids may be at risk for hypothalamic pituitary axis suppression and adrenal insufficiency in the perioperative period, and may require administration of stress-dose glucocorticoids, depending on the surgical procedure (table 1). These issues are discussed in detail separately. (See "The management of the surgical patient taking glucocorticoids" and "Major adverse effects of systemic glucocorticoids", section on 'Metabolic and endocrine effects'.)

The following approach applies to patients without underlying primary adrenal insufficiency.

- Patients who are currently taking glucocorticoids should take their usual daily dose of glucocorticoid (or the parenteral equivalent). Stress dose glucocorticoids should not routinely be administered before induction of anesthesia for these patients.

- Patients who have taken glucocorticoids of any dose for less than three weeks, daily prednisone less than 5 mg or its equivalent (table 2) for any duration, or less than 10 mg prednisone or its equivalent every other day in the six months prior to surgery are not at risk for hypothalamic-pituitary-adrenal axis suppression, and they should not receive stress dose glucocorticoids.

- Patients who have taken doses of 5 mg or more of prednisone (or its equivalent) for more than three weeks within six months of surgery or who appear Cushingoid should either receive stress dose glucocorticoids before induction of anesthesia, or they should have their hypothalamic pituitary axis tested preoperatively (table 1).

Immunotherapy — Long-term immunotherapy for MG may include administration of azathioprine, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, rituximab, and tacrolimus. Additionally, several newer biologics have been approved for use in MG. There are no published data to guide management of these immunomodulatory drugs around the time of surgery. Although parenteral substitution is possible for both cyclosporine and azathioprine, they likely can be held on the morning of surgery given the long duration of effect. The time course of immunomodulatory effects of these medications suggests that perioperative drug interruptions are not likely to cause significant symptomatic effect. (See "Chronic immunotherapy for myasthenia gravis".)

Preoperative laboratory assessment including electrolytes, renal and hepatic function tests, and complete blood count should be performed for patients taking these medications. While azathioprine injected at supratherapeutic doses has been shown to reverse existing nondepolarizing neuromuscular block in animals, this is not likely a clinically relevant effect in humans [10-12]. Prior administration of azathioprine has been shown to have no effect on dose response curves of nondepolarizing neuromuscular blockade.

Rapid immunomodulating therapy — Plasmapheresis and IV immune globulin (IVIG) are rapid therapies that work quickly (over days), but the benefits are only short-term (weeks). They are used preoperatively before thymectomy or other surgery, as a bridge to slower-acting immunotherapies, during myasthenic crisis, and periodically to maintain remission for patients with MG that is not well controlled otherwise. (See "Overview of the treatment of myasthenia gravis", section on 'Plasma exchange and IVIG as rescue or bridge therapies'.)

ANESTHESIA MANAGEMENT

Principles of the management of anesthesia for patients with MG

- If sugammadex is not available, avoid neuromuscular blocking agents (NMBAs) if at all possible.
- Whenever NMBAs are used in patients with MG, a quantitative neuromuscular monitor should be used to assess reversal and a train of four ratio > 0.9 confirmed prior to extubation.(See 'Neuromuscular blocking agents' below and "Monitoring neuromuscular blockade", section on 'Qualitative versus quantitative monitoring'.)
- Use of ultrashort- or short-acting sedatives, hypnotics, and anesthetic agents to minimize respiratory depression on emergence from anesthesia.

Premedication — In many cases, premedication with sedatives can be avoided by reassurance and explanation of expected procedures. If premedication is necessary, the smallest effective dose should be administered incrementally (eg, midazolam 0.5 mg intravenously [IV]), with continuous monitoring for signs of bulbar weakness and respiratory compromise.

Choice of anesthetic technique — When possible, local or regional anesthesia should be used. Regional anesthesia should be considered for peripheral procedures that can be done with relatively low-level neuraxial anesthesia, either epidural or spinal, or with peripheral nerve blocks. If local anesthetics are used, amide local anesthetics (ropivacaine, mepivacaine, bupivacaine, lidocaine) should be chosen over esters for patients who take anticholinesterases [13]. Anticholinesterases, used for treatment for patients with MG, may theoretically impair the hydrolysis of ester local anesthetics (eg, chloroprocaine) and result in prolonged block, although there are no studies providing evidence of this effect.

Additional concerns specific to the patient with MG include:

- **Neuraxial anesthesia** – Midthoracic or higher levels of neuraxial anesthesia can result in paralysis of accessory muscles of breathing. Patients with preoperative respiratory compromise or bulbar weakness may not tolerate such levels of motor block. (See "Overview of neuraxial anesthesia".)
- **Brachial plexus blocks** – In most patients, supraclavicular and interscalene brachial plexus blocks for upper-extremity surgery paralyze the diaphragm on the

side of the block by blocking the phrenic nerve, potentially for many hours, which may not be tolerated by patients with respiratory compromise. (See "Interscalene block procedure guide", section on 'Complications' and "Upper extremity nerve blocks: Techniques", section on 'Side effects and complications of supraclavicular block'.)

Induction and maintenance of anesthesia — A variety of strategies have been used for induction and maintenance of anesthesia for patients with MG. The overarching goals are to prevent prolonged effects on respiratory and bulbar muscles and to allow rapid recovery at the end of surgery. NMBAs should be avoided when possible [14].

- **Inhalation agents** – The potent inhaled anesthetics (isoflurane, sevoflurane, desflurane, halothane) provide dose-dependent neuromuscular relaxation in patients with MG [15-18]. These agents may provide adequate relaxation for endotracheal intubation and surgery, possibly equivalent to the level of relaxation achieved with NMBAs in normal patients. There are many reports of thymectomy performed with the use of potent inhalation agents, without the need for NMBAs [8,18,19]. Muscle strength recovers as the inhalation agent is eliminated, without the need for reversal agents.

- **Intravenous agents** – IV anesthetics have also been used for induction and maintenance of anesthesia for patients with MG, with or without small doses of NMBAs. Propofol is most commonly used for induction of anesthesia, as it provides rapid onset, short duration of action, and suppression of airway reflexes. Total IV anesthesia with infusions of propofol and remifentanil has been described for anesthesia without the use of NMBAs for patients with MG undergoing thymectomy [8,20,21].

  Remifentanil, an ultrashort-acting opioid, is particularly useful for intubation while avoiding NMBAs. For a high-dose remifentanil intubation, the administration of propofol (2 mg/kg) plus remifentanil (4 to 5 mcg/kg) provides good to excellent intubating conditions at 2.5 minutes after induction [22]. We give ephedrine (10 mg IV) along with the propofol for this type of induction to avoid the profound bradycardia and hypotension that may result from this dose of remifentanil. This combination of medications can be used for rapid sequence induction.

  Other IV agents may be used to reduce the reflexes in response to laryngoscopy and intubation while avoiding the administration of NMBAs. IV lidocaine (1 to 1.5 mg/kg IV), small doses of short-acting opioids (eg, fentanyl 50 to 100 mcg), and

esmolol (10 to 50 mg) can be given with induction. Use of both local anesthetics and beta blockers has been associated with worsening of myasthenic symptoms, so judicial use of these drugs is recommended. Intraoperative use of systemic lidocaine infusion is discussed below. (See 'Medications that may exacerbate myasthenia gravis' below.)

Neuromuscular blocking agents — For most surgical procedures, administration of NMBAs is not necessary for patients with myasthenia. Adequate relaxation for surgery is often provided by the administration of the potent inhalation agents and, to a lesser extent, by the depth of anesthesia achieved with the use of IV agents. (See 'Induction and maintenance of anesthesia' above.)

As a general rule, we suggest caution in the use of NMBAs in patients with myasthenia. If NMBAs are necessary, we suggest the use of rocuronium or vecuronium, and then reversal with sugammadex. If sugammadex is unavailable, we avoid the use of NMBAs if at all possible. (See 'Reversal of neuromuscular blocking agents' below.)

Myasthenic patients, including those with only ocular MG and those in remission, have a variable, unpredictable response to administration of NMBAs compared with normal patients, as well as a variable response to NMBA reversal, including the possibility of cholinergic crisis [23,24]. They tend to be resistant to depolarizing NMBAs and very sensitive to nondepolarizing NMBAs. In addition, treatment with anticholinesterase medication affects the degree of relaxation and duration of action of NMBAs. If NMBAs are administered, the degree of neuromuscular blockade should optimally be assessed with a quantitative train-of-four nerve monitor, so that reversal to a train-of-four ratio (TOFR) >0.9 can be verified. (See "Monitoring neuromuscular blockade", section on 'Quantitative monitoring'.)

Depolarizing neuromuscular blocking agents — Patients with MG are resistant to neuromuscular blockade with depolarizing NMBAs (eg, succinylcholine), possibly because they have a decreased number of acetylcholine receptors [25,26]. The 95 percent effective dose (ED_{95}) of succinylcholine for patients with MG is 2.6 times that of normals (0.8 versus 0.3 mg/kg). Because succinylcholine is metabolized by plasma cholinesterase, treatment with anticholinesterase medication (eg, pyridostigmine) may prolong the effect of succinylcholine [27].

Myasthenic patients are also at higher risk of development of phase II neuromuscular block (prolonged, unpredictable block with features of nondepolarizing block),

especially with repeated doses of succinylcholine [28]. (See "Clinical use of neuromuscular blocking agents in anesthesia", section on 'Phase II block'.)

Nondepolarizing neuromuscular blocking agents — Patients with MG are extremely sensitive to nondepolarizing NMBAs (eg, rocuronium, vecuronium, cisatracurium). Very small doses and residual drug effect may result in respiratory distress or loss of airway protection after emergence from anesthesia. Nondepolarizing NMBAs should be administered in incremental, small doses of 0.1 to 0.2 times the ED_{95}, titrated to effect and guided by the use of a quantitative train-of-four nerve monitor. (See "Monitoring neuromuscular blockade", section on 'Quantitative monitoring'.)

If the plan is to extubate the patient at the end of the anesthetic, we suggest the use of a steroidal NMBA (ie, rocuronium or vecuronium) to allow reversal with sugammadex rather than neostigmine. (See 'Reversal of neuromuscular blocking agents' below.)

Mivacurium is a nondepolarizing NMBA that is metabolized by plasma cholinesterase. Pyridostigmine inhibits metabolism of mivacurium. Therefore, paralysis with mivacurium may be prolonged in patients who have taken pyridostigmine on the morning of surgery, though this effect is variable [29,30]. Mivacurium is no longer available in the United States or Canada, though it is available in other countries.

Reversal of neuromuscular blocking agents — When neuromuscular blockade is necessary, we suggest reversal of neuromuscular blockade with sugammadex rather than neostigmine for patients with MG. Reversal with sugammadex is not affected by anticholinesterase medication (unlike neostigmine) and sugammadex has been reported to predictably, rapidly, and safely reverse neuromuscular blockade with rocuronium in patients with MG.

Adequacy of reversal should be confirmed by a TOFR of >0.9 using a quantitative train-of-four neuromuscular monitor. Subjective evaluation of the train-of-four with a standard, non-quantitative peripheral nerve stimulator is less reliable than quantitative monitoring and may provide inaccurate information for administration and reversal of NMBAs. Clinical measures (eg, five second head lift, vital capacity ≥15 mL/kg, strength of hand grip) are unreliable measures of neuromuscular reversal in any patient, including those with MG. (See "Monitoring neuromuscular blockade", section on 'Quantitative monitoring' and "Monitoring neuromuscular blockade", section on 'Clinical evaluation'.)

- Sugammadex – Sugammadex is a cyclodextrin medication that can be used to reverse neuromuscular blockade of the steroidal NMBAs (eg, vecuronium and

rocuronium) by encapsulation of the NMBA molecule, without the need for anticholinesterase medication (see "Clinical use of neuromuscular blocking agents in anesthesia", section on 'Sugammadex'). Sugammadex 2 to 4 mg/kg IV has been reported to reverse moderate to deep vecuronium and rocuronium blockade in patients with MG within four minutes. Reversal with sugammadex is not affected by anticholinesterase medication and it has been reported to predictably, rapidly, and safely reverse neuromuscular blockade with rocuronium. There are several reported cases of failure of reversal of neuromuscular blockade with sugammadex and subsequent reversal with neostigmine in patients with what was thought to be myasthenic crisis [31-36]. If after an appropriate dose of sugammadex the TOFR is <0.9, a small dose of neostigmine may be considered, though the optimal dose of neostigmine in this setting is unclear. If reversal is still inadequate, the patient may require mechanical ventilation until the underlying problem (eg, myasthenic crisis, cholinergic crisis) is diagnosed and treated.

In a retrospective database review that compared postoperative outcomes in over 1100 patients with MG who underwent thymectomy, postoperative complications were similar in patients who received rocuronium with sugammadex reversal versus no NMBA [37]. Conclusions from this study are limited by the lack of data on severity of MG, compounded by an exceedingly long hospital stay after thymectomy (median 19 and 25 days for patients who received rocuronium/sugammadex versus no NMBA, respectively).

A retrospective study of patients who underwent thymectomy for myasthenia gravis found a decrease in myasthenic crisis in those patients receiving sugammadex over those who did not (4.3 versus 8.7 percent, odds ratio 0.48, 95% CI 0.25–0.91) [38]. Conclusions from this study are limited by the lack of data on the use of NMBAs or neostigmine in patients in the control group.

- Neostigmine – Reversal of nondepolarizing NMBAs is unpredictable when using an anticholinesterase reversal agent (eg, neostigmine), especially for those patients who are taking anticholinesterase medication [39]. If sugammadex is unavailable, neostigmine should be titrated to effect to avoid cholinergic crisis. (See 'Cholinergic crisis' below.)

Medications that may exacerbate myasthenia gravis — A number of other medications commonly administered in the operating room can affect neuromuscular transmission in some way. (table 3) In normal patients, these effects are usually of no consequence, but in patients with MG, they can exacerbate muscle weakness,

especially in the presence of residual anesthetic agents. When any of these medications is given in the operating room or the recovery room, the potential for respiratory or bulbar weakness should be considered.

- **Antibiotics** – Several classes of antibiotics can affect neuromuscular transmission, including aminoglycosides [40] (eg, gentamicin) and polymyxins [41]. There are case reports of ampicillin (but not other penicillin-based antibiotics), macrolides [42] (eg, erythromycin, azithromycin), tetracycline, and fluoroquinolones [43] (eg, ciprofloxacin) causing weakness.

- **Glucocorticoids** – Glucocorticoids are known to cause weakness, even though they are often used to treat MG. Thus, it would be prudent to avoid starting a glucocorticoid in the perioperative period to prevent this potential side effect, unless stress dose glucocorticoids are required. (See 'Glucocorticoids' above.)

- **Local anesthetics** – Whether to avoid the use of local anesthetics, particularly when administered intravenously, in patients with MG is unclear. Patients with MG do not appear to be at increased risk of complications if local anesthetics are used for local infiltration or regional anesthesia (ie, neuraxial anesthesia or peripheral nerve block), and in fact regional anesthesia techniques may be preferred when possible. (See 'Choice of anesthetic technique' above.)

  There is experimental evidence that IV local anesthetics in high doses may affect the neuromuscular junction and can potentiate the effects of neuromuscular blocking agents [44-46]. This has raised the possibility that IV local anesthetics could exacerbate MG, though there is little evidence that this occurs. There are older anecdotal reports of patients with exacerbation of myasthenia after administration of local anesthetics, though none in contemporary literature [47].

  IV lidocaine is commonly used intraoperatively, as a bolus during induction to suppress airway reflexes, and in some cases as an infusion as part of multimodal opioid sparing analgesia. The decision to use lidocaine in patients with MG should involve a risk-benefit analysis, considering the unknown but likely small risk of exacerbation of MG versus potential benefits, including reduced need for opioids. For most patients with myasthenia, the authors routinely administer an induction bolus of lidocaine, but avoid lidocaine infusion. (See 'Induction and maintenance of anesthesia' above.)

- **Others** – Other medications with the potential to exacerbate weakness include beta blockers, calcium channel blockers, antiepileptics (gabapentin and

phenytoin), phenothiazines, diuretics, procainamide [48], magnesium, and opioids.

Extubation — The anesthetic strategy for patients with MG should be designed to maximize the possibility of extubation at the end of surgery. Components of the plan include the use of short-acting anesthetics and multimodal analgesia to minimize opioid side effects, pulmonary toilet, and avoiding medications known to interfere with neuromuscular transmission.

Criteria for extubation should be similar to those for any patient having surgery, with proof of adequate ventilation and oxygenation, strength, and the ability to protect the airway, once objective confirmation of reversal of NMBAs is obtained, if used. (See 'Reversal of neuromuscular blocking agents' above.)

POSTOPERATIVE CONSIDERATIONS FOR PATIENTS WITH MYASTHENIA GRAVIS

The need for postoperative monitoring and/or hospital admission for patients with MG should be individualized based on clinical features, the surgical procedure, the type of anesthetic, the intraoperative and immediate postoperative courses, and the need for postoperative care, including pain relief. Preoperative consultation with the patient's neurologist should include planning for postoperative care, the possibility of intensive care, and postoperative management of anticholinesterase medication. Chronic immunotherapies can be resumed when the patient is taking oral medications.

Ambulatory surgery can be considered for patients who have had minor surgical procedures, with monitored anesthesia care using short-acting sedatives, regional anesthesia, or general anesthesia either without neuromuscular blocking agents (NMBAs) or with NMBAs reversed with sugammadex. Patients who develop any signs of bulbar or respiratory weakness in the recovery room should be admitted to the hospital for monitoring.

Myasthenic crisis — Myasthenic crisis is defined as respiratory muscle and/or bulbar muscle weakness severe enough to necessitate intubation or to delay extubation after surgery. It can occur spontaneously with the stress of surgery, or as a result of a number of precipitants, including infection, residual anesthetics, withholding or tapering of MG medications, or any of a number of medications known to exacerbate MG. (See "Myasthenic crisis", section on 'Precipitants'.)

Myasthenic crisis must be distinguished from cholinergic crisis, another possible cause of weakness in patients with MG, as the treatment of the two conditions is very different. Formal neurophysiologic studies may be necessary and may provide more information, as excess cholinergic activity can be assessed, as well as cholinergic deficit. (See 'Cholinergic crisis' below.)

Myasthenic crisis may include weakness of respiratory and bulbar muscles. In awake patients, signs of impending crisis can include dysphagia, change in phonation, obstruction, weak cough, and difficulty handling secretions. Since the MG patient has a normal respiratory drive, the first sign of impending crisis may be an increase in respiratory rate with shallower tidal volume breaths [49]. Use of accessory muscles or paradoxical movement of the abdomen might be seen, even in patients who are still intubated at the end of surgery. Blood gases may initially show hypocapnia in spontaneously breathing patients. An increase in partial pressure of carbon dioxide (pCO_2) is a sign of impending respiratory failure.

Treatment of myasthenic crisis should be coordinated with a neurologist. If weakness at the end of surgery suggests myasthenic crisis, delay of extubation is required, as well as intensive care. Urgent rapid therapy with plasma exchange or intravenous immune globulin (IVIG) is often initiated, in addition to immunomodulating therapy. (See "Myasthenic crisis", section on 'Management'.)

Risk factors for postoperative myasthenic crisis after thymectomy are discussed above. (See 'Prediction of postoperative myasthenic crisis' above.)

Cholinergic crisis — Patients who receive anticholinesterases are at risk for cholinergic crisis, which is manifested by paradoxical weakness along with other signs of cholinergic excess, such as those identified by the mnemonic "SLUDGE": salivation, lacrimation, urination, defecation, gastrointestinal distress, and emesis [1]. It happens rarely in patients outside the operating room but may occur after administration of an anticholinesterase for reversal of neuromuscular blockade in patients with MG [50,51]. In such cases, prolonged paralysis often results.

NMBAs should be avoided during anesthesia unless sugammadex (rather than neostigmine) is available for reversal. (See 'Neuromuscular blocking agents' above.)

If cholinergic crisis is suspected, atropine (0.4 to 2 mg IV) or glycopyrrolate (0.2 to 1 mg IV) should be administered, if not already given, to counteract muscarinic effects, and further anticholinesterase should be withheld. Repeated dosing of anticholinergic may be required.

OBSTETRIC ANESTHESIA

Pregnant patients with MG should have antepartum anesthesia consultation. The plans for labor analgesia and anesthesia for potential instrumented or operative delivery should be determined well before the patient presents in labor. Like other surgical patients, obstetric patients should be assessed for the degree of bulbar dysfunction and respiratory muscle weakness, and also for the predicted ability to tolerate midthoracic levels of regional anesthetic block. Anesthesia concerns specific to labor and delivery include the following:

- **Labor analgesia** – Most patients require some degree of analgesia during labor. Neuraxial analgesia is the preferred method of pain control during labor for patients with MG because it reduces or eliminates the need for systemic opioid administration, thereby minimizing respiratory depression for patients with respiratory compromise. Excellent labor analgesia can be achieved with low levels of very dilute local anesthetic and opioid medications, which result in a minimal, if any, degree of motor block. (See "Neuraxial analgesia for labor and delivery (including instrumental delivery)", section on 'Drug choice for neuraxial analgesia'.)

- **Instrumented delivery** – The first stage of labor depends on uterine smooth muscle and is unaffected by MG. However, the second stage of labor requires the use of striated muscle, which may weaken, increasing the need for instrumented delivery. Neuraxial analgesia can be augmented to provide adequate lumbosacral levels of anesthesia for forceps- or vacuum-assisted delivery.

- **Cesarean delivery –** While neuraxial anesthesia (ie, spinal and epidural) is used most commonly for cesarean section, patients with MG may not tolerate the high level of block required. Neuraxial anesthesia results in both sensory and motor block; for cesarean section, a midthoracic level of anesthesia is required, which often affects the accessory muscles of respiration. For patients with significant bulbar or respiratory compromise, general anesthesia should be performed for cesarean section.

  Chloroprocaine is an ester local anesthetic commonly used for emergency epidural anesthesia for cesarean delivery; duration of action may be prolonged in patients who take cholinesterase inhibitors, though the extent to which this happens and the clinical relevance is unclear.

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome (LEMS) is a rare disorder of the neuromuscular junction, much less common than MG. It is often associated with small-cell lung cancer or other malignancies, but it can be associated with autoimmune processes as well. Patients with LEMS have muscle weakness caused by reduced acetylcholine release from presynaptic nerve terminals. Unlike MG, autonomic dysfunction is common with LEMS. Bulbar symptoms occur less commonly than with MG. Respiratory muscle weakness can rarely result in respiratory failure [52]. (See "Lambert-Eaton myasthenic syndrome: Clinical features and diagnosis" and "Lambert-Eaton myasthenic syndrome: Treatment and prognosis".)

Anesthetic concerns for patients with LEMS include the following:

- Patients with LEMS are very sensitive to **both** nondepolarizing and depolarizing neuromuscular blocking agents (NMBAs) [53], unlike patients with MG, who are resistant to depolarizing NMBAs and sensitive to nondepolarizing NMBAs. Patients with LEMS are more sensitive to nondepolarizing NMBAs than patients with MG, and reversal with neostigmine may be ineffective [54]. We avoid NMBAs for patients with LEMS unless sugammadex is available for reversal. Patients who do receive NMBAs should receive small, titrated doses and should be monitored with an accelerometer and quantitative peripheral nerve stimulator whenever possible. (See 'Neuromuscular blocking agents' above.)

- Patients with LEMS may be treated symptomatically with aminopyridines (eg, 3,4 Diaminopyridine) and anticholinesterases (eg, pyridostigmine). Other treatments include immunologic therapy with intravenous immune globulin (IVIG); oral immunosuppressive agents (eg, prednisone, azathioprine, mycophenolate, cyclosporine); and, least commonly, plasma exchange or rituximab. (See "Lambert-Eaton myasthenic syndrome: Treatment and prognosis".)

  Patients should continue these medications up to the time of surgery, as there are case reports of respiratory insufficiency when medications were held prior to surgery [55]. Patients who chronically take glucocorticoids may require stress doses at the time of induction of anesthesia. (See 'Myasthenia gravis treatments' above.)

- Autonomic dysfunction with LEMS may result in exaggerated hypotension with anesthesia induction agents and other vasodilators. A retrospective review of 60

anesthetics for patients with LEMS reported that hypotension occurred no more commonly in patients with autonomic dysfunction than in those without it, and all episodes of hypotension were treated easily with boluses of phenylephrine or ephedrine [55].

- Postoperative concerns for patients with LEMS are similar to those for patients with MG.

SUMMARY AND RECOMMENDATIONS

- **Preoperative evaluation and management**
  - For patients with myasthenia gravis (MG), elective surgery should be performed during a stable phase of the disease and should be scheduled early in the day. (See 'Preoperative evaluation' above.)
  - Preoperative evaluation should include assessment of bulbar and respiratory symptoms. Pulmonary function testing (PFT) may be performed to establish a baseline and to help plan for postoperative care. (See 'Preoperative pulmonary evaluation' above.)
  - For patients who take anticholinesterases (ie, pyridostigmine or neostigmine), we suggest continuing the medication up to and including the morning of surgery (**Grade 2C**) to avoid respiratory and bulbar weakness if medication is withheld. Anticholinesterases can prolong the effect of succinylcholine, delay the onset of nondepolarizing NMBAs, and make reversal of NMBAs with neostigmine unpredictable. (See 'Anticholinesterase agents' above.)
- **Choice of anesthetic technique**
  - Regional anesthesia should be used when possible. If general anesthesia is required, ultrashort- or short-acting sedatives, hypnotics, and anesthetic agents are preferred, to avoid postoperative respiratory depression. (See 'Choice of anesthetic technique' above and 'Induction and maintenance of anesthesia' above.)
  - During neuraxial anesthesia, some patients may not tolerate the level of motor block required for the planned surgery, which may include accessory muscles of respiration (eg, cesarean delivery). (See 'Obstetric anesthesia' above.)

- Preclinical evidence suggests that patients with MG may be at increased risk of exacerbation with administration of systemic local anesthetics, though there is little evidence that this occurs. For most patients with MG, the authors routinely administer an induction bolus of lidocaine, but avoid lidocaine infusion. Drugs that should be used with caution or avoided in patients with MG are shown in a table. (See 'Medications that may exacerbate myasthenia gravis' above.)

- **Neuromuscular blocking agents**

  - Patients with MG are unpredictably resistant to depolarizing neuromuscular blocking agents (NMBAs) (eg, succinylcholine) and unpredictably sensitive to nondepolarizing NMBAs (eg, rocuronium, vecuronium, cisatracurium). (See 'Neuromuscular blocking agents' above.)

  - NMBAs are not necessary for most patients with MG. For patients who require neuromuscular block, we suggest using rocuronium or vecuronium to allow reversal with sugammadex (**Grade 2C**). Reversal with sugammadex (unlike neostigmine) is not affected by anticholinesterase medication and sugammadex has been reported to predictably, rapidly, and safely reverse neuromuscular blockade with rocuronium in patients with MG. (See 'Reversal of neuromuscular blocking agents' above.)

    If sugammadex is not available, we avoid NMBAs unless absolutely necessary. (See 'Nondepolarizing neuromuscular blocking agents' above.)

  - NMBAs should be used cautiously in patients with MG. Small doses of NMBA should be titrated to effect, guided by a quantitative neuromuscular monitor whenever possible. (See "Monitoring neuromuscular blockade", section on 'Quantitative monitoring'.)

  - For patients with MG who receive vecuronium or rocuronium, we suggest reversal of neuromuscular blockade with sugammadex rather than neostigmine (**Grade 2C**). (See 'Reversal of neuromuscular blocking agents' above.)

  - If neostigmine must be used for reversal, it should be titrated to effect to avoid cholinergic crisis. (See 'Reversal of neuromuscular blocking agents' above.)

  - Adequacy of reversal should be confirmed by a train-of-four ratio (TOFR) of >0.9 using a quantitative train-of-four neuromuscular monitor. (See 'Reversal

of neuromuscular blocking agents' above and "Clinical use of neuromuscular blocking agents in anesthesia", section on 'Reversal of neuromuscular block'.)

- **Postoperative care**
  - The need for postoperative monitoring and/or hospital admission for patients with MG should be individualized based on the clinical features, the risk factors for myasthenic crisis, the surgical procedure, the type of anesthetic, the intraoperative and immediate postoperative course, and the need for postoperative care. (See 'Postoperative considerations for patients with myasthenia gravis' above.)
  - Myasthenic crisis can be precipitated by surgery, administration of NMBAs, or any number of medications and conditions. Myasthenic crisis requires endotracheal intubation and ventilation, intensive care, and often rapid immunomodulating therapy. It should be distinguished from cholinergic crisis, which results from excessive administration of anticholinesterases and may also require ventilatory support. (See 'Myasthenic crisis' above and 'Cholinergic crisis' above and "Myasthenic crisis".)
- **Lambert-Eaton myasthenic syndrome** – Unlike patients with MG, these patients are sensitive to both depolarizing and nondepolarizing NMBAs. Anesthesia concerns for patients with Lambert-Eaton myasthenic syndrome (LEMS) are otherwise similar to those for patients with MG. (See 'Lambert-Eaton myasthenic syndrome' above.)

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Topic 94256 Version 26.0

GRAPHICS

Corticosteroid coverage for surgery in patients taking exogenous corticosteroids

For minor procedures or surgery under local anesthesia (eg, inguinal hernia repair), take usual morning steroid dose. No extra supplementation is necessary.
For moderate surgical stress (eg, lower extremity revascularization, total joint replacement), take usual morning steroid dose. Give 50 mg hydrocortisone intravenously just before the procedure and 25 mg of hydrocortisone every eight hours for 24 hours. Resume usual dose thereafter.
For major surgical stress (eg, esophagogastrectomy, total proctocolectomy, open heart surgery), take usual morning steroid dose. Give 100 mg of intravenous hydrocortisone before induction of anesthesia and 50 mg every eight hours for 24 hours. Taper dose by half per day to maintenance level.

Graphic 69479 Version 5.0

Comparison of systemic glucocorticoid preparations

	Equivalent doses (mg)	Antiinflammatory activity relative to hydrocortisone*	Duration of action (hours)
Glucocorticoids			
Short acting			
Hydrocortisone (cortisol)	20	1	8 to 12
Cortisone acetate	25	0.8	8 to 12
Intermediate acting			
Prednisone	5	4	12 to 36
Prednisolone	5	4	12 to 36
Methylprednisolone	4	5	12 to 36
Triamcinolone	4	5	12 to 36
Long acting			
Dexamethasone	0.75	30	36 to 72
Betamethasone	0.6	30	36 to 72
Mineralocorticoids			
Fludrocortisone	Not used for an antiinflammatory effect¶. The typical dose of fludrocortisone for mineralocorticoid replacement is 0.1 to 0.2 mg.		12 to 36

The mineralocorticoid effect of commonly administered glucocorticoids may be estimated as follows:

- When given at replacement doses, triamcinolone, dexamethasone, and betamethasone have no clinically important mineralocorticoid activity.
- 20 mg hydrocortisone and 25 mg of cortisone acetate each provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg fludrocortisone.
- Prednisone or prednisolone given at antiinflammatory doses ≥50 mg per day provide a mineralocorticoid effect that is approximately equivalent to 0.1 mg of fludrocortisone.

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* Equivalent antiinflammatory dose shown is for oral or intravenous (IV) administration. Relative potency for intraarticular or intramuscular administration may vary considerably.

¶ The antiinflammatory potency is 10 to 15 times that of hydrocortisone; however, fludrocortisone is not used clinically as an antiinflammatory agent.

Data from:

1. *Schimmer BP, Funder JW. ACTH, adrenal steroids, and pharmacology of the adrenal cortex. In: Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 12th ed, Brunton LL, Chabner BA, Knollmann BC (Eds), McGraw-Hill Education 2011.*
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Graphic 64138 Version 23.0

Drugs to avoid or use with caution in patients with myasthenia gravis*

Anesthetic agents
Neuromuscular blocking agents (eg, rocuronium, vecuronium, succinylcholine)¶
Antibiotics
Aminoglycosides$^{\Delta}$ (eg, amikacin, gentamicin, neomycin, tobramycin)
Fluoroquinolones$^{\Delta}$ (eg, ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)
Macrolides (eg, azithromycin, clarithromycin, erythromycin)
Cardiovascular drugs
Beta blockers (eg, atenolol, labetalol, metoprolol, propranolol)
Procainamide
Quinidine
Others
Botulinum toxin
Chloroquine
Deferoxamine (desferrioxamine)
Glucocorticoids (eg, dexamethasone, prednisone)◇
Statins (HMG-CoA reductase inhibitors; eg, atorvastatin, pravastatin, rosuvastatin)
Hydroxychloroquine
Immune checkpoint inhibitors (eg, atezolizumab, ipilimumab, nivolumab, pembrolizumab)
Iodinated contrast§
Magnesium¥
Penicillamine‡
Quinine

HMG-CoA: hydroxymethylglutaryl coenzyme A; IVIG: intravenous immune globulin.

* This is not a complete list of all drugs that may, in individual patients, adversely affect neuromuscular transmission and worsen myasthenia gravis symptoms. If such drugs are used, they should be administered cautiously with appropriate monitoring. Refer to UpToDate for additional information.

¶ Response to neuromuscular blocking agents is unpredictable in patients with myasthenia. Use only when necessary, guided by neuromuscular monitoring.

Δ Reserve use for hospitalized patients when alternative agents are unavailable.

◇ Glucocorticoids at high dose may cause transient worsening of symptoms during first one to two weeks of treatment. They should be used with caution; when administered for hospitalized patients in myasthenic crisis, concurrent plasmapheresis or IVIG should be coadministered.

§ Increased weakness in MG has been reported with use of older iodinated contrast agents; modern iodinated contrast agents appear generally safe.

¥ Intravenous administration (eg, with magnesium sulfate, magnesium chloride) is relatively contraindicated due to significant inhibitory effect on acetylcholine release.

‡ Strongly associated with worsening myasthenia gravis; avoid use.

Graphic 100362 Version 9.0

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