An Update on Myasthenic Crisis

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Opinion statement

Myasthenia gravis (MG) is the most common disorder of the neuromuscular junction. Myasthenia crisis, defined as respiratory failure requiring mechanical ventilation in MG, is a common life-threatening complication that occurs in approximately 15% to 20% of patients with MG during their life time. The advent of effective mechanical ventilation, specialized neurointensive care units and the widespread use of immunotherapies have substantially altered the prognosis of myasthenic crisis. Early intubation and mechanical ventilation is perhaps the most important step in the management of myasthenic crisis. The authors favor an orotracheal approach for intubation, and placement of small bore duodenal tubes that may help decrease the risk of aspiration and may be more comfortable than regular nasogastric tubes for the patient. Plasma exchange may be more effective than the intravenous immunoglobulin in the treatment of myasthenic crisis involving respiratory failure. A randomized trial is required to confirm the superior efficacy of plasma exchange compared with intravenous immunoglobulin. In the acute setting, the role of immunosuppression and intravenous/intramuscular pyridostigmine and the newer agents such as tacrolimus remains limited and at times controversial. The therapy should be tailored at an individual basis using best clinical judgment.

Introduction

Myasthenia gravis (MG) is the most common disorder of the neuromuscular junction. The estimated prevalence in the United States is five to seven (published estimates from 0.5 to 15) per 100,000 (or about 40,000 cases) [1, Class III]. Myasthenic crisis, defined as respiratory failure requiring mechanical ventilation, is a potentially life-threatening complication that occurs in approximately 15% to 20% of patients with MG [1, Class III].

HISTORICAL PERSPECTIVE

Thomas Willis of Oxford provided perhaps the first clinical description of MG in 1672. Approximately 200 years later, Samuel Wilks [2, Class III] described a series of patients with weakness without identifiable brain lesion.

The experience before the 1960s suggested a high mortality of 30% to 70% from MG. MG recently has become more treatable with minimal mortality (3% to

8%). This has been made possible with the increasing use of cholinesterase inhibitors beginning in the 1930s. Thymectomy became prevalent in 1950s followed by the use of corticosteroids and other immunosuppressive agents, which gained wide acceptance in the 1960s.

Plasma exchange (PE) in the mid-1970s and intravenous immunoglobulin (IVIg) and new immunosuppressant (in the 1980s and 1990s) eventually were introduced for treatment of MG. Use of neurointensive care units in the 1990s dramatically helped with reduction of mortality. With the advent of effective mechanical ventilation in the 1960s, greater improvement in morbidity and mortality rates of patients with MG was seen [3, Class III].

EPIDEMIOLOGY

The reported prevalence of myasthenic crisis increased from the 1950s to the 1990s [4, Class III]. This largely reflects the increased life span of patients with MG because of improved treatment. MG prevalence is higher in women under the age of 50 years than in men of the same age. For men older than 50 years of age, the prevalence of MG is higher than in women. African-Americans are affected more by this disease in all age ranges [5, Class III]. With an increase of the number of older patients in population demographics, the number of patients older than age 50 years may be twice the number of those younger than age 50 years by the year 2005.

There are estimated 40,000 cases of MG in the US; approximately 20% (8000 cases) are expected to have a very benign ocular MG, and a similar number of patients are expected to experience at least one life-threatening myasthenic crisis in their lifetime.

CLINICAL FEATURES

The weakness in MG characteristically becomes worse with repeated activity. Signs of weakness are usually first evident in the eyelids and extraocular muscles, and generalized weakness follows in 85% of cases [4, Class III]. The proximal limb muscles often are affected, and weakness can involve the diaphragm and thoracic musculature. The deficit in myasthenia is purely motor. Deep tendon reflexes usually are preserved.

Myasthenic crisis is defined by an acute episode of respiratory muscle weakness (defined by vital capacity

[VC] of 1 L or less, negative inspiratory force [NIF] 20 cm H₂O or requirement of mechanical ventilation). Rapid progression to respiratory failure in MG can occur in patients with recent worsening of symptoms, especially if the oropharyngeal muscles are involved. The crisis could manifest as oropharyngeal bulbar crisis where the upper airway is compromised or it could also be the respiratory failure secondary to muscle weakness. Respiratory support usually is required [6, Class III]. The advent of specialized neurointensive care units and the widespread use of immunotherapies have substantially altered the management of myasthenic crisis.

CONDITIONS MIMICKING CRISIS

In cases of excessive acute or chronic overdose of anticholinesterase medications, muscle weakness mimicking myasthenic crisis may develop. This is caused by excess of acetylcholine (ACh) at the motor effector sites. The possibility that the deterioration could be caused by cholinergic crisis is best excluded by temporarily stopping anticholinesterase drugs while the patient is presumptively treated for the myasthenic crisis. Acute treatment in such a setting is supportive does not require any specific or different intervention for myasthenic versus cholinergic crisis.

DIAGNOSTIC TESTING

A quick bedside technique for diagnosing MG is the ice test. Improvement of the ptosis after putting the ice on the eyelid for 2 minutes, suggests a disorder of neuromuscular transmission [7,8, Class III].

Laboratory studies The most sensitive and specific test for MG is the presence of acetylcholine receptor antibodies (AChR-Ab), it can be confirmed clinically by edrophonium (Tensilon) administration and by electrodiagnostics. Muscle-specific receptor tyrosine Kinase (MuSK) [9, Class III] is most useful when testing patients who have MG but are AChR-Ab negative.

Radiographic studies Approximately 20% of patients with MG have a thymoma present, whereas approximately 70% have thymic hyperplasia [10, Class III]. All patients with MG should have a CT scan of chest done with contrast.

Treatment

- The algorithm for the treatment of myasthenic crisis consists of an approach that includes: initiation of supportive care, elimination of possible other conditions that may mimic crisis, removal of trigger or exacerbating factors, and treatment of underlying MG.
- Management of myasthenic crisis should be done in an intensive care unit staffed with physicians who are experienced in the management of the disease itself, respiratory insufficiency, infectious disease, and fluid and electrolyte

Table 1. Pulmonary function tests in patients with myasthenia crisis

Test	Normal	Criteria for intubation
Vital capacity	>60 mL/kg	>15 mL/kg
Negative inspiratory force	>70cm H ₂ O	<20 cm H ₂ O
Positive expiratory force	>100cm H ₂ O	<40 cm H ₂ O

(Adapted from Thomas et al. [14]; with permission.)

balances. An experienced neurointensivist provides an optimal patient care. In the absence of the expertise of the neurointensivist, a team of neurologist and critical care physicians is required. After stabilizing the patient and securing the airway, respiration, and hemodynamics, options for specific treatment include use of acetylcholinesterase (AChE) inhibitors, PE, IVIg, and immunosuppressive drugs. The prognosis has improved strikingly as a result of advances in treatment; virtually all patients with myasthenic crisis can be returned to full productive lives with proper therapy [11, Class III].

Supportive care

- The patient should be stabilized at the time of presentation. After securing the airway, respiration, and circulation, usually in the emergency room, the patient is transferred to an intensive care setting.
- There are intensive care issues that are specific to the management of the MG. Unlike most other patients that are close to respiratory failure, patients with MG, especially younger patients, are able to maintain good oxygen saturation. The patient suspected of going into crisis should have monitoring of VC and NIF every hour. Clinical state, use of accessory muscles, and subjective feeling of air hunger are other reliable indicators of impending respiratory failure. The authors recommend liberal intubation of patients with MG; early intubation and mechanical ventilation is perhaps the most important step in the management of myasthenic crisis [1,12•, Class III].
- The authors base the decision to intubate on the clinical evaluation that includes the assessment of strength of cough and sniff. Patients are asked to count loudly as long as possible in one breath. Normally, one can count easily up to 30, whereas the patients who count less than 20 have significant impairment of respiratory muscles. Consider intubation if a patient with myasthenic crisis has the following pulmonary function tests [12•, Class III] (Table 1).
- The authors favor an orotracheal approach for intubation; a soft low-pressure cuff is recommended. Tracheostomy generally is unnecessary, because the duration of intubation is frequently less than 2 weeks [13,14, Class III]. After the patient is placed on a respirator, synchronized intermittent mandatory ventilation with minimal sedation is recommended for the initial setting. Relatively larger tidal volumes, 8 to 10 mL/kg with pressure support of 8 to 15 cm H₂O are encouraged. This prevents the development of atelectasis. Caution should be used to keep peak airway pressures less than 45 cm of H₂O. The adequacy of ventilatory support is determined by the patient comfort and lack of CO₂ retention. Supplemental oxygen above 30% FiO₂ is rarely necessary. The authors recommend keeping the inspired humidity of 60% to 90%, depending on the amount of secretions. The patient then is observed for usual ventilator care and frequent checks of cuff pressure, tube placement, and blood gases. Frequent aseptic deep suctioning, preferably with a soft suctioning catheter, is helpful in avoiding complications [15•, Class III].

- Weaning attempts in the patients with myasthenic crisis should always begin when: 1) Overall strength is improving; 2) VC exceeds 10 mL/kg; 3) NIF negatively exceeds -20cm H₂O; 4) oxygenation is normal (FiO₂ 40%); and 5) the patient is free of infection or other medical complications. The trial should start early in the day initially with continuous peak airway pressure and high-pressure support. After weaning the rate to 0, it usually is helpful early on to set the pressure support to 8 to 15 cm H₂O. If the patient is able to tolerate this for at least 1 day, pressure support is decreased by 1 to 2 cm H₂O to at least 5 cm H₂O (just enough to overcome the circuit resistance). If the results of previous assessments reveal fatigue with tachypnea, patients are rested again on synchronized intermittent mandatory ventilation with a set rate of at least 6 [16••, Class III].
- As in any other critically ill patients, negative energy balance will interfere with weaning efforts, an early start of appropriate nutrition is essential. This becomes even more important in patients with MG, because of the relative borderline strength of respiratory muscles. Clinicians should remember that patients in myasthenic crisis are not being ventilated because of pulmonary or systemic problems, but because of the problems with muscle strength. The authors favor early placement of small bore tubes that end in the duodenum that may help decrease the risk of aspiration and may be more comfortable than a regular nasogastric tubes for the patient [12•, Class III].
- In addition to the specific measures mentioned, general intensive care monitoring should be optimized with aggressive treatment of other systems. Hypokalemia, hypomagnesemia, and hypophosphatemia that may exacerbate weakness should be treated aggressively. Anemia will affect the oxygen carrying capacity and also may additionally exacerbate weakness; therefore, transfusions for a hematocrit value of 30% and below are recommended. Deep venous thrombosis prophylaxis with the use of subcutaneous heparin or the use of sequential compression devices is necessary.

Identification and elimination of exacerbating factors

- In addition to concurrent illness and surgery, several drugs can precipitate or aggravate the MG into myasthenic crisis. The principal offenders are antibiotics (aminoglycosides), cardiac drugs (lidocaine, procainamide, or quinidine), and magnesium [17, Class III]. Aminoglycosides can precipitate a myasthenic syndrome that resolves when the drugs are discontinued. Magnesium blocks the presynaptic release of ACh and can be particularly detrimental in patients with myasthenic crisis (Table 2) [14, Class III].
- The most common cause of crisis is concurrent infection. This should be treated immediately, because the mechanical and immunologic defenses of the patient are compromised. The patient with MG with fever and early infection should be treated like any other patient who is immunocompromised. Early and effective antibiotic therapy, respiratory assistance, and pulmonary physiotherapy are essential to the treatment regimen. As will be discussed later, PE and IVIg frequently are helpful in hastening recovery.

Pharmacologic treatment

- The immediate pharmacologic treatment of myasthenic crisis includes use of anticholinesterase medications, PE, or IVIg. Long-term immunosuppression with steroids beginning in the acute phase and extending into intermediate periods of days to weeks may be helpful. All other forms of immunosuppression usually are reserved for the longer-term and usually are not initiated or

Table 2. The experience of 73 patients with myasthenic crisis

	Primary participant, <i>n</i> (%)	Possible contributing factor, <i>n</i> (%)
Infection	28(38)	6(8)
Bacterial pneumonia	12(16)	2(2)
Viral URI	6(8)	0(0)
Bacterial URI	4(5)	1(1)
Sepsis	3(4)	1(1)
Other	3(4)	2(2)
No obvious precipitant	22(30)	—
Aspiration pneumonitis	7(10)	7(10)
Medication-related	6(8)	2(2)
Steroid administration	2(2)	0(0)
Steroid withdrawal	2(2)	1(1)
Aminoglycoside use	1(1)	1(1)
Pregnancy/postpartum	3(4)	3(4)
Upper airway obstruction	3(4)	3(4)
Surgery	2(2)	0(0)
Other	2(2)	15(21)

URI—upper respiratory infection.
(Adapted from Thomas *et al.* [14]; with permission.)

maintained during acute crisis. The other modalities of immunosuppression are briefly discussed for the sake of completeness because many patients with MG are chronically treated with it when they present with crisis.

Anticholinesterase medications

- There is no substantial difference in efficacy among the various anticholinesterase drugs; oral pyridostigmine is the one most widely used in the US. As a rule, the beneficial action of oral pyridostigmine begins within 15 to 30 minutes and lasts for 3 to 4 hours, but individual responses vary in patients with myasthenic crisis.
- In case of myasthenic crisis, the following also should be considered when using anticholinesterase medications:
 - Overdosage with AChE inhibitors may exacerbate weakness. These agents also make it more difficult to assess response to other therapies, and the authors think that a period of withdrawal may increase response to these medications. For these reasons, the authors recommend stopping AChE inhibitors for patients in myasthenic crisis and re-instituting them orally when patients are getting stronger and are about to be extubated [18•,19,20, Class III]. The authors restart the medications at a low dosage, and gradually increase to a dosage that produces clear benefit. Pyridostigmine also has been shown to increase sensitivity to non-depolarizing anesthetics such as vecuronium, which may be potentially hazardous in patients planned for thymectomy [21, Class I].
 - An alternative approach is to use intravenous pyridostigmine infusion at 1 to 2 mg per hour during crisis. Each milligram of intravenous pyridostigmine is equivalent to 30 mg of oral pyridostigmine (some authorities think it is as low as 8 to 10 mg), and is infused with normal saline. In one small retrospective study [13, Class III], crisis patients receiving intravenous pyridostigmine showed clinical improvement comparable with those receiving PE. However, some patients have

experienced significant, sometimes fatal, cardiac arrhythmias while receiving intravenous pyridostigmine [13,18•, Class III]. To reduce side effects, one approach is to administer intramuscular pyridostigmine that may be equally effective, but may reduce the risk of cardiac arrhythmias. Furthermore, AChE inhibitors can promote excessive secretions, which block feeding or endotracheal tubes, cause mucus plugging and lead to atelectasis [12•, Class III].

- In most settings, it may become difficult to differentiate between weakness caused by excessive AChE and myasthenic crisis as explained; therefore, the authors consider stopping the AChE drugs at least until early improvement is detected clinically.
- Long-acting pyridostigmine tablets may help to improve patient's symptoms through the night, but because of variable absorption should never be used for myasthenic crisis.

Pyridostigmine bromide

Standard dosage	The average dose of oral pyridostigmine is 15 to 60 mg tablets or 10 5-mL teaspoonfuls daily, which are spaced to provide maximum relief.
Contraindications	Pyridostigmine is contraindicated in patients with mechanical intestinal or urinary obstruction.
Main drug interactions	Corticosteroids and quinidine reduce the effect of pyridostigmine. The effect of succinylcholine is moderately increased in the presence of pyridostigmine. Atropine antagonizes the muscarinic effects of pyridostigmine, and this interaction is used to counteract the muscarinic symptoms of pyridostigmine toxicity.
Main side effects	Diarrhea, abdominal cramps, salivation, and nausea and vomiting.
Special points	The muscarinic side effects of the AChE medication may limit the dose tolerated by some patients. In these cases, propantheline bromide may be used to block the autonomic side effects without altering the beneficial effects on skeletal muscle. Loperamide also is useful for the treatment of diarrhea induced by AChE medications.
Cost/cost effectiveness	60 mg three times daily costs \$60 to \$100 per month.

Plasma exchange

Plasma exchange has been used therapeutically in patients with myasthenic crisis. Plasma, which contains the pathogenic antibodies, is mechanically separated from other blood components, which are returned to the patient.

The retrospective multicenter analysis done by the authors' group suggests that the PE is more effective than the IVIg in the treatment of myasthenic crisis involving respiratory failure. However, of 54 episodes of myasthenic crisis, more patients had complications related to PE than IVIg [22•, Class III]. An analysis of the ventilatory status at 2 weeks ($P=0.02$) and at 1 month ($P=0.04$) revealed a higher rate of successful extubation in the group treated with PE. A randomized trial is required to confirm the superior efficacy of PE compared with IVIg.

Gajdos *et al.* [23•, Class III] did not find any differences in efficacy and tolerance of two regimens of IVIg (3- and 5-day courses of 400 mg/kg per day) compared with three cycles of PE in patients presenting with MG exacerbation that included, but was not restricted to, respiratory failure. The difference between results of the authors' study and the previous study may be attributed to higher frequency of mechanically ventilated patients (42 of 54 versus nine of 87 episodes), and larger number of exchanges done per person in the authors' study. In contrast, Stricker *et al.* [24, Class III] reported four patients with myasthenic crisis who initially were treated with IVIg without any clinical improvement. All four patients improved with subsequent PE.

Standard procedure	A course of five exchanges (3 to 4 L per exchange) generally is administered over an alternate day regimen for 10 days [25•, Class III].
Contraindications	Contraindications related to extracorporeal lines and anticoagulation include precarious hemodynamics, unstable angina pectoris, and active internal bleeding. Contraindication related to immunosuppression is mainly concern for sepsis and septic shock.

Complications	Immediate complications usually are related to extracorporeal lines, anticoagulation, and replacement fluids, and include excessive bleeding, pneumothorax, and exacerbation of underlying congestive heart failure. Delayed complications include hypercoagulable state and predisposition to infections secondary to immuno-suppressed state.
Special points	Plasma exchange produces a short-term reduction in anti-AchR-ab, with clinical improvement in many patients. It is useful as a temporary expedient in patients with myasthenic crisis or to improve the patient's condition before surgery (thymectomy).
Cost/cost effectiveness	The approximate cost for each PE is \$1500.

Intravenous immunoglobulin

	<p>The indications for the use of IVIg are the same as those for PE. It produces rapid improvement to help the patient through a difficult period of myasthenic crisis or before surgery.</p> <p>This treatment has the advantages of not requiring special equipment or large-bore venous access. Although there have been no direct trials comparing PE with IVIg, the latter has been compared with placebo in a small double-blinded random, controlled trial. Among 15 patients, Wolfe <i>et al.</i> [26, Class II] found no difference at 42 days but some trend towards improvement at 6 months in patients receiving 2 gm/kg of IVIg. Improvement occurs in about 70% of patients, beginning during treatment, or within 4 to 5 days thereafter, and continuing for weeks to months.</p>
Standard dosage	The usual dose is 2 g/kg, which typically is administered over 5 days (400 mg/kg per day). If tolerated, the course of IVIg can be shortened to administer the entire dose over a 3-day period.
Contraindications	This treatment should not be given to patients with isolated immunoglobulin A (IgA) deficiency. Such individuals have the potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA.
Main drug interactions	Antibodies present in immune globulin may interfere with the immune response to certain live viral vaccines including measles, mumps, rubella, and varicella vaccines.
Main side effects	Adverse reactions are uncommon, but include headache, fluid overload, and rarely renal shutdown [22•, Class III].
Special points	The mechanism of action of IVIg is not known; the treatment has no consistent effect on the measurable amount of circulating AchR-Ab.
Cost/cost effectiveness	The cost for an adult course is between \$8000 and \$12,000, depending on the amount and number of doses used.

Immunosuppression

- Immunosuppression using glucocorticoids, azathioprine, and other drugs is effective in nearly all patients with myasthenic crisis. The choice of drugs or other immunomodulatory treatments should be guided by the relative benefits and risks for each individual patient and the urgency of treatment. It is helpful to develop a treatment plan based on short-term, intermediate-term, and long-term objectives. Immediate improvement is essential because of the severity of weakness in myasthenic crisis; therefore, plasmapheresis should be undertaken or IVIg should be administered. For the intermediate-term, glucocorticoids and cyclosporine generally produce clinical improvement within a period of 1 to 3 months. The beneficial effects of azathioprine and mycophenolate mofetil usually begin after many months (up to a year); these drugs have advantages for the long-term treatment of patients with MG.
- Longer-term treatment strategy with various immunosuppressive agents, including glucocorticoids, should be considered as the initial improvement from the time myasthenic crisis is observed. Side effects of each drug may preclude its use in certain patients.

- Corticosteroids are relatively contraindicated in patients with myasthenic crisis with severe diabetes, ongoing infections, or severe osteoporosis. Tuberculosis should be excluded before starting corticosteroid therapy or other forms of chronic immunosuppression.
- To evaluate the effectiveness of treatment and assess the drug-induced side effects, it is important to have an idea of patient's clinical status at baseline and on repeated interval examinations in a systematic manner. The most useful clinical tests include forward arm abduction time (up to a full 5 minutes), forced VC, range of eye movements, and time for development of ptosis on upward gaze. Manual muscle testing also is important. A progressive reduction in the patient's AChR antibody level also provides serologic valuable confirmation of the effectiveness of treatment.

Glucocorticoid therapy

- Glucocorticoids, when used properly, produce improvement in myasthenic weakness in the majority of patients [17, Class III]. Unfortunately, relief may take weeks to become optimal. Furthermore, 1/3 of the patients have some exacerbation of their symptoms during the first few days of therapy [17, Class III]. Therefore, the initial dose of prednisone should be relatively low (15 to 25 mg per day) in patients with myasthenic crisis, especially if the patient is not intubated.
- The authors prefer to start prednisone when the patient is still intubated and maintained on the ventilator, so that any early exacerbation can be managed appropriately. Maximum dose is initiated on patients who are intubated; otherwise the dose is increased in a stepwise fashion, as tolerated by the patient (usually by 5 mg per day at 2- to 3-day intervals), until there is marked clinical improvement or a dose of 100 mg per day is reached. Some authors have disputed the early exacerbation on initiation of steroids, especially in the setting of concomitant use of PE or IVIg. Therefore, they advocate high-dose intravenous steroids in this setting to hasten the intermediate-term benefit of the steroids.
- The maximum dose is maintained for 1 to 3 months and then is gradually modified to an alternate-day regimen over the course of an additional 1 to 3 months; the goal is to reduce the dose to zero or to a minimal level on the "off day." Generally, patients begin to improve within a few weeks after reaching the maximum dose, and improvement continues to progress for months or years.

Oral prednisone

Standard dosage	Prednisone is given in dosages of 60 to 100 mg per day. Intravenous dosing rarely is used, although some authors advocate use of high-dose intravenous steroids during acute exacerbation at 500 to 1000 mg per day for 3 days followed by an oral regimen.
Contraindications	Systemic infections and known hypersensitivity to components.
Main drug interactions	Drugs that induce hepatic enzymes, such as phenobarbital, phenytoin, and rifampin, may increase the clearance of corticosteroids and may require increases in corticosteroid dose to achieve the desired response. Drugs such as troleandomycin and ketoconazole may inhibit the metabolism of corticosteroids and decrease their clearance. Corticosteroids may increase the clearance of chronic high-dose aspirin. The effect of corticosteroids on oral anticoagulants is variable.
Main side effects	Sodium retention, fluid retention, congestive heart failure in susceptible patients, potassium loss, hypokalemic alkalosis, and hypertension. Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, tendon rupture, particularly of the Achilles tendon, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, and pathologic fracture of long bones are also known side effects.

Peptic ulcer may develop with possible perforation and hemorrhage. Impaired wound healing and may suppress reactions to skin tests. Prednisone also may cause increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment, convulsions, vertigo, and headache.

Prednisone also causes menstrual irregularities, development of Cushingoid state, secondary adrenocortical and pituitary unresponsiveness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in patients with diabetes.

Special points Corticosteroids may mask some signs of infection, and new infections may appear during their use.

Cost/cost effectiveness Prednisone therapy, even in high doses, does not cost more than \$20 per month.

Azathioprine

Azathioprine has been the most widely used agent because of its relative safety in most patients and long track record. Its therapeutic effect may add to that of glucocorticoids or allow the reduction of the steroid dose.

Standard dosage 3 to 5 mg/kg daily.

Contraindications Azathioprine should not be given to patients who have shown hypersensitivity to the drug or those who are pregnant.

Main drug interactions Allopurinol increases the levels of azathioprine. A combination of angiotensin-converting enzyme inhibitors with azathioprine increases the adverse effect profiles of each drug.

Main side effects Leukopenia, liver function abnormality, increased risk of malignancy [27, Class III], nausea, vomiting, diarrhea, fever, malaise, and myalgias.

Special points Azathioprine takes at least 6 weeks to start to show effect and months or even longer to peak, and it is seldom initiated during the treatment of myasthenic crisis.

Cost/cost effectiveness One month of azathioprine therapy costs approximately \$50.

Cyclosporine

Cyclosporine may be as effective as azathioprine and is being used increasingly in the management of myasthenic crisis. Its beneficial effects seem similar to those of azathioprine. Therefore, it may be a useful adjunct to glucocorticoids for the intermediate phases of improvement of myasthenic crisis.

Standard dosage 3 to 8 mg/kg per day. The authors usually administer the drug in two divided doses to minimize the side effects.

Contraindications In patients with a hypersensitivity to cyclosporine and polyoxyethylated castor oil.

Main drug interactions The use of bosentan with cyclosporine is contraindicated, because it may dramatically increase the effect of bosentan and decrease cyclosporine levels. The use of tacrolimus increases the adverse event profile of the drugs. The other drugs that should be avoided in combination include amphotericin B, barbiturates, hydantoins, macrolide antibiotics, digoxin, and carbamazepine.

Main side effects The primary adverse reactions of cyclosporine therapy are renal dysfunction, tremor, hirsutism, hypertension, chronic renal failure, and gum hyperplasia.

Special points It may be used alone, but usually is used as an adjunct to glucocorticoids to permit reduction of the steroid dose.

Cost/cost effectiveness One month of cyclosporine therapy costs approximately \$300.

Mycophenolate mofetil

Mycophenolate mofetil, which has been used for immunosuppression in transplant patients, proved useful in the treatment of MG [28, Class I]. It has been shown to improve single fiber EMG findings of "jitter" in a randomized controlled trial [29, Class I].

The advantage of mycophenolate is in its relative lack of adverse side effects.

Standard dosage 0.5 to 1.5 g twice per day orally.

Contraindications Mycophenolate mofetil is contraindicated in patients with hypersensitivity to mycophenolate mofetil, mycophenolic acid, or any component of the drug product.

Main drug interactions	The effect of mycophenolate is significantly decreased in combination with cholestyramine, magnesium hydroxides, and aluminum hydroxides, and should be avoided in combination.
Main side effects	Adverse reactions associated with the administration of mycophenolate mofetil include diarrhea, leukopenia, sepsis, and vomiting.
Special points	This drug may become preferred for long-term treatment of patients with myasthenic crisis. Unfortunately, it has minimal use for the acute setting.
Cost/cost effectiveness	Mycophenolate therapy for 1 month costs approximately \$500 ranging from \$250 to \$800 depending on the dosage used.

Cyclophosphamide

	Cyclophosphamide is reserved for patients who are refractory to the other drugs, because of its relatively high risk of adverse side effects, including late development of malignancies. It has been shown in a double-blinded, random, controlled trial to decrease overall steroid requirements when used chronically in patients with severe MG [30, Class I].
Standard dosage	Oral dosing is usually in the range of 1 to 5 mg/kg per day.
Contraindications	Cyclophosphamide is contraindicated in patients who have demonstrated a previous hypersensitivity.
Main drug interactions	The combination of succinylcholine and digoxin should be avoided with cyclophosphamide because of interactions increasing the effect of succinylcholine and decreasing the effect of digoxin when used with cyclophosphamide.
Main side effects	Hemorrhagic cystitis, pneumonitis, polyneuropathy, cardiomyopathy, and alopecia. Malignancies have developed in patients treated with cyclophosphamide.
Special points	This drug also has minimal use in the acute or intermediate setting.
Cost/cost effectiveness	Cyclophosphamide therapy for 1 month costs approximately \$150.

FK 506 (Tacrolimus)

	FK 506 should be considered as an alternative treatment for patients with disabling MG that is not responsive to conventional immunosuppressants, or when other agents are contraindicated. It may be of particular benefit in patients whose sera test positive for anti-Ryanodine receptors [31, Class III].
Standard dosage	Oral dosage is recommended in the range of 0.1 to 0.15 mg/kg daily divided every 12 hours. The intravenous infusion could be given at 0.03 to 0.05 mg/kg/d intravenous infusion.
Contraindication	Hypersensitivity to the drug. Hypersensitivity to the castor oil products.
Main Side effects	Gastrointestinal upset, renal failure, seizure, neuropathy, hyperkalemia, and tremor.
Special points	The blood trough levels may be used for monitoring and levels range from 5 to 20 mg/mL. May benefit refractory MG patients [32,33, Class III].
Cost/ cost effectiveness	FK 506 therapy for 1 month costs \$300 to \$350.

Reboot of the immune system with G-CSF/Cyclophosphamide

	Lymphocytes and committed hematopoietic progenitors are rapidly killed by high-dose cyclophosphamide, because they express low levels of aldehyde dehydrogenase [34,35, Class III]. After the treatment, the hematopoietic stem cells proliferate, enhanced by administration of granulocyte colony stimulating factor (G-CSF), and reconstitute the immune system. In principal, the newly developing (or "rebooted") immune system may recognize the autoantigen as "self", thereby tolerating it.
Standard procedure	A recent study used extremely high doses (50 mg/kg per day intravenously for 4 days followed by G-CSF) in three refractory patients with MG who did not respond to conventional immunotherapeutic agents or could not tolerate their side effects. All three patients tolerated therapy and improved, allowing for a reduction in immune medications. AchR-Ab titers fell in two patients and anti-MuSK titers fell in the third [36•, Class III].

Table 3. Relation between myasthenic crisis frequency and thymectomy

	Thymectomized patients (n=110)	Non-thymectomized patients	P
Patients with myasthenic crisis (n=62)	20	42*	0.001
Episodes of myasthenic crisis (n=89)	25	64†	0.016

*This group had more probability of having crisis with an odds ratio of 2.8 (with 95% CI of 1.5 to 5.2)

†Myasthenic crisis was more prevalent in this group with a RR of 2.6 (with 95% CI of 1.8 to 3.8)
(Modified from Soleimani et al. [40])

Special points This therapy is good for refractory patients who failed to respond to thymectomy, plasmapheresis, and conventional immunotherapeutic agents or can not tolerate their side effects.

Cost/cost effectiveness Approximately \$4000 for the entire course of therapy.

Surgery

Thymectomy

- Thymectomy may be done for surgical removal of thymoma, and as a treatment for MG. Surgical removal of a thymoma is necessary because of the possibility of local tumor spread, although most thymomas are benign. In the absence of a tumor, the available evidence suggests that as many as 85% of patients experience improvement after thymectomy, primarily those with early onset MG who do not have anti-titin or anti-Ryanodine receptor antibodies [37, Class II]. A multicenter, international trial currently is being done [38, Class I]. Of these, approximately 35% achieved drug-free remission. In view of these potential benefits and of the negligible risk in skilled hands, thymectomy has gained widespread acceptance in the treatment of MG. However, the improvement is typically delayed for months to years. It should not be attempted without minimizing patient weakness first. As a result, it is rarely used during hospitalization for crisis [39•, Class III]. Thymectomy seems to have a preventive role on rate and severity of future attacks [40, Class I] (Table 3).

Prognosis

- Median duration of hospitalization for crisis is 1 month. The patient usually spends half of this time intubated in the intensive care unit [13,14,19,41•, Class III]. Approximately 25% of patients are extubated on hospital day 7, 50% by hospital day 13, and 75% by hospital day 31. Risk factors for prolonged intubation (greater than 2 weeks) include patient age older than 50 years, pre-intubation serum carbon dioxide levels above 30 mg/dL, and highest VC of less than 25 mL/kg during the first week of intubation [14, Class III]. In a study of 73 episodes of crisis [14, Class III], the risk of prolonged intubation was 0% in patients with none of these risk factors, 20% in those with one risk factor, 50% in those with two risk factors, and 90% in those with three risk factors.
- Duration of intubation is an important predictor of functional outcome after crisis. In the same study [14, Class III], 77% of patients intubated for more than 2 weeks had functional dependence at discharge compared with 36% of patients intubated for less than 2 weeks. The mortality rate during hospitalization for crisis has decreased from nearly 50% in the early 1960s to between 3% and 10% today. With the incidence of crisis remaining stable over the past 30 years, this decrease in mortality rates reflects improvements in intensive care assessment and management of these patients.

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