TEHRAN UNIVERSITY OF MEDICAL SCIENCES

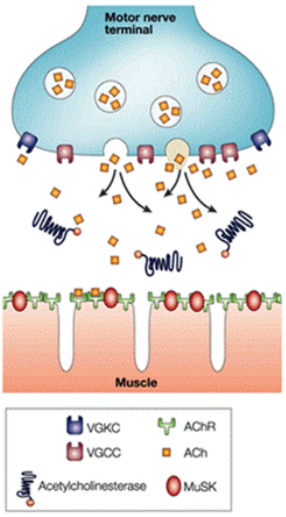
Neuromuscular Research Center
NMRC

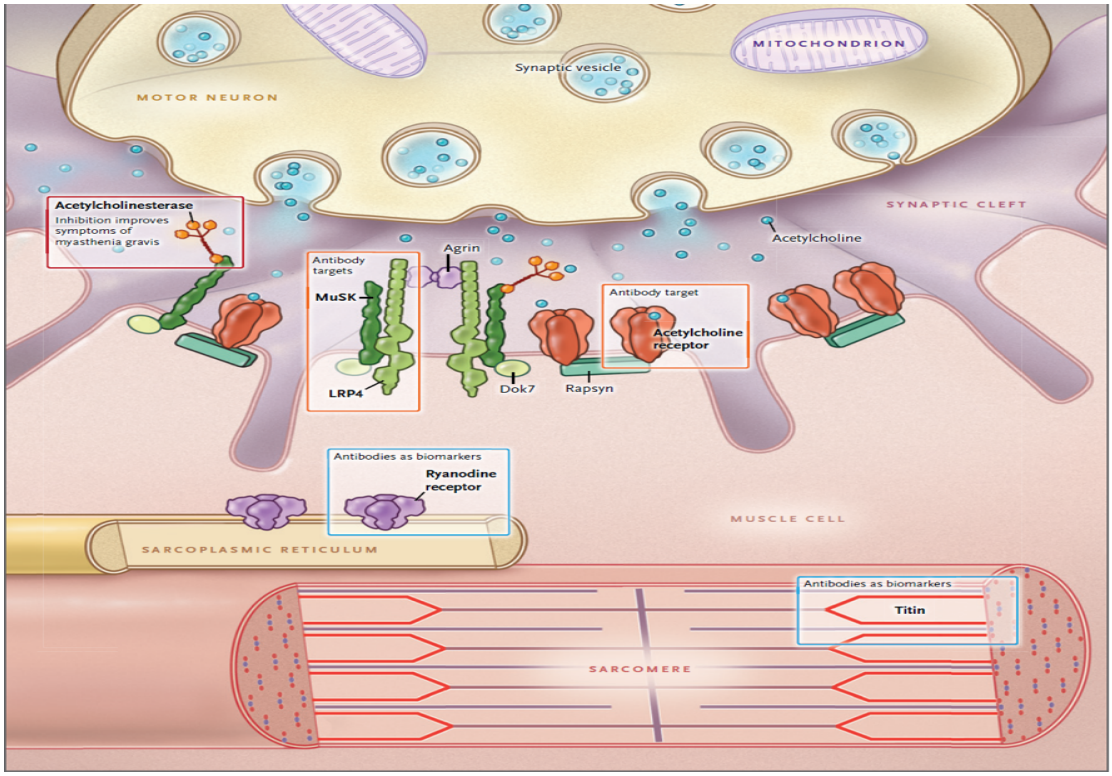
Myasthenia gravis crisis

Ali Asghar Okhovat, MD
Associate Professor of Neurology
Neuromuscular Fellowship
Neuromuscular Research Center,
Shariati Hospital, TUMS

Introduction

- Immune myasthenia gravis (MG) is one of the best delineated immune mediated disease among all human autoimmune disorders.
- B-cell mediated





Gilhus NE, N Engl J Med. December 2016;375;2570-81

Epidemiology

- Myasthenia gravis is an uncommon to rare disease
- The incidence: 9 to 30 per 1,000,000
- Prevalence: 100 to 140 per 1,000,000
- Prevalence is increasing due to:
- Improved diagnostic techniques.
- Longer life span in affected patients due to more effective treatment.
- Increased life expectancy in general
- Women are more likely to have MG than men in the first 5 decades of life whereas men are more likely to be diagnosed with MG after the age of 50.

Binks S. J Neurol 2016;263(4):826-834

Myasthenic crisis

- Myasthenic crisis is a life-threatening exacerbation of myasthenia gravis that is defined as worsening of myasthenic weakness requiring intubation or noninvasive ventilation
- Definition of impending myasthenic crisis: Rapid clinical worsening of MG that, in the opinion of the treating physician, could lead to crisis in the short term (days to weeks).
- Definition of manifest myasthenic crisis: Worsening of myasthenic weakness requiring intubation or noninvasive ventilation to avoid intubation, except when these measures are employed during routine postoperative management

Impending and manifest myasthenic crisis

- Impending crisis requires **hospital admission** and close observation of respiratory and bulbar function, with the ability to transfer to an intensive care unit if it progresses to manifest crisis.
- Myasthenic crisis requires admission to an **intensive care** to monitor for or manage respiratory failure and bulbar dysfunction.

Sanders DB. International consensus guidance for management of myasthenia gravis.Neurology 2016:26;87(4):419-25.

Epidemiology

- Occurs in 10–20% of MG patients

- the annual risk of myasthenic crisis among patients with myasthenia gravis is approximately 2 to 3 percent
- the first manifestation of myasthenia gravis in up to 20 percent of patients
- - First few years post-diagnosis most common

Risk factors

- Risk factors for myasthenic crisis include
- greater disease severity at diagnosis,
- the presence of thymoma,
- diagnosis after age 50 years (late-onset myasthenia gravis),
- the association with muscle-specific receptor tyrosine kinase antibodies

Precipitants

- Myasthenic crisis may be precipitated by a variety of factors, most often a concurrent infection.
- It can also follow a surgical intervention (eg, thymectomy), pregnancy, childbirth, or tapering of immunotherapeutic medications.
- myasthenic crisis can occur spontaneously as part of the natural history of myasthenia gravis itself.

Drugs

✓ **Avoid**

- Telithromycin: antibiotic for community-acquired pneumonia. "Black box" warning for use in MG.
- Botulinum toxin: for cosmetic or medical use (e.g., migraine, spasticity)
- D-penicillamine: for Wilson disease/rarely for rheumatoid arthritis. Associated with causing MG.

✓ **Avoid or use with caution if no reasonable alternative, benefit outweighs risk**

- Fluoroquinolones (e.g., ciprofloxacin, moxifloxacin, and levofloxacin): broad-spectrum antibiotics associated with worsening MG. "Black box" warning for use in MG.
- Magnesium: may worsen MG if given intravenously, i.e., for eclampsia during late pregnancy or for hypomagnesemia. Use only if no alternative and observe for worsening.
- Quinine: occasionally used for leg cramps. Use prohibited except in malaria in the United States.
- Macrolides (e.g., erythromycin, azithromycin, clarithromycin): antibiotics for gram-positive infections.
- Aminoglycosides (e.g., gentamycin, neomycin, tobramycin): antibiotics for gram-negative infections.
- Immune checkpoint Inhibitors for cancer such as anti-PD1 and CTLA-4 agents (e.g., pembrolizumab, ipilimumab, nivolumab, atezolimumab, etc.)
- Live or live-attenuated vaccines: avoid for patients on immunosuppressive therapy due to concern for development of active infection. Not associated with MG disease worsening.

✓ **May worsen MG—use with caution and observe**[a]

- Corticosteroids: standard treatment for MG, may cause transient worsening within the first 2 weeks. Monitor for this possibility and do not discontinue if worsening occurs.
- Procainamide: antiarrhythmic.
- Deferoxamine: Chelating agent used for hemochromatosis.
- Beta-blockers: used hypertension, heart disease, migraine, and tremor. Risk primarily with new starts of higher doses, intravenously.
- Chloroquine and hydroxychloroquine: used to treat malaria and some autoimmune diseases.
- Statins (e.g., atorvastatin, simvastatin etc.): used to reduce serum cholesterol.
- Iodine contrast dye: older varieties.
- Neuromuscular blocking agents: MG patients sensitive to nondepolarizing NMBA and resistant to succinylcholine (depolarizing NMBA).

► **TABLE 25-5. DIFFERENTIAL DIAGNOSIS OF MG**

Brain/Cranial Nerves
Abnormality of brainstem nuclei due to inflammatory or neoplastic etiology[a]
Chronic meningitis[a]
Wernicke encephalopathy[a]
Rabies[a]
Cerebral aneurysm[a]
Cavernous sinus thrombosis[a]
Anterior horn cell
ALS
Kennedy syndrome[a]
Spinal muscular atrophy[a]
Enterovirus or West Nile Virus infection[a]
Root/nerve
Chronic meningitis[a]
Miller Fisher syndrome[a]
Diphtheria[a]
Immune-mediated polyradiculopathies[a]
NMJ
Congenital myasthenic syndromes
Lambert–Eaton myasthenic syndrome
Botulism (including iatrogenic botulinum toxin)
Tick paralysis
Muscle
Oculopharyngeal muscular dystrophy (OPMD)
Myotonic muscular dystrophy[a]
Mitochondrial myopathy
Congenital myopathy[a]
Inflammatory myopathy[a]
Immune checkpoint inhibitor-related myositis
Orbital myositis
Miscellaneous
Depression[a]
Chronic fatigue syndrome[a]
Dysthyroid ophthalmopathy
Orbital pseudotumor[a]
Blepharospasm
Levator muscle dehiscense

Management of myasthenic crisis

Admit to intensive care unit
Measure VC frequently, as often as every two hours if respiratory status is deteriorating
•Consider elective intubation based upon overall clinical status, particularly in the presence of any of the following conditions: • Declines in serial measures of VC below 15 to 20 mL/kg ideal body weight •Declines in serial measurements of MIP less negative than –25 to –30 cmH2O (ie, 0 to –30 cmH2O) •Clinical signs of respiratory distress •Evidence of progressive respiratory acidosis •Difficulty handling oral secretions
Withdraw anticholinesterase medications temporarily to avoid excess airway secretions for patients who are intubated
Seek and treat any precipitating or contributing factors, particularly infections
Begin rapid therapy with plasma exchange or IVIG
Begin immunomodulating therapy with high-dose glucocorticoids (eg, prednisone 60 to 80 mg per day); consider azathioprine, mycophenolate mofetil, or cyclosporine if glucocorticoids are contraindicated or previously ineffective
After starting immunomodulating therapy and resuming anticholinesterase medications, consider weaning from mechanical ventilation when respiratory muscle strength is improving (ie, VC >15 to 20 mL/kg and MIP more negative than –25 to –30 cmH2O) in patients with an adequate cough and manageable respiratory secretions

Ventilatory support

- Elective intubation
- Ideally, endotracheal intubation should be performed electively rather than as an emergent response to precipitous respiratory collapse.
- The threshold for elective intubation should be low if serial measurements demonstrate one or both of the following:
- **VC falls below 15 to 20 mL/kg**
- **MIP is less negative than -25 to -30 cmH0 (ie, between 0 and -30 cmH0)**

Indications for Mechanical Ventilation

- clinical signs of respiratory distress,
- progressive respiratory acidosis despite therapy,
- inadequate secretion clearance (eg, recurrent episodes of acute hypoxemia due to mucus plugging).

- ventilatory assistance should consist of endotracheal intubation with positive pressure mechanical ventilation.
- This provides full support and allows for clearance of secretions for patients in whom a prolonged course of crisis is anticipated.
- The optimal mode of mechanical ventilation is unknown.
- It is important to avoid overventilation, which may impair respiratory drive especially when attempting to wean from ventilatory support.

- For intubation, both a **sedative and a neuromuscular blocking agent** should be co-administered.
- A non-depolarizing neuromuscular blocking agent (eg,rocuronium) might be preferred to a depolarizing agent (succinylcholine).
- Due to the relative paucity of acetylcholine receptors in myasthenia gravis, there is a relative resistance to succinylcholine, necessitating higher doses, and a relative sensitivity to non-depolarizing neuromuscular blockers, necessitating lower doses.

Therapies for myasthenia gravis

- **temporarily discontinue acetylcholinesterase inhibitors**
- **Treat with a rapid-acting immunotherapy**
- **Add chronic immunotherapy**

3]

Rapid therapies for myasthenia gravis

	Plasmapheresis	Intravenous immune globulin (IVIG)
Usual adult dose	5 exchange treatments of 3 to 5 liters with 5% albumin over 7 to 14 days	2 g/kg in evenly divided doses over 2 to 5 days Examples: 400 mg/kg daily for 5 days or 1 g/kg on 2 consecutive days*[1]
Onset of effect	1 to 7 days	4 to 7 days
Maximal effect	1 to 3 weeks	1 to 3 weeks
Adverse effects	Line infection, hypotension, thromboembolism, bleeding, adverse reaction(s) to citrate anticoagulant added during procedure (hypocalcemia, metabolic alkalosis)	Rate-related reactions (common): headache, chills, flushing, low backache, nausea, tachycardia, dyspnea Delayed reactions (rare): thromboembolism, kidney failure, hematologic complications (hemolysis, neutropenia) Other (rare): transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), hypersensitivity (eg, anaphylaxis)

PLEX &IVIG

- Myasthenic crisis
- Preoperatively before thymectomy
- As a "bridge" while initiating slower acting immunotherapies
- As an adjuvant to other immunotherapeutic medications in patients with refractory MG

PLEX &IVIG

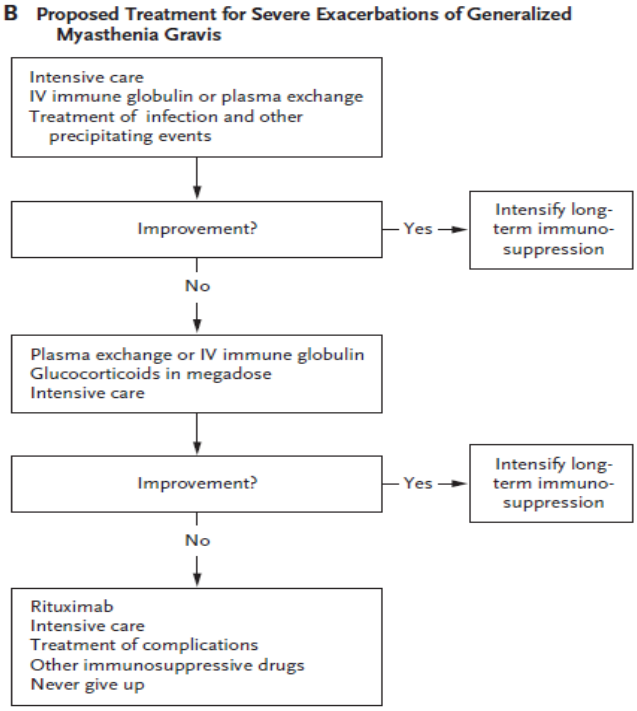
- Both treatments are similarly effective, although plasma exchange may be slightly faster and more effective in a Myasthenic crisis and more useful in patients with MuSK MG.
- Exchanges done every other day are probably more effective in reducing the antibody levels due to the time it takes for the extravascular immunoglobulin to reequilibrate after each plasma exchange.

Although clinical trials suggest that IVIg and PLEX are equally effective in the treatment of impending or manifest myasthenic crisis, **expert consensus suggests that PLEX is more effective and works more quickly**.

Sanders DB. International consensus guidance for management of myasthenia gravis.Neurology 2016:26;87(4):419-25.

PLEX &IVIG

- IVIg or PLEX have no effect on the long-term course of MG and, with few exceptions, are not indicated for the chronic management of MG.
- These two treatment **can be given in sequence if necessary**, as patients can respond to one but not to the other.
- In patients with an acute exacerbation that does **not respond to IVIG or PLEX**, **corticosteroids in high doses** can be tried.



Gilhus NE, N Engl J Med. December 2016;375;2570-81

Commonly used therapies for MG

	Time to onset of effect*	Time to maximal effect*
Symptomatic therapy		
Pyridostigmine	10 to 15 minutes	2 hours
Chronic oral immunotherapies		
Prednisone	2 to 3 weeks	5 to 6 months
Azathioprine	~12 months	1 to 2 years
Mycophenolate mofetil	6 to 12 months	1 to 2 years
Cyclosporine	~6 months	~7 months
Tacrolimus	~6 months	~12 months
Antibody-based biologic therapies		
Fc receptor inhibitors		
Efgartigimod alfa	2 to 3 weeks	~4 weeks
Rozanolixizumab	2 to 3 weeks	~4 weeks
Complement inhibitors		
Eculizumab	2 to 3 weeks	~4 weeks
Ravulizumab	2 to 3 weeks	~4 to 10 weeks
Zilucoplan	2 to 3 weeks	~4 weeks
B-cell depletion therapy		
Rituximab	4 weeks	~8 weeks
Rapid immunotherapies		
Plasmapheresis	1 to 7 days	1 to 3 weeks
Intravenous immune globulin	1 to 2 weeks	1 to 3 weeks

PROGNOSIS

- Mortality
- Myasthenic crisis is associated with an in-hospital mortality rate of 5 to 12 percent with modern therapies and specialized neurologic intensive care.
- The most common causes of death are a multiorgan failure due to sepsis and respiratory failure maximal care

Prognostic factors

- Factors associated with poor outcomes include:
- lower baseline and admission vital capacity,
- the presence of medical comorbidities,
- duration of ventilatory support,
- the onset of crisis triggered by systemic infection

Many Thanks for Your Attention!