**Myasthenic Crisis  Introduction**

Myasthenic crisis is an acute, life-threatening exacerbation of myasthenia gravis characterized by severe muscle weakness resulting in respiratory failure. Rapid recognition and urgent intervention are imperative.

**Clinical Presentation**

Myasthenia gravis (MG) manifests with a diverse array of clinical symptoms, primarily stemming from muscle weakness and fatigue due to impaired neuromuscular transmission. The disease commonly presents in two main forms: generalized MG and ocular MG. Understanding these clinical presentations is crucial for clinical pharmacists to recognize the disease promptly and initiate appropriate management.

**Generalized Myasthenia Gravis:**

* Muscle Weakness: Generalized weakness is the hallmark of MG, affecting various  muscle groups. Patients often experience difficulty performing tasks that involve  repetitive movements or sustained muscle contractions, such as holding objects or  walking long distances. The weakness can fluctuate throughout the day, being more pronounced after exertion and improving with rest.

* Ocular Symptoms: Ocular MG initially presents as isolated eye muscle weakness,  resulting in ptosis (drooping of the eyelids) and diplopia (double vision). Ptosis may be  asymmetrical and worsens as the day progresses. Diplopia is usually horizontal and can  be exacerbated by looking in certain directions.

* Bulbar Symptoms: Bulbar involvement affects muscles controlling speech and  swallowing. Dysarthria (difficulty articulating speech) and dysphagia (difficulty  swallowing) can lead to speech slurring and choking episodes. Patients may avoid  certain foods due to the risk of aspiration.
* Respiratory Compromise: In severe cases, respiratory muscles can be affected, leading  to respiratory distress and respiratory failure. This life-threatening complication requires immediate intervention.

* Muscle Fatigability: One of the distinguishing features of MG is the characteristic  muscle fatigability. Patients experience a decline in muscle strength with repetitive  movements or sustained effort. This fatigue can be objectively demonstrated during  clinical examinations, such as the Tensilon (edrophonium) test

**Risk Factors:**

1. Gender and Age: MG is more common in females, with a peak incidence in young adult females and older males. Females under 40 and males over 60 are at higher risk.

2. Thymic Abnormalities: Approximately two-thirds of MG patients have thymic abnormalities. These can include thymoma (a tumor in the thymus gland) or thymic hyperplasia (enlarged thymus). In some cases, thymectomy may be considered as part of the management.

 3. Family History: MG can have a genetic component, with a higher risk for individuals with family members affected by the disease

**Diagnostic Approach**

* Clinical suspicion in known MG patients with acute weakness
* Measure vital capacity and negative inspiratory force
* Assess arterial blood gas - hypercapnia indicates respiratory failure
* Order acetylcholine receptor antibody test if no established MG diagnosis
* Rule out other causes like stroke, electrolyte abnormalities

Rapid diagnosis is crucial to initiate ventilatory support urgently before respiratory arrest occurs.

### Management – Overview

* Secure airway and assist ventilation
* ICU monitoring
* Modulate underlying MG treatment
* Optimize cholinesterase inhibitors
* Administer IVIG or plasmapheresis
* Add or increase immunosuppression
* Identify and treat trigger, such as infection
* Avoid medications that may exacerbate MG
* Coordinate multidisciplinary care

### Pharmacotherapy

The pharmacotherapy for myasthenic crisis focuses on providing ventilatory support, optimizing underlying myasthenia gravis treatment, and avoiding medications that may exacerbate neuromuscular weakness.

**Ventilatory Support**

* Endotracheal intubation and mechanical ventilation are required in myasthenic crisis to maintain airway patency and support respiratory function.
* Non-invasive positive pressure ventilation may be trialed in milder cases without immediate need for intubation.
* Careful patient selection is necessary to avoid delaying intubation when required.
* Medication selection requires careful consideration during intubation and mechanical ventilation in myasthenic crisis patients to avoid exacerbating neuromuscular weakness.

**Intubation Medications**

**Induction Agents**

* Propofol 1-2 mg/kg IV
  + Rapid onset anesthetic induction
  + Dose-dependent hypotension and respiratory depression
* Ketamine 1-2 mg/kg IV
  + Maintains respiratory drive and airway reflexes
  + Sympathomimetic - less hypotension
* Etomidate 0.3 mg/kg IV
  + Minimal hemodynamic effects
  + May cause myoclonus - negative impact on endotracheal intubation

**Paralytic Agents**

Patients with myasthenia gravis have a varied pharmacokinetic and pharmacodynamic response to neuromuscular blocking agents due to antibodies at the acetylcholine receptor. There is research that displays that patients receiving depolarizing neuromuscular blocking agents can be resistant to the desired paralysis and non-depolarizing agents could potentially aggravated responses even at lower doses. This is in addition to medications to treat the condition interfering with the metabolism of these agents.

* Rocuronium 0.6-1 mg/kg IV
  + Reduced dose of 0.6 mg/kg due to enhanced neuromuscular blockade
  + Onset of action 1-2 minutes
  + Duration 30-60 minutes

* Succinylcholine is avoided
  + Depolarizing agent - triggers extensive depolarization
  + May fail to achieve adequate intubation conditions due to reduced acetylcholine receptors
  + Prolonged paralysis and inability to ventilate possible

Managing myasthenic crisis requires a multifaceted pharmacological approach beyond just airway protection with intubation. Key treatment modalities include immunomodulating agents, immunosuppressants, and avoidance of medications exacerbating neuromuscular weakness.

**Glucocorticoids**

* High dose intravenous glucocorticoids form the cornerstone of treatment.
* Agents: Methylprednisolone or Dexamethasone
* Dosing:
* Methylprednisolone 500-1000 mg IV daily for 3-5 days
* Dexamethasone 40 mg IV daily for 3-5 days
* Transition to high dose oral prednisone 1-1.5 mg/kg/day after pulse.
* Effects may take several weeks - bridge with plasmapheresis/IVIG.
* Monitor glucose, electrolytes, mental status.
* Never discontinue abruptly - taper gradually.

**Plasmapheresis**

* Mode of action: Filters and removes pathogenic antibodies.
* Dosing: Exchange 1-1.5 plasma volumes on alternate days. Total of 5-6 exchanges.
* Replacement with albumin or plasma to maintain oncotic pressure.
* Adverse effects: Hypotension, hypocalcemia, bleeding, infections.
* Provides passive immunomodulation until steroids/immunosuppressants effective.

**IV Immunoglobulin (IVIG)**

* Mechanism: Provides IgG antibodies for immunomodulation.
* Dosing: 2 g/kg ideal body weight divided over 2-5 days.
* Onset within 3-7 days, effects last 3-6 weeks.
* Adverse effects: Headache, fever, renal dysfunction, thrombotic events.
* Provides passive immunomodulation until steroids/immunosuppressants effective.

**Immunosuppressants**

* Initiate steroid-sparing immunosuppressants like azathioprine, mycophenolate mofetil, or cyclosporine.
* Do NOT rely solely on immunosuppressants in acute setting due to slow onset.
* Tailor regimen based on prior MG treatment history.
* Monitor for bone marrow suppression, hepatic toxicity.

**Avoid Exacerbating Medications**

* Prevent worsening of neuromuscular blockade:
* Aminoglycosides, magnesium, fluoroquinolones
* Anticholinesterase inhibitors if cholinergic crisis
* Beta-blockers, calcium channel blockers
* Use peripheral nerve stimulation monitoring with paralytics.

### Key Guidelines and Evidence

Clinical practice guidelines provide crucial evidence-based recommendations for the diagnosis and management of myasthenic crisis:

**American Academy of Neurology (AAN) Guidelines**

* For patients with nonthymomatous AChR ab+ generalized MG, treatment with thymectomy plus prednisone is probably more effective than treatment with prednisone alone for increasing the chance of attaining minimal manifestation status
  + Gronseth GS, Barohn R, Narayanaswami P. Practice advisory: Thymectomy for myasthenia gravis (practice parameter update): Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2020 Apr 21;94(16):705-709.

### ****International consensus guidance for management of myasthenia gravis****

* PLEX and IVIg are used as short-term treatment for impending and manifest myasthenic crisis and in patients with significant respiratory and/or bulbar dysfunction. Corticosteroids\* or other IS agents are often started at the same time to achieve a sustained clinical response
* 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. The choice between the two therapies depends on patient co-morbidity\* and other factors, including availability and cost. A greater risk of 36 hemodynamic and venous access complications with PLEX should also be considered in the decision
  + Sanders DB, et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology. 2016 Jul 26;87(4):419-25.

**Select Studies**

## **Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Myasthenia Gravis Clinical Study Group**

* Eighty-seven patients with MG exacerbation were randomized to receive either three PE (n = 41), or i.v.Ig (n = 46) 0.4 gm/kg daily further allocated to 3 (n = 23) or 5 days (n = 23)
* The main end point was the variation of a myasthenic muscular score (MSS) between randomization and day 15. The MSS variation was similar in both groups (median value, +18 in the PE group and +15.5 in the i.v.Ig group, p = 0.65).
* Similar efficacy, although slightly reduced in the 5-day group was observed with both i.v.Ig schedules.
* The tolerance of i.v.Ig was better than that of PE with a total of 14 side effects observed in 9 patients, 8 in the PE group and 1 in the i.v.Ig group (p = 0.01).
* Reference: Gajdos P, Chevret S, Clair B, Tranchant C, Chastang C. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. Ann Neurol. 1997 Dec;42(6):789-96.

## **Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: a randomized double-blind clinical trial**

* **Design:**Randomized double-blind placebo-controlled multicenter trial designed to demonstrate superiority of the 2 g/kg dose over the 1 g/kg dose of IVIG, conducted between November 13, 1996, and October 26, 2002.
* **Participants:**One hundred seventy-three patients aged 15 to 85 years with acute exacerbation of myasthenia gravis.
* **Intervention:**Participants were randomly assigned to receive 1 g/kg of IVIG on day 1 and placebo on day 2 (group 1) vs 1 g/kg of IVIG on 2 consecutive days (group 2).
* **Main outcome measure:**Improvement in the myasthenic muscular score after 2 weeks.
* **Results:**The mean improvements in the myasthenic muscular scores after 2 weeks were 15.49 points (95% confidence interval, 12.09-18.90 points) in group 1 and 19.33 points (95% confidence interval, 15.82-22.85 points) in group 2. However, the difference between the 2 groups was not significant (effect size, 3.84 [95% confidence interval, -1.03 to 8.71]; P = .12).
* **Conclusion:**This trial found no significant superiority of 2 g/kg over 1 g/kg of IVIG in the treatment of myasthenia gravis exacerbation.
* Reference: Gajdos P, Tranchant C, Clair B, Bolgert F, Eymard B, Stojkovic T, Attarian S, Chevret S; Myasthenia Gravis Clinical Study Group. Treatment of myasthenia gravis exacerbation with intravenous immunoglobulin: a randomized double-blind clinical trial. Arch Neurol. 2005 Nov;62(11):1689-93. doi: 10.1001/archneur.62.11.1689. PMID: 16286541.

**Clinical Scenarios**

A 45-year-old woman with myasthenia gravis well-controlled on pyridostigmine presents with an acute exacerbation of dyspnea and dysphagia. She is started on azithromycin for presumed pneumonia. After two days, she experiences respiratory failure requiring intubation.

* What factors may have precipitated her myasthenic crisis?
  + This scenario highlights the risk of crisis due to infection as well as medications that can exacerbate MG. The azithromycin likely precipitated neuromuscular blockade leading to rapid decompensation. Vigilance is needed to recognize factors precipitating crisis and modify therapy accordingly.

**Myasthenic Crisis Summary**

Myasthenic crisis is an acute exacerbation of muscle weakness in myasthenia gravis leading to respiratory failure. Emergency and critical care pharmacists play a vital role through prompt recognition, airway protection, individualized pharmacotherapy, and multidisciplinary care coordination. Optimizing therapy while avoiding medications exacerbating neuromuscular weakness is imperative for favorable outcomes.

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