Myasthenia gravis & myasthenic crisis

March 6, 2019 by Josh Farkas

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pathophysiology of MG

basics
Autoantibodies are formed which bind to acetylcholine receptors on skeletal muscle.

- Anti-acetylcholine antibodies impair transmission at the neuromuscular junction in a few ways:
  - Direct inhibition of acetylcholine binding to the muscle
  - Antibodies accelerate degradation of acetylcholine receptors, decreasing the number of receptors.
  - Clinically this causes skeletal muscle weakness.

**treatments**

- Acetylcholinesterase inhibitors (e.g. physostigmine) – these decrease the breakdown of acetylcholine within the neuromuscular junction. This may boost signaling of the muscle cell.
- Immunosuppressive therapies are aimed at reduction in the synthesis of auto-antibodies.
- Plasmapheresis may directly remove auto-antibodies.

**presentation of MG**

**distribution**

- Eyes and bulbar muscles tend to be involved early (ptosis and diplopia are common).
  - Only skeletal muscles are involved (not the pupils)
- Generalized weakness can also occur (e.g. involving diaphragm and limbs).

**features of weakness**

- Fatiguability: ongoing effort rapidly provokes worsening weakness. Strength improves with rest.
- Fluctuation of severity over time.
- Normal sensation, normal deep tendon reflexes, and normal pupillary reflexes.

**epidemiology**

- Incidence in women peaks in their thirties, whereas incidence in men peaks in their sixties.
- Can be associated with:
  - Thymoma or thymic hyperplasia
  - Other autoimmune diseases (e.g., hyperthyroidism, lupus, rheumatoid arthritis, polymyositis)
  - Lymphoma
  - Checkpoint inhibitor use

**specific disease phenotypes**

- Antibodies to muscle-specific receptor tyrosine kinase (MuSK)
  - Often lack typical anti-ACh antibodies (MuSK is a different protein involved in acetylcholine signaling).
  - Typically, young women with prominent involvement of bulbar muscles and diaphragm. Disease tends to be severe with high frequency of respiratory crises. Patients tend to respond well to plasma exchange, but less well to IVIG or pyridostigmine.¹
- Antibodies to titin & ryanodine receptor
  - Often older patients with thymoma; tends to be severe.

**diagnosis of MG**
anti-AcH antibody

- Sensitivity >80% among patients with severe myasthenia gravis requiring ICU-level care.
- Patients with myasthenia gravis who lack anti-AcH antibody may have antibodies to other antigens (especially MuSK antibodies) or no detectable antibodies ("seronegative myasthenia gravis").
- Sluggish turn-around time limits the ability of this test to guide immediate treatment decisions.

ice pack test

- Place ice pack over patient's eye that is affected with ptosis or ophthalmoparesis for two minutes.
- Improvement following ice supports a diagnosis of myasthenia gravis (see video below).
- Test is cheap, safe, noninvasive – and surprisingly sensitive (~90%) and specific (~80%).

edrophonium test ("tensilon test")

Myasthenia Gravis - Before and After Tensilon

- Note: edrophonium seems to be currently unavailable in the United States.
- Edrophonium is an acetylcholinesterase inhibitor with a very short half-life. It can be used to test the clinical response to an increase in acetylcholine levels.
- Test performance requires some objective measurement of weakness (e.g. ptosis, ophthalmoparesis, or forced vital capacity).
- How to perform test:
  - First give 2 mg IV as a test dose for adverse effects.
  - If no response in 1-2 minutes, then give an additional 8 mg IV.
- Edrophonium may cause bradycardia, bronchospasm, or heart block – so be prepared to manage these (e.g. with atropine & epinephrine available).
- Clear improvement following edrophonium strongly supports a diagnosis of myasthenia gravis, but lack of a response doesn’t exclude the diagnosis.

**electrodiagnostic testing (EMG)**

- (1) Repeated stimulation causes rapid deterioration in muscle responses (fatiguability).
  - Sensitivity isn’t fantastic.
- (2) Single-fiber EMG
  - Compares contraction in closely adjacent muscle fibers in the same motor unit. Desynchronized activity of adjacent fibers (“jitter”) supports a diagnosis of myasthenia gravis.
  - Better sensitivity than repeated stimulation, but logistically challenging.

### drugs to avoid in MG

- **Antibiotics**
  - Aminoglycosides
  - Fluoroquinolones
  - Tetracyclines, clindamycin
  - Macrolides (e.g. azithromycin, erythromycin)
- **Muscle relaxants**
  - Succinylcholine (may not work)
  - Dantrolene
  - Anti-spasmodics: cyclobenzaprine, baclofen, carisoprodol, methocarbamol
- **Neuro/psych**
  - Lithium
  - Haloperidol, prochlorperazine
  - Phenytoin
- **Cardiac**
  - Beta-blockers (even ophthalmic!), calcium channel blockers
  - Lidocaine, procainamide, quinidine
  - Statins
- **Other**
  - Antihistamines, anticholinergics
  - Steroid (may cause transient exacerbation)
  - Magnesium
  - IV contrast

### diagnosis of myasthenic crisis

**definition?**

- The term “myasthenic crisis” is used by different authors in various ways, which may lead to confusion:
  - #1 Some authors use “myasthenic crisis” to refer solely to patients with myasthenia gravis exacerbation requiring intubation or noninvasive ventilation.³
  - #2 Some authors use “myasthenic crisis” to refer to any exacerbation of myasthenia gravis which causes or threatens to cause frank respiratory failure.²
The broader definition of myasthenic crisis (#2) is used here.

Don't assume that every patient with myasthenia gravis who presents with dyspnea has a myasthenic crisis! Patients with myasthenia gravis can have cardiopulmonary disease like anyone else (e.g. pneumonia, heart failure, pulmonary embolism).

**diagnosis of a myasthenic crisis requires two components:**

- (1) Careful cardiopulmonary evaluation with exclusion of other active processes
  - At a *minimum* this should involve a thoughtful history, chest X-ray, EKG, and lung ultrasonography.
  - Other tests added as necessary (e.g. CT angiography to exclude PE).
- (2) Evidence of worsening muscular weakness
  - History and physical may be helpful (e.g. patient reports increasing limb weakness and this is confirmed on exam).
  - Forced Vital Capacity (FVC) should be measured if the patient isn't extremely dyspneic. Forced vital capacity should be reduced in order to make a diagnosis of myasthenic crisis.

### myasthenic vs cholinergic crisis

#### what is a cholinergic crisis?

- *Excessive* doses of acetylcholinesterase inhibitor (e.g. pyridostigmine) lead to excessive levels of acetylcholine, which acts as a *depolarizing paralytic*! (similar to succinylcholine).
- Cholinergic crisis is widely feared, but in modern practice this is almost nonexistent
  - Historically, higher doses of pyridostigmine were used, so cholinergic crises were a more relevant problem.

#### clinical features of a cholinergic crisis

- (1) Patient has a history of using *escalating doses* of acetylcholinesterase inhibitor medication.
  - Cholinergic crisis is unlikely if pyridostigmine dose is below 120 mg q3hr.
- (2) Fasciculation of skeletal muscles.
- (3) Features of acetylcholine excess affecting the autonomic nervous system:
  - Nausea/vomiting, diarrhea, salivation, lacrimation, diaphoresis
  - Miosis
  - Bradycardia

#### management of cholinergic crisis

- Withhold any further administration of acetylcholinesterase inhibitor.
- Supportive therapy (e.g. intubation if clinically warranted).
- Once patient has recovered, lower doses of acetylcholinesterase may be re-introduced.

### triggers of myasthenic crisis
In addition to treatment of the myasthenic crisis, management of the cause may be needed. In some patients, myasthenic crisis may be the initial presentation of myasthenia. In many other patients, myasthenic crisis may be precipitated by another problem.

**common causes**

- Infection (especially pneumonia)
- Electrolyte abnormality (essentially any abnormality, including Ca/Phos/Mg)
- Thyroid disease (either hypo- or hyper-thyroid; note that myasthenia gravis is associated with thyroid disease)
- Surgery/trauma
- Pregnancy, delivery
- Medications
  - Medications that exacerbate myasthenia ([list](#drugs_to_avoid_in_MG) above)
  - Tapering of immunosuppressive medications

**beware of adrenal crisis**

- Many patients with myasthenia are maintained on chronic prednisone for months or years.
- Adrenal crisis may occur in the following situations
  - (1) Prednisone is abruptly stopped (e.g. due to weakness or inability to swallow medications).
  - (2) Patient on chronic low-dose prednisone (e.g. 5 mg) is exposed to a new source of physiologic stress.
- The chapter on adrenal crisis is [here](https://emcrit.org/ibcc/adrenal-crisis/).

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**blood gas monitoring**

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**worthless in patients without chronic respiratory dysfunction**

- Patients without chronic respiratory dysfunction should have a normal respiratory drive. These patients shouldn't become hypercapneic until they are totally exhausted and frankly dying.
  - This assumes that they aren't on other medications that would blunt their respiratory drive (e.g. opioids).
- Hypercapnia is an extremely late finding in this context.
- It is generally accepted that blood gas monitoring has no role in most patients with myasthenia.

**blood gas measurement may be somewhat useful in patients with chronic hypercapnia**

- Patients with chronic hypercapnia (e.g. due to severe COPD) don't have a normal respiratory drive. These patients may develop insidiously worsening hypercapnia without looking terrible.
  - Rather than developing respiratory extremis, these patients may quietly accumulate CO2 and become sleepy (due to CO2 narcosis).
- Blood gas analysis may therefore be useful in a patient with altered mental status plus chronic hypercapnia.
- Please note however that the decision to intubate is still clinical. Blood gas is mainly useful to determine whether or not the patient is profoundly hypercapneic (not to track the precise pCO2 value over time).
  - For example: In a COPD patient with myasthenia gravis and hypercapnia, if the patient looked OK clinically then treatment with BiPAP might be the best option.

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**bedside pulmonary function tests**

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**bedside respiratory monitoring consists of two tests:**
• **Negative Inspiratory Force (NIF)**
  - This is the largest amount of negative pressure that the patient is able to exert when inhaling (video above).
  - This test is uncomfortable and effort-dependent. There is no role for this test in myasthenia gravis (more on this below).

• **Forced Vital Capacity (FVC)**
  - This is the largest volume breath the patient is able to take.
  - Forced vital capacity is an *integrated* reflection of multiple parameters: inspiratory strength, expiratory strength, and lung compliance.
    - The holistic nature of the forced vital capacity may make it a better predictor of respiratory failure than the negative inspiratory force (which measures *only* diaphragmatic strength).
  - Forced vital capacity is more reproducible and less uncomfortable than the negative inspiratory force.

Respiratory monitoring is grossly over-utilized. There is no evidence to support frequent monitoring of respiratory mechanics in myasthenia gravis. Available data are *borrowed* from wholly unimpressive studies of patients with Guillain-Barre Syndrome.\(^4\)\(^-\)\(^9\) Guillain-Barre Syndrome is fundamentally different from myasthenia gravis, so this data doesn’t apply (myasthenic patients *fluctuate* more than patients Guillain-Barre Syndrome). Available studies involving myasthenia gravis actually show that pulmonary function testing fails to predict outcomes\(^10\)\(^,\)\(^11\) Let’s start off by debunking some common problems with respiratory monitoring:

**(1) why *frequent* respiratory monitoring may cause problems**

• Interferes with sleep/rest (waking up patients to check pulmonary function tests is just plain evil).
• May exhaust the patient.
- May cause panic due to random variation in testing (if you do enough repeat testing, then eventually the numbers will decrease solely due to random chance).

" Measures such as vital capacity and blood gas levels have limited value, since deterioration can be rapid and unexpected as a result of the characteristic myasthenic fatigability. -Gilhus NE 2016

(2) why the negative inspiratory force (NIF) should rarely be measured

- NIF is more uncomfortable and less reproducible than the forced vital capacity.
- NIF has not been shown to add any independent information beyond what is provided by the forced vital capacity.
  - Just use the forced vital capacity alone – this is a simpler and better approach.
  - (Theoretically in a patient with abnormal anatomy – such as prior pneumonectomy – NIF could be helpful.)

(3) intubation should never be performed solely based on pulmonary function tests

- Never decide to intubate based solely on pulmonary function tests for the following reasons:
  - Studies relating risk of intubation to pulmonary function tests are generally low quality and retrospective.
  - Pulmonary function tests are highly effort-dependent.
- The decision to intubate is primarily clinical. Trends in pulmonary function tests may be helpful, but this is only a small piece of the decision (more on this below).

(4) beware of positional changes

- Patients with diaphragmatic weakness (such as myasthenia patients) will have a higher forced vital capacity when sitting up, compared to lying down.
- Any serial monitoring should ideally be done using a uniform position.

That said, there are some situations where pulmonary function testing can be useful.

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>cc/kg*</th>
<th>Smaller person (55 kg)</th>
<th>Average person (70 kg)</th>
<th>Larger person (90 kg)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>60 cc/kg</td>
<td>3.3 liters</td>
<td>4.2 liters</td>
<td>5.4 liters</td>
</tr>
<tr>
<td>Concerningly low</td>
<td>&lt;30 cc/kg</td>
<td>&lt;1.6 liters</td>
<td>&lt;2.1 liters</td>
<td>&lt;2.7 liters</td>
</tr>
<tr>
<td>- Consider monitoring in ICU</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very worrisome</td>
<td>&lt;15 cc/kg</td>
<td>&lt;0.8 liters</td>
<td>&lt;1 liter</td>
<td>&lt;1.3 liters</td>
</tr>
<tr>
<td>- At risk for intubation</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Most studies don’t specify, but in obesity the weight should probably be the ideal body weight (not actual weight).

(1) Establishing the diagnosis & triage.

- Admission forced vital capacity is probably the most useful measurement.
- If admission FVC is normal and the patient is dyspneic, this suggests that something else is going on (e.g. pulmonary embolism, heart failure). It also suggests that the patient may not require ICU level monitoring for myasthenia gravis.
- If the admission FVC is significantly low (e.g. <30 cc/kg):
  - This supports the diagnosis of myasthenic crisis.
  - This supports triage to an ICU for higher intensity monitoring.

(2) Tracking response to therapy

- Intermittently measuring the FVC can help determine how the patient is responding to therapy.
- Response to treatment takes time, so measuring the FVC twice or three times daily is probably fine.
- To be significant, changes should represent a consistent trend over several measurements (not just one aberrant measurement).
noninvasive respiratory support (HFNC or BiPAP)

- In order to work, high-flow nasal cannula (HFNC) or BiPAP must be started early, when the patient is in only mild respiratory distress. The goal is to reduce the work of breathing and thereby prevent respiratory exhaustion.
  - These modalities will fail if initiated when the patient is already in extremis.
- When in doubt regarding whether the patient needs any support at all, consider high-flow nasal cannula (HFNC). This is extremely safe and may reduce work of breathing (due to reduced anatomic dead space, with improved ventilatory efficiency).
- Evidentiary support is strongest for BiPAP, so this might be the first-line therapy for mild-moderate dyspnea. If BiPAP cannot be tolerated or is contraindicated (e.g. due to intolerance or significant respiratory secretions), then HFNC may be tried.
- Close supervision in an ICU is required to ensure that these modalities are working (e.g. on BiPAP, the minute ventilation and tidal volume should be monitored).

decision to intubate

- The decision to intubate should NOT be made solely on the basis of pulmonary function tests, as discussed above.
- Intubation is always a clinical decision. Components to consider may include:
  - **Look**: Patient appearance, respiratory rate, and work of breathing (and, perhaps more importantly, the **trajectory** of these parameters).
  - **Cough**: Cough efficacy, ability to clear secretions, and ability to protect airway.
  - **Strength**: Trends in weakness (e.g. especially neck weakness, which may function as a surrogate of oropharyngeal musculature).
  - **FVC**: Trends in forced vital capacity.
  - **Oxygenation**: Generally, myasthenia shouldn't cause significant hypoxemia. Progressively worsening hypoxemia is a fairly poor sign which may suggest progressiveatelectasis or aspiration.
  - **Chest radiograph**: signs of worsening lobar collapse or aspiration would support the need for intubation.
- When in doubt, prepare for intubation and continue to monitor the patient carefully.

intubation procedure

- A non-depolarizing paralytic should be used (e.g. rocuronium). The dose should be reduced by ~50% compared to the usual dose (e.g. a dose of ~0.6 mg/kg rocuronium may be reasonable).
  - **Succinylcholine may fail to work** due to reduced acetylcholine receptor density on muscle.

nutrition & GI access

Some patients may have bulbar weakness causing dysphagia and risk of aspiration.

- If the patient is unable to protect their airway (e.g. inability to handle secretions, gurgling), then intubation is required.
- If the patient is able to protect their airway but is at increased risk for aspiration, there should be a low threshold to place a small-bore nasoenteric feeding tube.

pyridostigmine

basics

- Pyridostigmine is an acetylcholinesterase inhibitor. It increases levels of acetylcholine in the synapse, improving nerve transmission.
- Excessive doses of pyridostigmine can be problematic for a few reasons:
  - (1) Increased secretions can be problematic, especially in patients with bulbar weakness or weak cough
  - (2) Profoundly excessive doses can cause a cholinergic crisis (with currently used dosing, this is rare; more on this above)
- Glycopyrrolate or hyoscymine may be used to reduce secretions caused by pyridostigmine (e.g. 1 mg glycopyrrolate or 0.125 mg hyoscymine with each dose of physostigmine).3 15

general dosing information

https://emcrit.org/ibcc/myasthenia/
- The starting dose is often 60 mg PO q6hr.
- Dose may be up-titrated to a maximum dose of 120 mg q4hr.
- Pyridostigmine can be given intravenously, but at 1/30th the dose of oral medication.
- Always be cautious for emergence of anticholinergic side-effects (e.g. increased secretions, bradycardia).

**approach to pyridostigmine in a myasthenic crisis ??**

- This seems to be an evidentiary vacuum, with considerable conflict in the literature. Reasonable practice might be as follows:
  - Among intubated patients:
    - Pyridostigmine is generally held initially to reduce airway secretions and increase sensitivity to pyridostigmine (a brief drug holiday may increase responsiveness when treatment is resumed).
    - Pyridostigmine should be restarted prior to extubation.¹
  - Non-intubated patients:
    - If the patient is pyridostigmine naive, it may be reasonable to start a low dose (e.g. 60 mg PO q6hr).
    - In most other cases, it may be reasonable to continue the patient's home dosing regimen.

### steroid & immunomodulatory treatment

**steroid**

- Generally used to reduce production of anti-acetylcholine antibody.
  - A reasonable dose may be ~1 mg/kg prednisone daily (or equivalent).
- Steroid takes 2-3 weeks to cause clinical improvement. Initiation of steroid may actually cause a brief clinical deterioration. Therefore, it might be ideal to delay steroid initiation for several days after initial admission (until patient has started improving).¹ An alternative approach is to start steroid at a low dose (e.g. 20 mg prednisone) and gradually up-titrated the dose.
- There's no rush to start steroid immediately.

**alternative immunosuppression**

- If steroid is contraindicated or previously ineffective, other treatments may be used (e.g. azathioprine, cyclosporine, rituximab, methotrexate).
- These agents will take forever to start working – so again, there's no rush here.

### PLEX versus IVIG

There is no high-quality evidence regarding the selection of PLEX vs. IVIG. However, most experts and guidelines believe that plasma exchange works more quickly.¹

![plasma exchange vs IVIG](https://emcrit.org/wp-content/uploads/2019/02/plex.svg)

**plasma exchange (PLEX) is often first-line for severe exacerbation**

- Plasma exchange usually causes improvement in a few days. It *directly* removes anti-acetylcholine receptor antibody from the body.
- The main advantage of plasma exchange is more rapid response compared to IVIG (which may take some weeks to see improvement).
- Follow electrolytes and correct abnormalities which may occur.

**IVIG may be useful for less severe exacerbations**

- IVIG takes longer to work (e.g. 2-3 weeks), but the efficacy may be more sustained.
- IVIG can be used in situations where plasma exchange is unavailable or contraindicated.
Myasthenia gravis & myasthenic crisis - EMCrit Project

- The dose of IVIG is 2 grams/kg, usually divided over 2 or 5 days.

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**checklist**

- **Evaluation**
  - Chest X-ray and lung ultrasound (exclude other lung disease)
  - Forced vital capacity (FVC)
  - Electrolytes (including Ca/Mg/Phos), CBC with differential
  - Beta-HCG if pregnancy possible
  - Infectious workup or TSH level if symptoms of infection or thyroid disease

- **Respiratory support**
  - Consider early HFNC or BiPAP if mild-moderate respiratory distress or tachypnea.
  - Intubation only if clinically indicated.

- **Pyridostigmine**
  - New diagnosis of MG: May initiate at 60 mg q6
  - Chronic MG not intubated: Continue prior dose unless extremely high
  - May add glycopyrrolate to reduce oral secretions (e.g. 1 mg with each dose)

- **Plasma exchange/IVIG**
  - Plasma exchange is the fastest approach to stabilize disease.
  - If plasma exchange is contraindicated/unavailable may use IVIG.

- **Monitoring**
  - Most useful: Usual monitoring (vital signs, clinical appearance, subjective dyspnea, etc.)
  - Forced vital capacity: Monitor 2-3 times daily. DO NOT wake up patient for this.
  - Do not measure negative inspiratory force (NIF).

- **Drugs to avoid** (main ones)
  - Antibiotics: aminoglycosides, fluoroquinolones, tetracyclines, macrolides
  - Muscle relaxants: dantrolene, cyclobenzaprine, baclofen, methocarbamol, succinylcholine
  - Neuro: Lithium, haloperidol, prochlorperazine, phenytoin
  - Cardiovascular: Beta-blockers, calcium channel blockers, lidocaine, procainamide, statins
  - Other: Antihistamines, anticholinergic, high-dose magnesium, IV contrast

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**podcast**


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**questions & discussion**

To keep this page small and fast, questions & discussion about this post can be found on another page here (https://emcrit.org/pulmcrit/myastenia/).
- Don't assume that a dyspneic patient with myasthenia gravis is necessarily having a myasthenic crisis: these patients may also have any other cause of respiratory failure (e.g. pneumonia, heart failure).
- Don't harass patients with scheduled and extremely frequent measurements of pulmonary mechanics.
- Don't intubate patients based on arbitrary cutoff values in pulmonary mechanics (there's zero data to support this practice).
- Be extremely careful about starting new medications in patients with myasthenia gravis – consider the list of contraindicated medications above, and when in doubt check a pharmacopeia and discuss with your unit pharmacist.

**Going further:**

- **Five pearls for the dyspneic patient with GBS or MG** ([PulmCrit](https://emcrit.org/pulmcrit/five-pearls-for-the-dyspneic-patient-with-guillain-barre-syndrome-or-myasthenia-gravis/))
- **Myasthenia Gravis** ([Chris Nickson, LITFL](https://lifeinthefastlane.com/ccc/myasthenia-gravis/))
- **Myasthenia Gravis** ([First10EM, Justin Morgenstern](https://www.ncbi.nlm.nih.gov/pubmed/29655452))
- **Myasthenia Gravis** ([WikiEM](https://wikem.org/wiki/Myasthenia_gravis))

**References**
