Myasthenia Gravis Treatment, Adult, Inpatient, Guideline

5/20/2022

Clinical pathway summary

CLINICAL PATHWAY NAME: Myasthenia Gravis Treatment Guideline

PATIENT POPULATION AND DIAGNOSIS: Patient presenting with generalized weakness, ocular and/or bulbar weakness

APPLICABLE TO: Butterworth and Blodgett hospital

BRIEF DESCRIPTION: Approach to treatment of myasthenia gravis in inpatient settings

OPTIMIZED EPIC ELEMENTS (if applicable):

IMPLEMENTATION DATE: February 2022

LAST REVISED: 5/20/2022

Clinical pathways clinical approach

RATIONALE:
Myasthenia gravis is an auto-immune post-synaptic neuromuscular junction disorder. It is an anti-body mediated, T-cell dependent immunologic attack targeted at proteins in the post-synaptic membrane namely acetylcholine receptors and/or receptor associated proteins. Since it is a T-cell dependent process, thymus is speculated to play a role in dysregulation of self-tolerance and pathogenesis of myasthenia gravis.[1] It is characterized by fatigable weakness of ocular, bulbar, limb and respiratory muscles with varied involvement.

Clinical manifestations
The cardinal feature of myasthenia gravis is fatigable weakness which is typically worse at the end of the day or after exertion/exercise. The weakness involves different muscle groups including ocular, bulbar, limb and respiratory muscles. Clinical symptoms may vary with ptosis, binocular diplopia, dysphagia, flaccid dysarthria, hypophonia, nasal speech, facial weakness, neck flexion/extension weakness, proximal limb weakness, respiratory muscle weakness causing respiratory insufficiency and respiratory failure. [7]

There are two main clinical types of myasthenia gravis namely ocular and generalized flare based on type of muscle involvement. In ocular myasthenia gravis, the weakness is restricted to eyelids and extra-ocular muscles. In generalized flare, there is variable involvement of limb, bulbar, ocular, and respiratory muscles. Common triggers of myasthenia gravis include antecedent illness, physical and emotional stress, medications, surgery, extreme temperatures, pregnancy and menstrual periods.

Diagnosis

Diagnosis of myasthenia gravis is based on clinical and serological testing. Bedside tests like ice pack and tensilon tests are sensitive but are not confirmatory for myasthenia gravis due to high false positive rates. Antibodies that are routinely tested for myasthenia gravis include acetyl choline receptor (binding, blocking, and modulating) antibody (AChR-Ab), muscle specific tyrosine kinase antibody (MuSK-Ab), low-density lipoprotein receptor-related protein 4 (LRP4). If the above antibodies are positive, it is known as seropositive myasthenia gravis which account for majority of the cases. There are few cases of seronegative myasthenia gravis in about 6 to 10 percent of the patients. Some patients are seronegative on initial testing and seroconvert on repeat testing after a period of time. Seronegative cases are seen in approximately about 50% of ocular myasthenia and 20% of generalized flare.

EMG is a confirmatory test for myasthenia gravis where repetitive nerve stimulation (RNS) reveals greater than 10 percent decrement in compound muscle action potential (CMAP) and single fiber EMG reveals abnormal jitter. CT thorax is also routinely done to evaluate for thymoma which is commonly associated with myasthenia gravis. Thyroid function testing should be performed since myasthenia gravis is associated with other autoimmune disorders, especially autoimmune thyroid disease.

Treatment

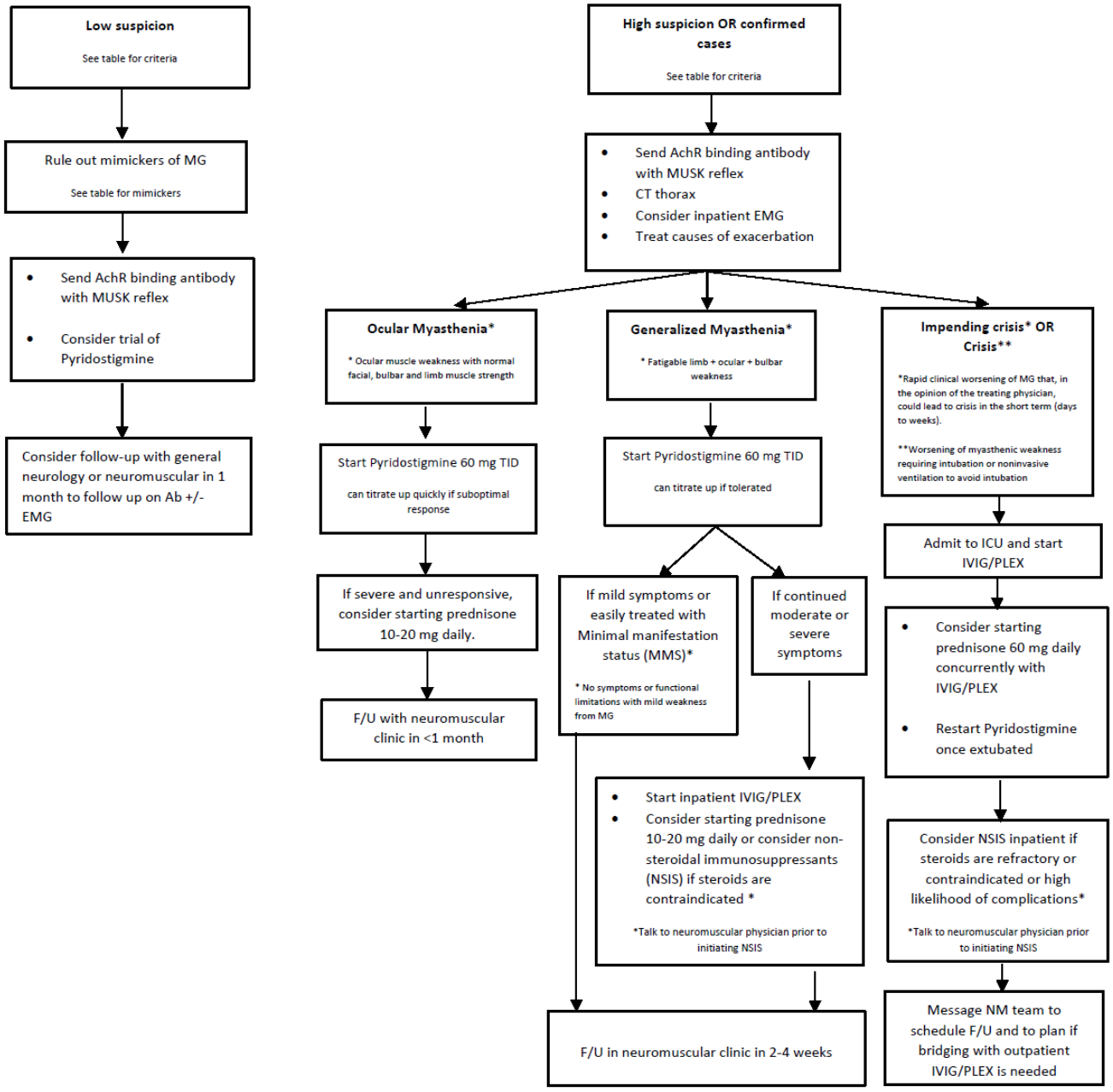
Myasthenia gravis is often treatable with immunomodulation and thymectomy. The goal of treatment is to achieve remission (no signs or symptoms from myasthenia gravis) or to achieve minimal manifestation status (no subjective symptoms with mild weakness on exam which does not impede normal functioning) with minimal side effects from medications. Treatment is custom made based on their age and comorbidities. Appropriate treatment leads to remission with good prognosis and low mortality rates of <5%.

In patients with mild symptoms or minimal manifestation status, pyridostigmine is the initial choice of symptomatic treatment. If remission is achieved or if symptoms are well controlled on pyridostigmine, recommend clinical monitoring with no additional treatment. [8]

Long term immune suppression is considered in severe cases or if symptoms are not well controlled on pyridostigmine or if symptoms recur after a temporary response to pyridostigmine. Oral glucocorticoids are the initial mainstay of immunosuppressants. Comorbidities like uncontrolled diabetes mellitus, weight, avascular necrosis, osteoporosis, elderly population, peptic ulcer disease and psychiatric illness amongst others should be considered prior to initiating corticosteroids. Since high doses of steroids can exacerbate bulbar weakness, they are typically started at lower doses in outpatient settings with slow titration until target dose is achieved.

In patients who require long term immunosuppression and/or corticosteroids are contraindicated, non-steroidal immunosuppressants are used. Mycophenolate mofetil and azathioprine are most used oral long term immunosuppressants. Rituximab is a monoclonal antibody targeted against CD20 given intravenously which is reserved for patients with severe and refractory generalized myasthenia gravis, especially in MuSK positive patients.[9,10] Eculizumab is a monoclonal antibody targeted against complement C5 which has recently been approved by FDA for treatment of AChR positive generalized myasthenia gravis.[11]
In patients presenting with myasthenic crisis or impending crisis, short-term rescue immunomodulating treatments like plasma exchange or intravenous immune globulin (IVIG) are utilized. Either of the above treatments can be used based on patient's comorbidities for a therapeutic 5 plasma exchange treatments over 7-14 days or 2 gm/kg of IVIG over 2-5 days. It is also used as long-term maintenance therapy for refractory patients who cannot tolerate oral immunosuppressants. Patient's with thymoma should be referred to for surgical resection of thymoma. Thymectomy should be done immediately or as soon as the patient is strong enough after initiating immunomodulatory treatment or after crisis is treated appropriately to undergo surgery.[12] Thymectomy is generally not indicated in patients older than 65 years of age. In patient's without thymoma, role of thymectomy is controversial. There was a double blinded trial which compared thymectomy plus prednisone with prednisone alone in adult patients with AChR positive generalized myasthenia gravis which demonstrated that thymectomy improves clinical outcome. [13] Avoidance of medications that can exacerbate myasthenia will help avoid developing crisis or impending crisis.

TREATMENT AND MANAGEMENT:



Low suspicion	High suspicion
• Generalized weakness or fatigue without ocular or bulbar weakness • Asymmetric features • Non-fatigable symptoms • Other causes of weakness/mimickers a) Generalized weakness- Check TSH, stroke evaluation, CK (myopathy) b) Ocular symptoms- CTA head/neck (aneurysms) • Isolated symptoms • Normal physical exam • Chronic or insidious progression	• Diurnal variance or fatiguability • >2 classic symptoms: a) Diplopia & ptosis b) Dysarthria & dysphagia c) Limb weakness & bulbar/ocular symptoms • Antecedent event- illness, stress, medications • Subacute worsening

Considerations for starting steroids	Considerations for starting NSIS
• Diabetes • Weight • Avascular necrosis • Peptic ulcer disease • Psychiatric disease • Elderly patients • Osteoporosis	• Lymphopenia • Liver disease (azathioprine) • Woman of childbearing potential (Cellcept contraindicated in pregnancy)

Criteria for intubation	Considerations for neuromuscular blocking agents
• Vital capacity (VC) less than 1 L (or <20-25 mL/kg) • Negative inspiratory force (NIF) < -30 cm H2O • Positive expiratory force (PEF) <40 cm H2O • Recruitment of accessory muscles • Weak cough • Difficulty counting to 20 in a single breath • Respiratory acidosis • Inadequate secretion clearance	• Depolarizing agents (for example, succinylcholine) are less potent in myasthenics because fewer functional post-synaptic AChR are available. This decrease in receptors also results in a decrease in the safety margin or remaining AChR available for neuromuscular transmission. • Nondepolarizing agents (for example, vecuronium) have increased potency, and reduced doses are required for paralysis

* (NIV) may be used to prevent intubation or reintubation of patients in myasthenic crisis however the evidence is inconsistent

Medications to avoid
• Telithromycin (Ketek) • Ciprofloxacin and levofloxacin • Zithromax (e.g. "Z-pak") • Gentamycin, neomycin (aminoglycoside antibiotics; tobramycin may be least offensive) • Ampicillin • Macrolides • Quinolones • Ciprofloxacin • Botulinum toxin (e.g. "Botox") • Steroids (e.g. prednisone) • Quinine • Procainamide • Magnesium in patients with kidney disease; potentially dangerous if given intravenous • D-penicillamine • Beta-blockers • Calcium channel blockers

Pathway information

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EXPERT IMPROVEMENT TEAM (EIT): Inpatient Neurology/Neuromuscular

CLINICAL PRACTICE COUNCIL (CPC): Neuroscience

CPC APPROVAL DATE: February 18, 2022

OTHER TEAM(S) IMPACTED: Neurohospitalist and neurocritical care services

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