MYASTHENIA GRAVIS

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PATIENT CASE

- A 30 year old woman presents to her televisit with ptosis and fatigue after a night shift that resolved with sufficient rest. She reports that she can no longer keep up with her children during bicycle rides. She denies SOB.

- What is the most likely diagnosis?
- What is the best test to confirm the diagnosis?
- What is the next best step in therapy?

KEY CLINICAL FEATURES

- A **30** year old **woman** presents to her televisit with **ptosis** and **fatigue after a night shift** that **resolved with sufficient rest.** She reports that she **can't keep up** with her children **during bicycle rides.** She denies SOB.

- What is the most likely **diagnosis?**
- What is the **best test to confirm** the diagnosis?
- What is **the next best step in therapy?**

MYASTHENIA GRAVIS

NMJ disorder

Postsynaptic membrane

Autoimmune (antibody-mediated)

EPIDEMIOLOGY

01

Affects all age groups

02

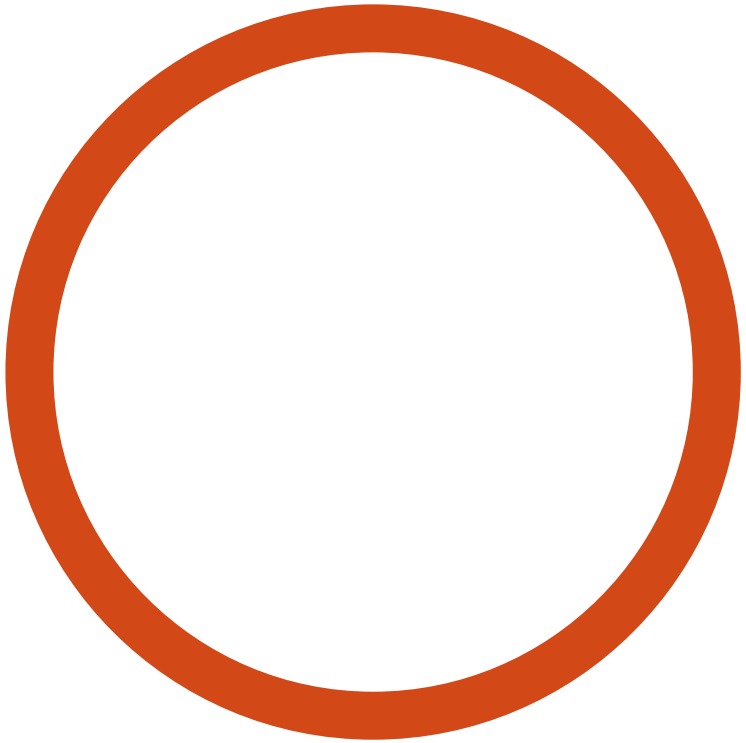
Bimodal age of onset (AchR +)

03

Prevalence 20/100,000.

04

Women: men (3:2)



MG ANTIBODIES

- Nicotinic Ach R-85%
- MuSK-8%
- Seronegative-5%
- LRP4-1%

SERONEGATIVE PATIENTS

No detectable antibody (Anti-Ach R, MuSK, LRP4) on standard tests due to lack of test sensitivity.

Other Ab against postsynaptic membrane (Agrin)

Cell based assays (VERY sensitive)

Currently been developed for anti-Ach R, MuSK, LRP4.

SERONEGATIVE PATIENTS

Check

for AchR Ab

If seronegative (AchR Ab negative) then…

Check

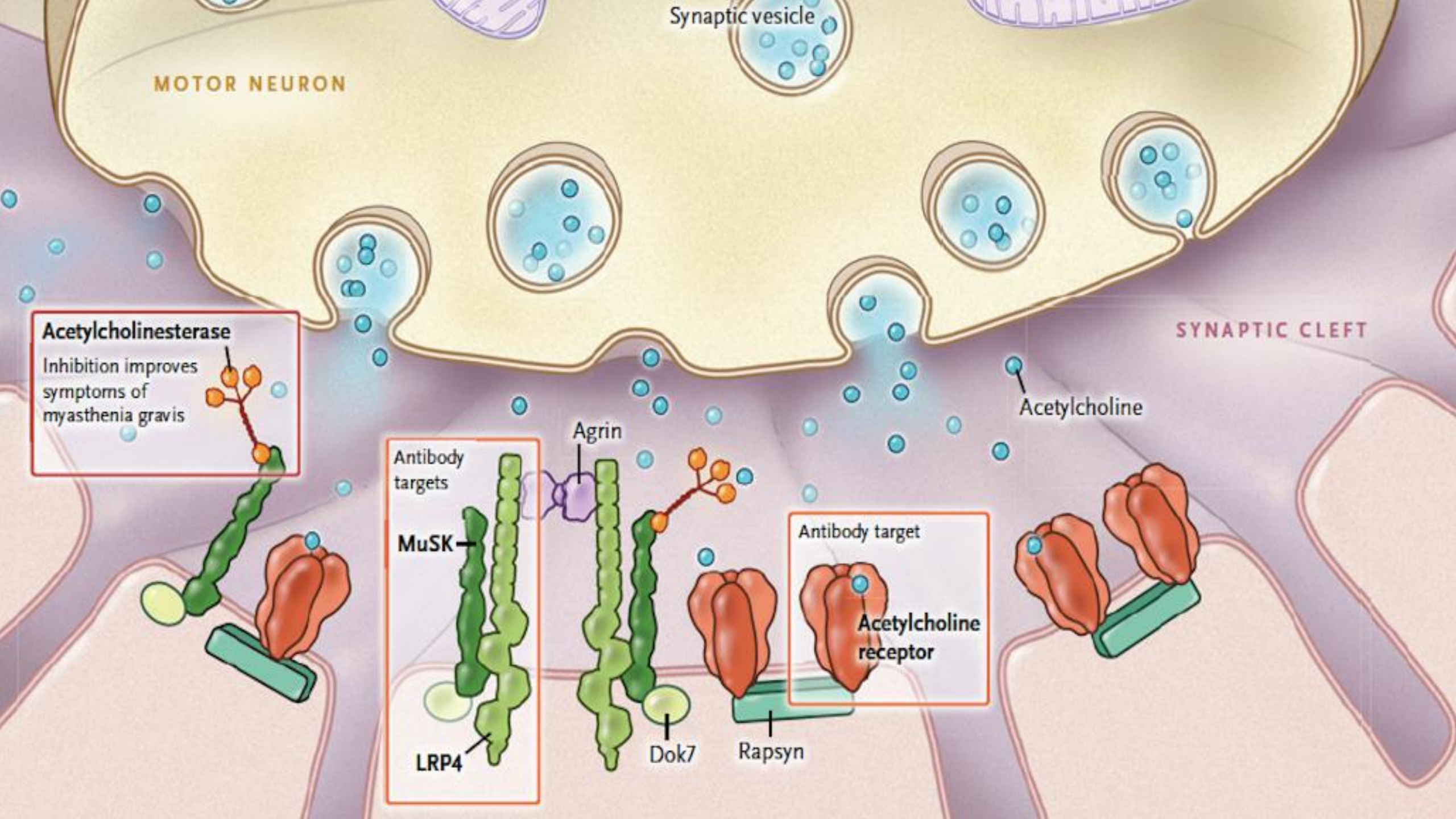
for MuSK Ab

If seronegative (double seronegative; AchR Ab and MuSK Ab negative) then ..

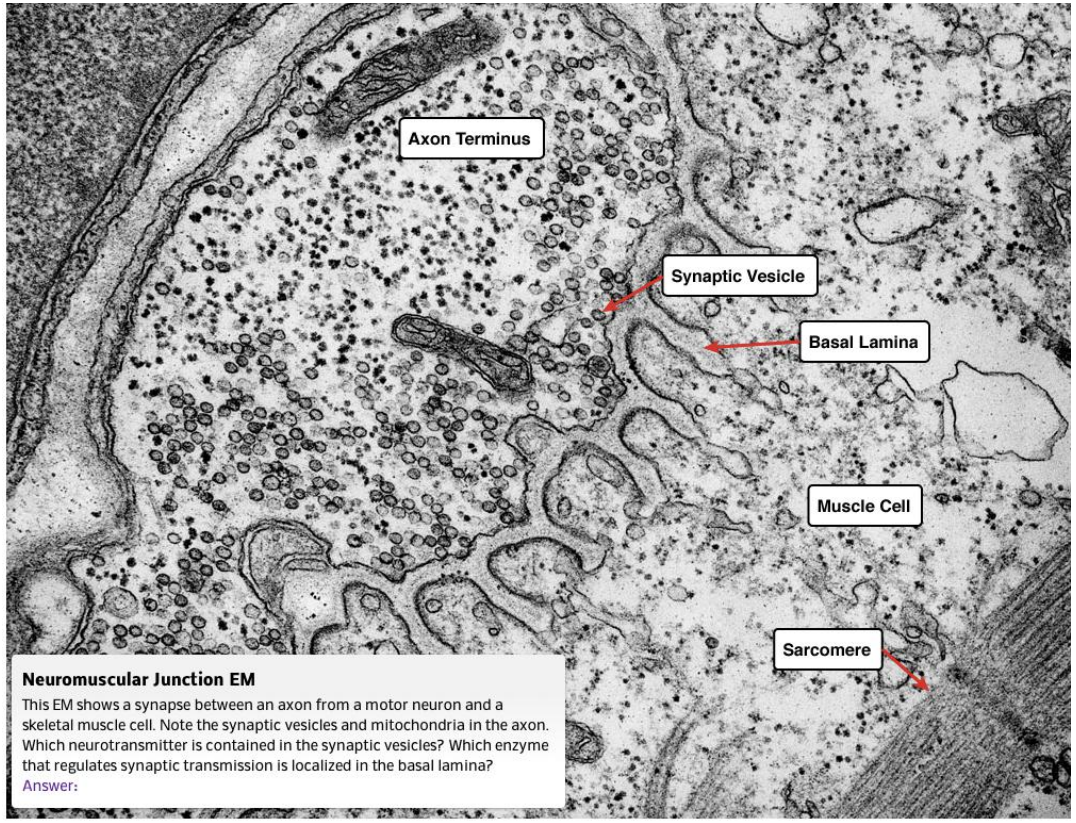
Check

for LRP4 Ab

If seronegative (triple seronegative; AchR and MuSK and LRP4 Ab negative) then do CELL BASED ASSAY.


Synaptic vesicle
MOTOR NEURON
Acetylcholinesterase
Inhibition improves symptoms of myasthenia gravis
SYNAPTIC CLEFT
Acetylcholine
Agrin
Antibody targets
MuSK
LRP4
Dok7
Rapsyn
Antibody target
Acetylcholine receptor

NORMAL NMJ (ELECTRON MICROSCOPE)

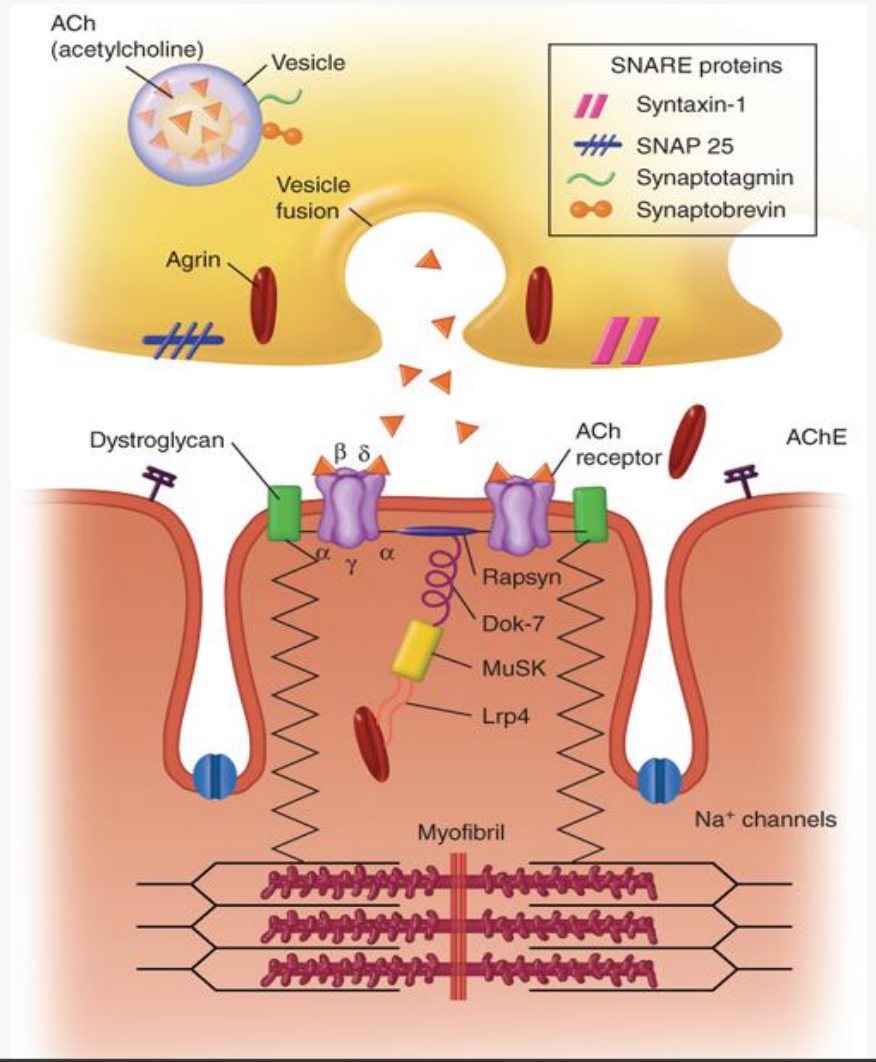


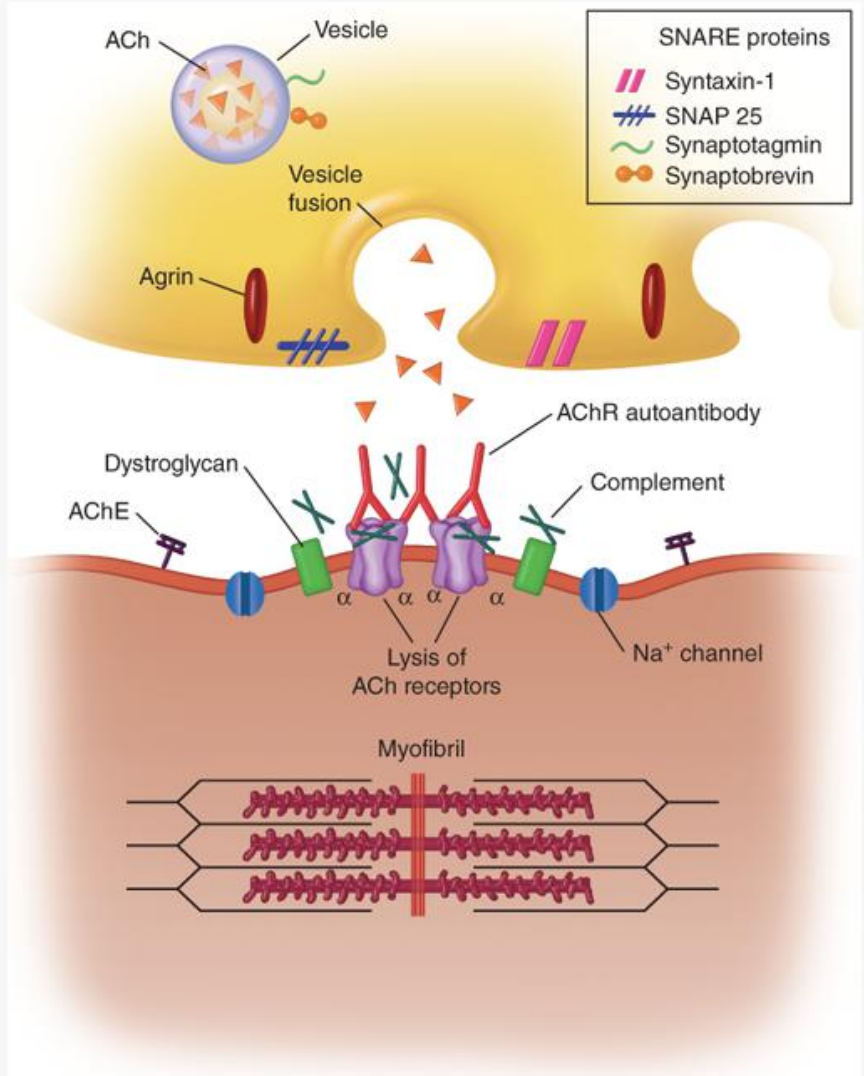
Healthy undulating membrane

AchR densely packed at peaks of postsynaptic folds

Close to nerve terminal

PATHOPHYSIOLOGY

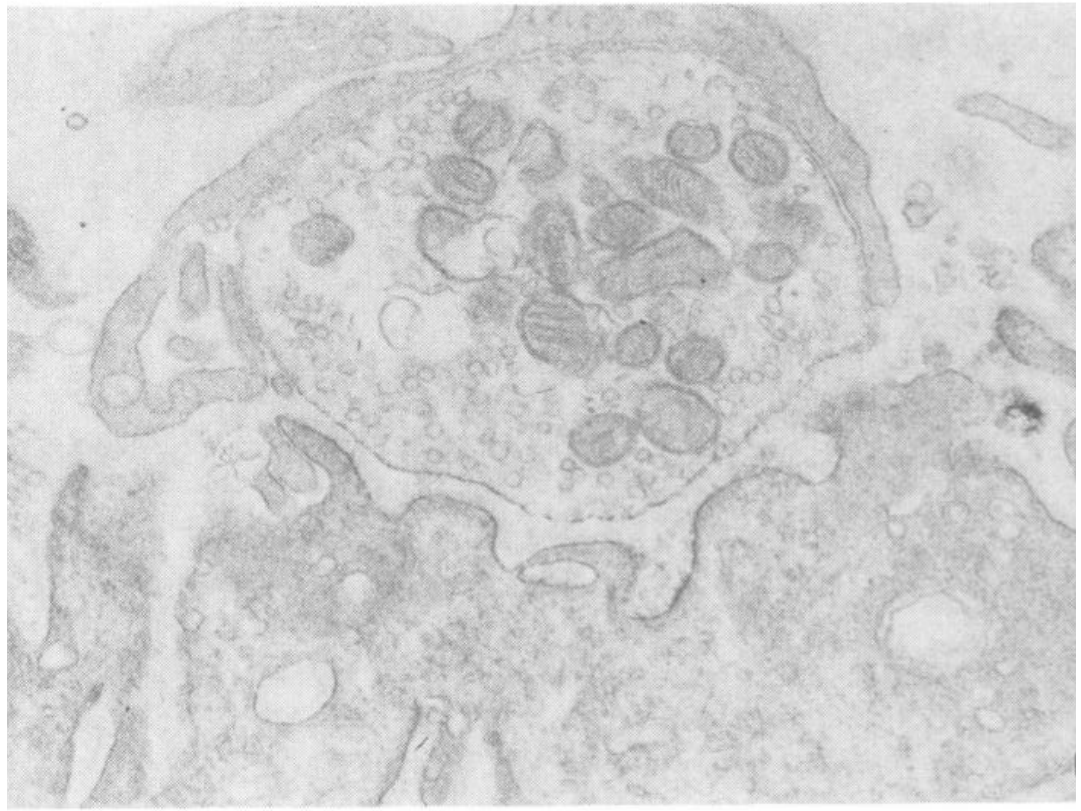




PATHOPHYSIOLOGY

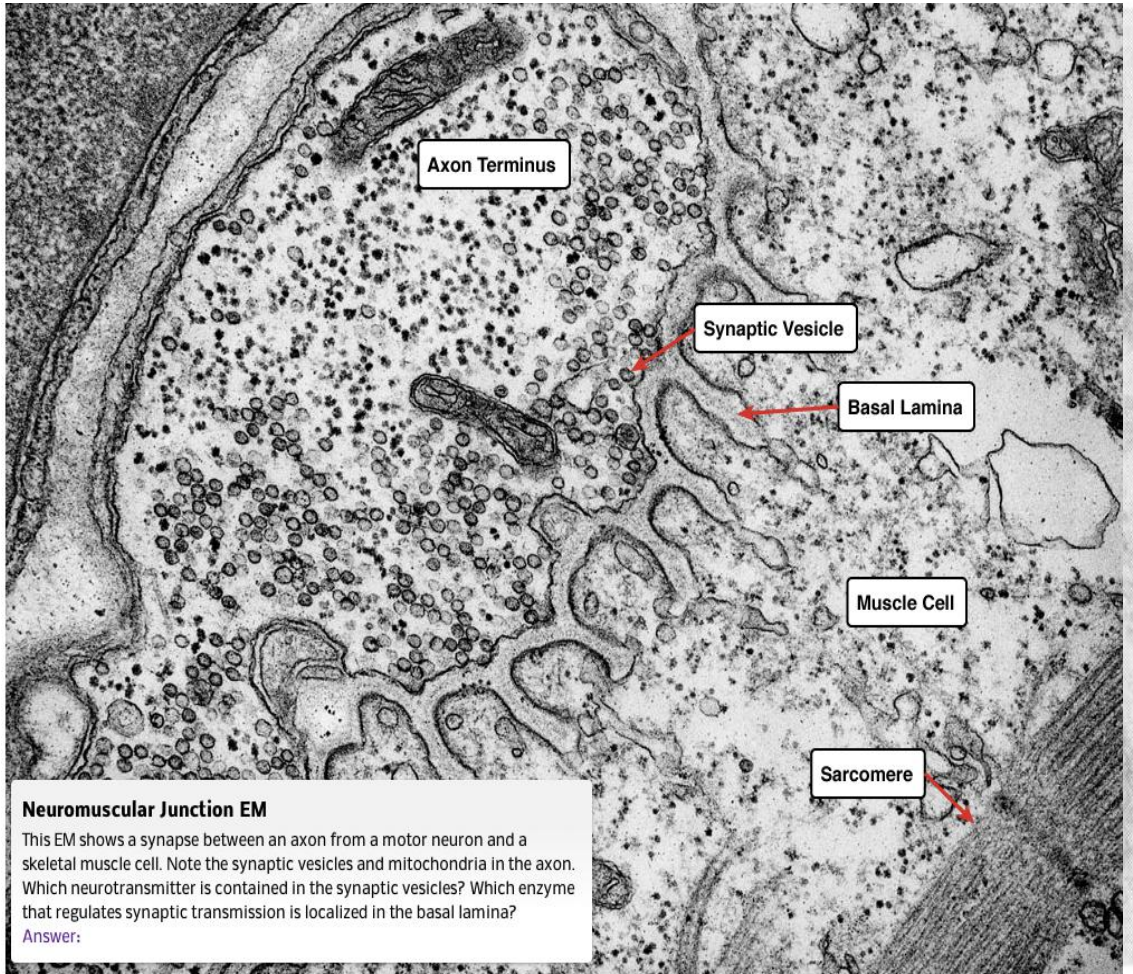
- 3 major mechanisms for reduction of AchR at NMJ;
  - Blockade of active site of AchR
  - Accelerated turnover of AchR
  - Damage to postsynaptic membrane (Ab-Complement)

NMJ IN MG



- Reduced # of AchRs
- Flattened, simplified post synaptic folds
- Widened synaptic space

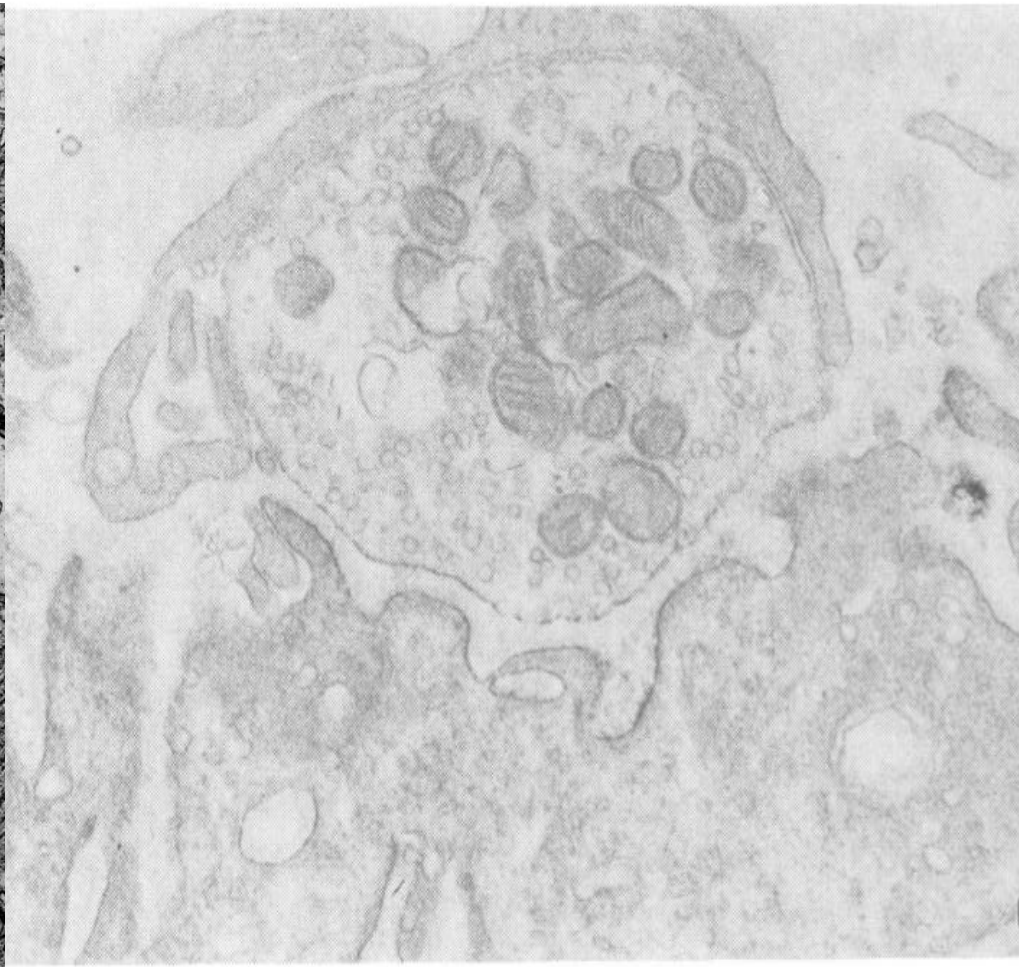
MEMBRANE COMPARISON

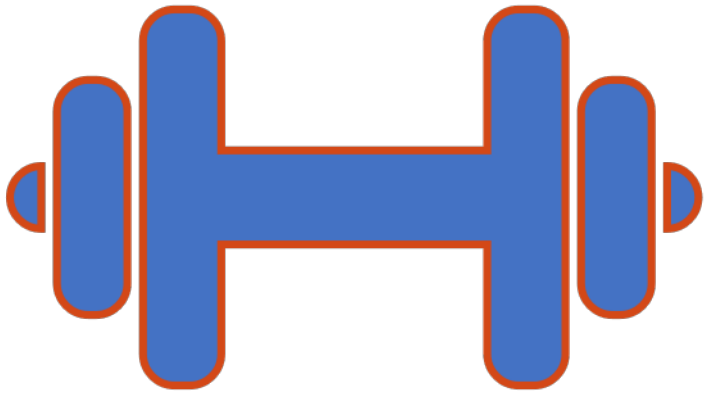


Neuromuscular Junction EM

This EM shows a synapse between an axon from a motor neuron and a skeletal muscle cell. Note the synaptic vesicles and mitochondria in the axon. Which neurotransmitter is contained in the synaptic vesicles? Which enzyme that regulates synaptic transmission is localized in the basal lamina?

Answer:





CARDINAL CLINICAL FEATURES

Muscle weakness that increases with repeated use.

Muscle fatigability.

DTR and sensation intact.

DISTRIBUTION OF MUSCLE WEAKNESS

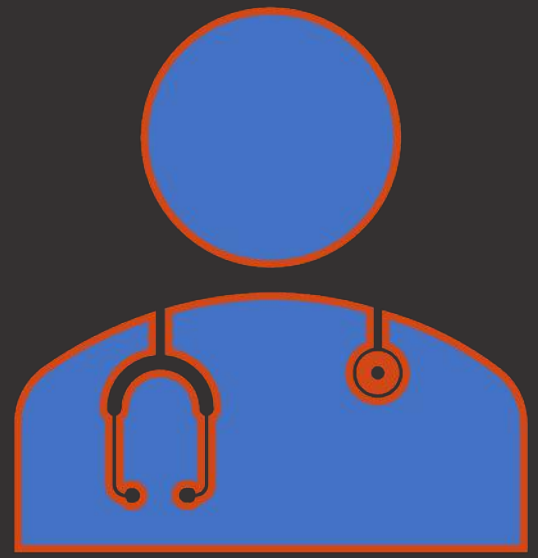
Characteristic pattern

SYMMETRIC, affects skeletal muscles.

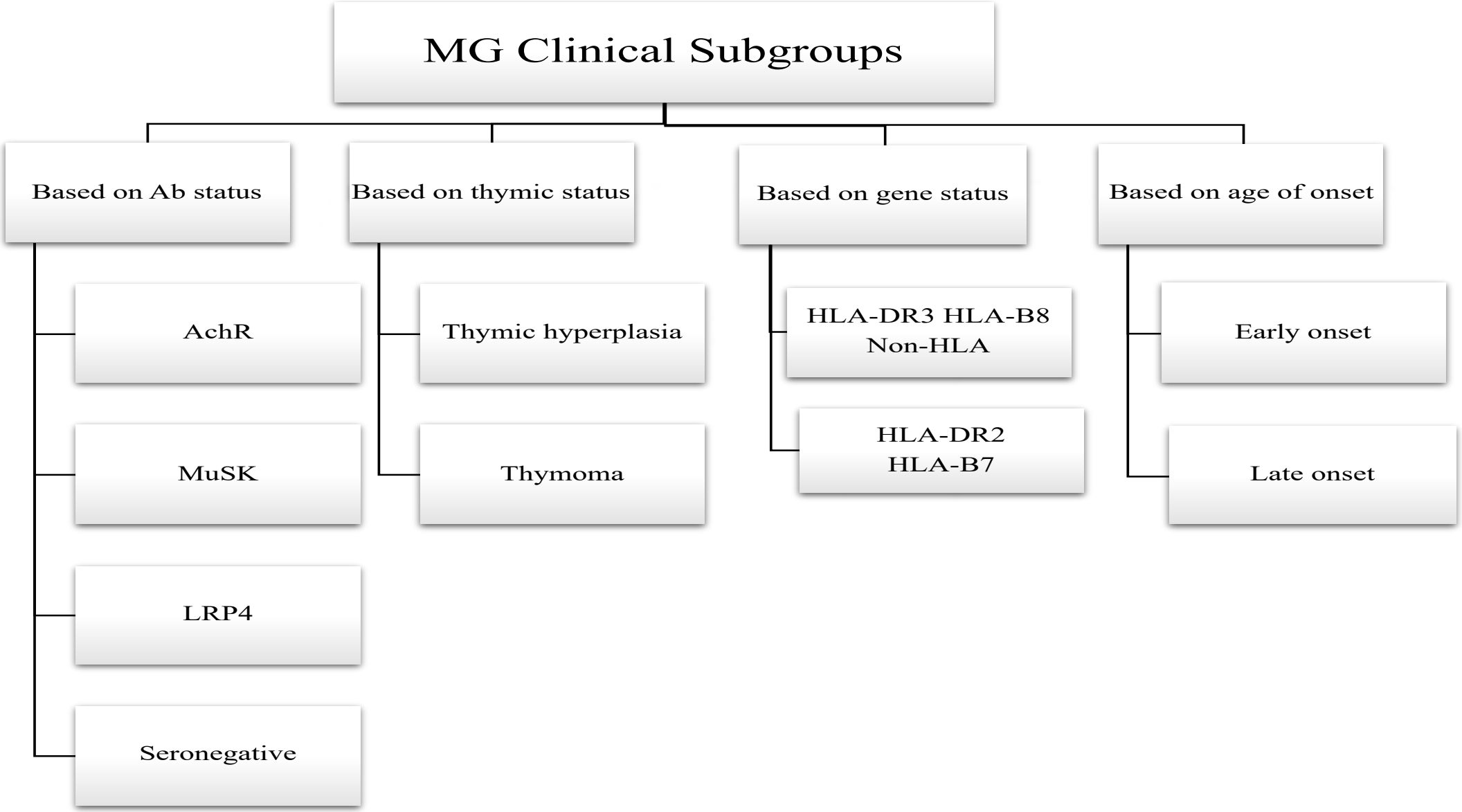
- Cranial muscles **(Ptosis, diplopia)**
- Bulbar muscles (Dysarthria, dysphagia, dysphonia)
- Neck muscles **(Drop head syndrome; MuSK)**
- Facial muscles (“Myasthenic snarl”)
- Limbs; shoulders, hips
- **Respiratory muscles (Diaphragm)**

CLINICAL COURSE

- Course is variable.
- Generalized vs ocular.
- Exacerbations, remissions and crises may occur especially during first few years of onset.



CLINICAL VARIANTS



ROLE OF THYMUS

AchR positive patients.

Thymic hyperplasia vs thymoma.

MYOID cells in thymus.

CAUTION!!!!!!!!

- MG comorbidities (DM, CAD, COPD)
- **MG triggers (infection, aminoglycosides, fluoroquinolones, macrolides, comorbidities, pregnancy, stress, steroids)**
- MG and pregnancy (IgG and neonatal myasthenia, IVIG, PLEX, Maternal-Fetal medicine)
- Plan pregnancy, avoid after 1-year Rituximab.
- MG and other autoimmune disorders (Thyroiditis, SLE, RA)

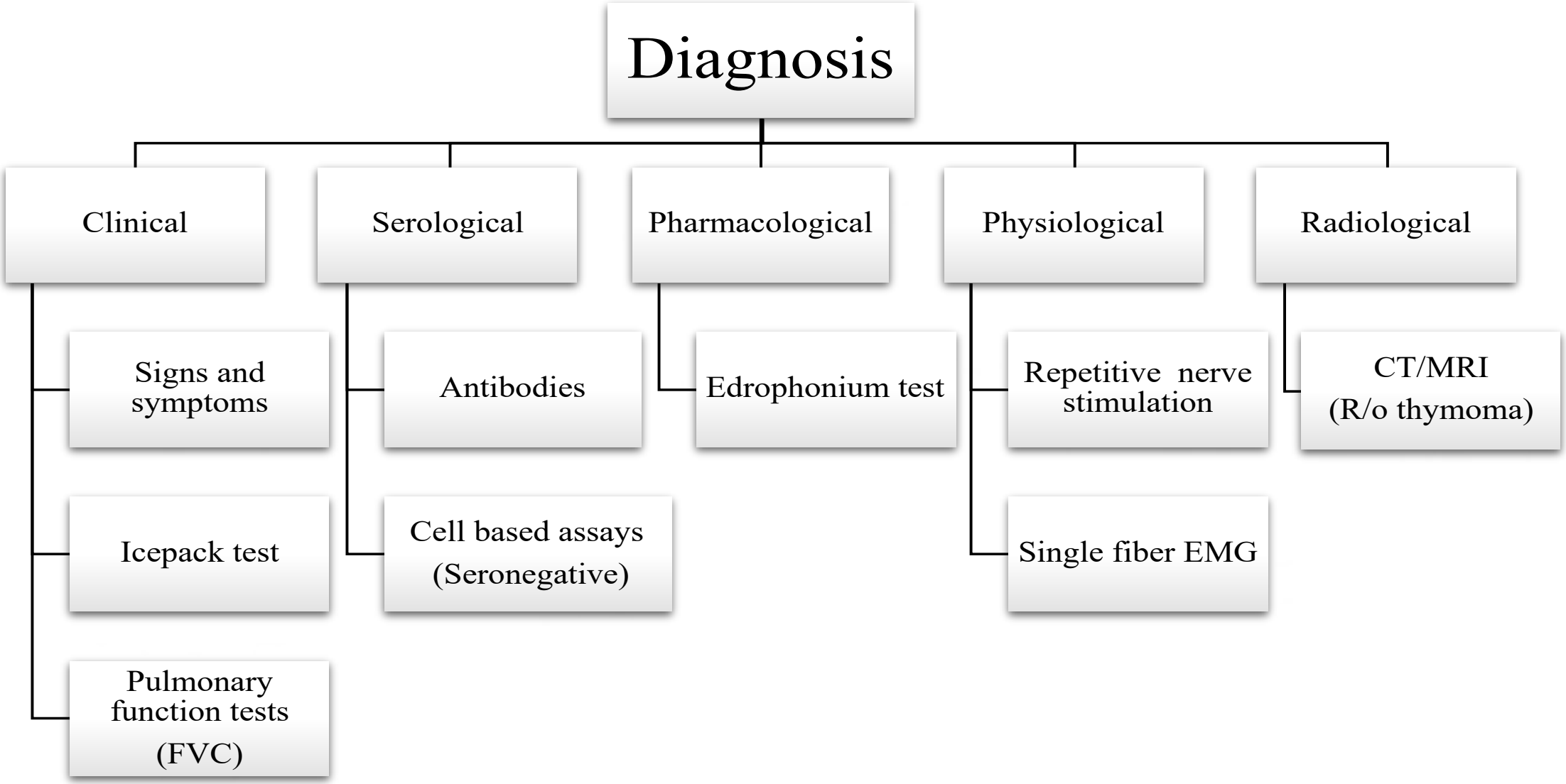
MEDICATION INTERACTIONS IN MG

TABLE 440-4

Drugs with Interactions in Myasthenia Gravis (MG)

Drugs That May Exacerbate MG
Antibiotics
Aminoglycosides: e.g., streptomycin, tobramycin, kanamycin
Quinolones: e.g., ciprofloxacin, levofloxacin, ofloxacin, gatifloxacin
Macrolides: e.g., erythromycin, azithromycin
Nondepolarizing muscle relaxants for surgery
D-Tubocurarine (curare), pancuronium, vecuronium, atracurium
Beta-blocking agents
Propranolol, atenolol, metoprolol
Local anesthetics and related agents
Procaine, Xylocaine in large amounts
Procainamide (for arrhythmias)
Botulinum toxin
Botox exacerbates weakness
Quinine derivatives
Quinine, quinidine, chloroquine, mefloquine (Lariam)
Magnesium
Decreases acetylcholine release
Penicillamine
May cause MG

Check point inhibitors
May cause MG and other autoimmune neuromuscular disorders (e.g., myositis, inflammatory neuropathy)
Drugs with Important Interactions in MG
Cyclosporine and Tacrolimus
Broad range of drug interactions, which may raise or lower levels.
Azathioprine
Avoid allopurinol—combination may result in myelosuppression.


Diagnosis
Clinical
Serological
Pharmacological
Physiological
Radiological
Signs and symptoms
Icepack test
Pulmonary function tests (FVC)
Antibodies
Cell based assays (Seronegative)
Edrophonium test
Repetitive nerve stimulation
Single fiber EMG
CT/MRI (R/o thymoma)

DIAGNOSIS

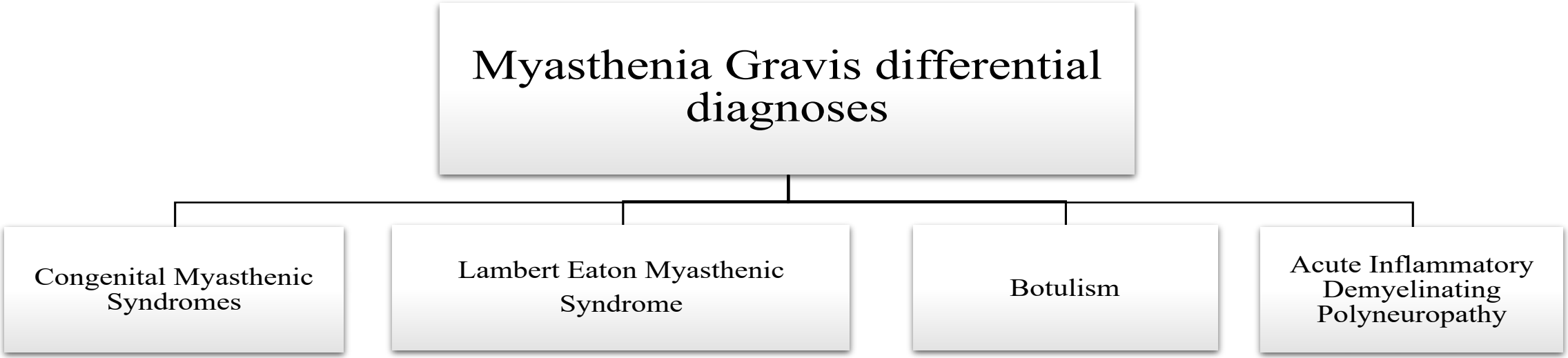
TABLE 440-1

Diagnosis of Myasthenia Gravis (MG)

History
Diplopia, ptosis, dysarthria, dysphagia, dyspnea
Weakness in characteristic distribution: proximal limbs, neck extensors, generalized
Fluctuation and fatigue: worse with repeated activity, improved by rest
Effects of previous treatments
Physical examination
Evaluation for ptosis at rest and following one minute of exercise, extraocular muscles and subjective diplopia, orbicularis oculi and oris strength, jaw opening and closure
Assessment of muscle strength in neck and extremities
Weakness following repeated shoulder abduction
Vital capacity measurement
Absence of other neurologic signs
Laboratory testing
Anti-AChR radioimmunoassay: ~85% positive in generalized MG; 50% in ocular MG; definite diagnosis if positive; negative result does not exclude MG; ~40% of AChR antibody–negative patients with generalized MG have anti-MuSK antibodies
Repetitive nerve stimulation: decrement of >10% at 3 Hz: highly probable
Single-fiber electromyography: blocking and jitter, with normal fiber density; confirmatory, but not specific
Edrophonium chloride (Enlon®) 2 mg + 8 mg IV; highly probable diagnosis if unequivocally positive
For ocular or cranial MG: exclude intracranial lesions by CT or MRI

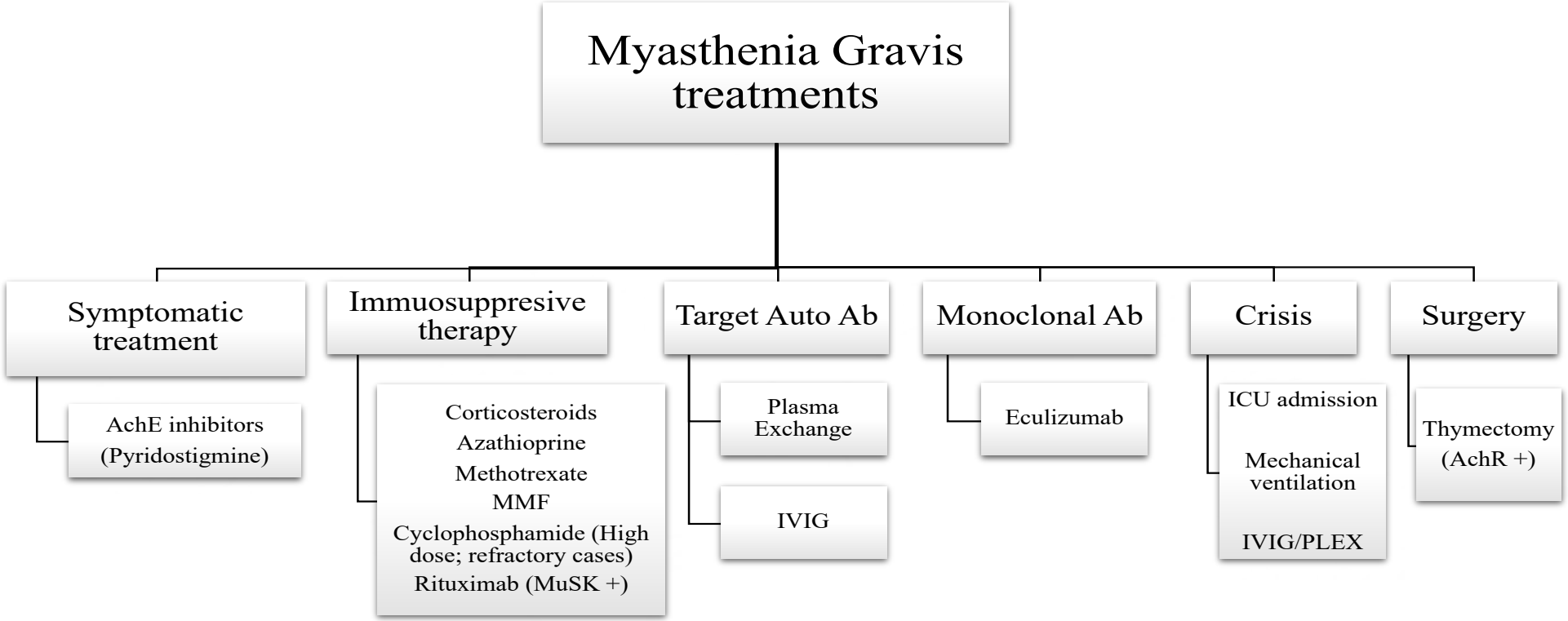
Abbreviations: AChR, acetylcholine receptor; CT, computed tomography; MRI, magnetic resonance imaging; MuSK, muscle-specific tyrosine kinase.

DIFFERENTIAL DIAGNOSES



Disorder	CMS	LEMS	AIDP	BOTULISM
Location	NMJ	NMJ (presynaptic)	Peripheral nerve	Presynaptic
Pathophysiology	Mutation against NMJ components (ε AchR, rapsyn)	Ab against presynaptic voltage gated Ca channels (P/Q)	Ab against myelin (GMI most common)	Irreversibly bind to presynaptic cholinergic receptors Protease cleaves presynaptic proteins for release of Ach **(Inhibits SNARE proteins)**
Cardinal clinical features	Begins in childhood/infancy Variable, MG-like s/s	PMW (Hip then shoulder) Gait before eyes Autonomic dysfunction (dry mouth)	ACUTE Ascending paralysis Antecedent event Autonomic dysfunction **Absent DTR**	ACUTE Descending paralysis Autonomic dysfunction 12 D's of botulism
Tests	RNS decremental response Genetic tests for NMJ proteins	Transient incremental response on RNS Look for SCLC (CT/MRI)	Cytoalbuminologic dissociation	Toxin in serum/stool
Treatment	Varies based on type of mutation.	3,4 diaminopyridine IVIG	IVIG/PLEX	Antitoxin

MG TREATMENT OPTIONS



MG THERAPIES

Table 2. Drugs Used Most Frequently for the Treatment of Myasthenia Gravis.

Drug	Mode of Action	Dose	Side Effects	Risks and Contraindications
Pyridostigmine	Symptomatic; acetylcholinesterase inhibition	Single dose: 10–120 mg; daily dose: 40–600 mg	Cholinergic autonomic effects	Cholinergic crisis
Prednisone or prednisolone	Immunomodulation	Induction dose: 40–80 mg daily; stable dose: 5–20 mg daily; alternate-day treatment is an alternative	Widespread dose-dependent glucocorticoid effects	Gastrointestinal bleeding, cushingoid appearance
Azathioprine	Suppression of B and T cells	50–250 mg daily	Nausea, vomiting, tiredness, infections, night sweats	Leukopenia, liver toxicity
Mycophenolate mofetil	Suppression of B and T cells	1.5–2 g daily	Nausea, vomiting, diarrhea, joint pain, infections, tiredness	Leukopenia, progressive multifocal leukoencephalopathy; contraindicated during pregnancy
Rituximab	Suppression of B cells	0.5–1 g, repeated after 2 wk; can be repeated at 6-mo intervals	Nausea, infections, infusion-related problems	Progressive multifocal leukoencephalopathy
Methotrexate	Inhibition of folate metabolism	Gradual increase to 20 mg/wk	Nausea, infections, lung disease	Leukopenia, liver toxicity; contraindicated during pregnancy
Cyclosporine	Suppression of T cells and natural killer cells	2.5–5 mg/kg of body weight daily	Nausea, hypertension, infections, hypertrichosis	Kidney toxicity
Tacrolimus	Suppression of T cells and natural killer cells	3 mg daily	Nausea, infections, lung disease, hypertension, neuropsychiatric problems	Liver and kidney toxicity
Cyclophosphamide	Suppression of B and T cells	1–5 mg per kg administered by intravenous infusion every 4 wk for a limited period	Nausea, vomiting, alopecia, discoloration of nails and skin, infections	Leukopenia
Intravenous immune globulin	Suppression of B and T cells, neutralization of autoantibodies	2 g per kg administered over a period of 2 to 5 days	Nausea, headache, fever, hypotension or hypertension, local skin reactions	IgA deficiency, allergic reactions

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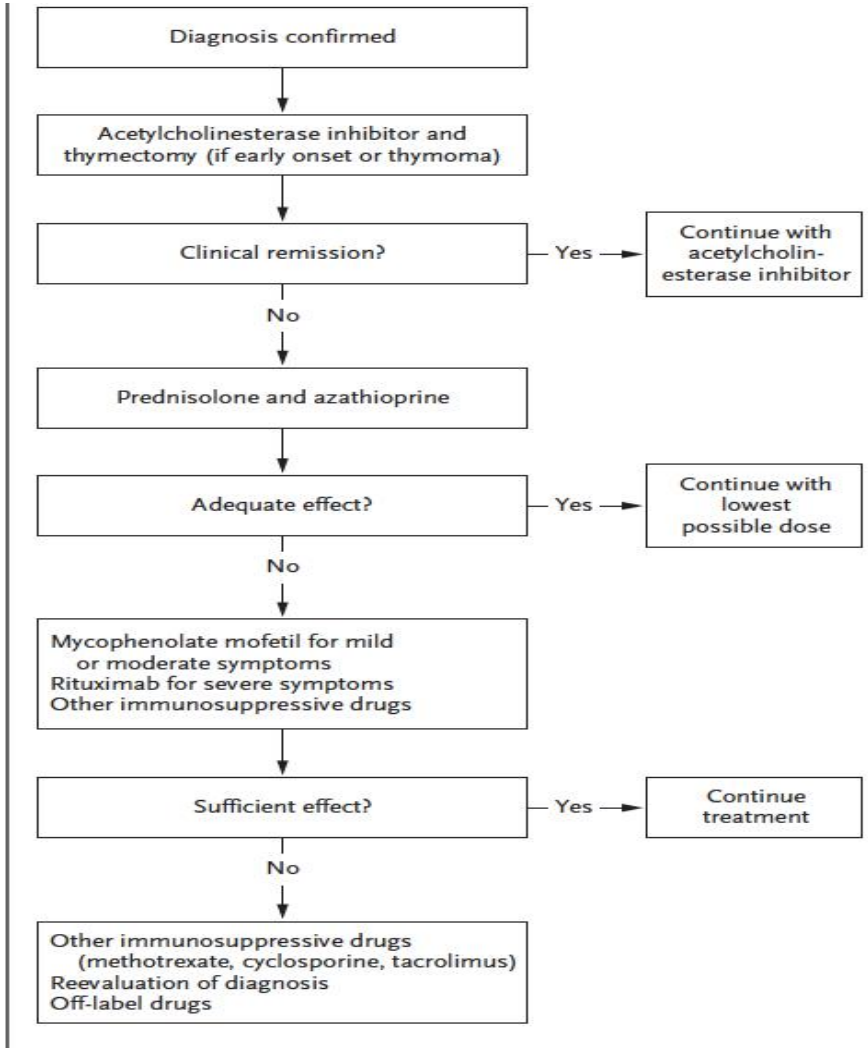
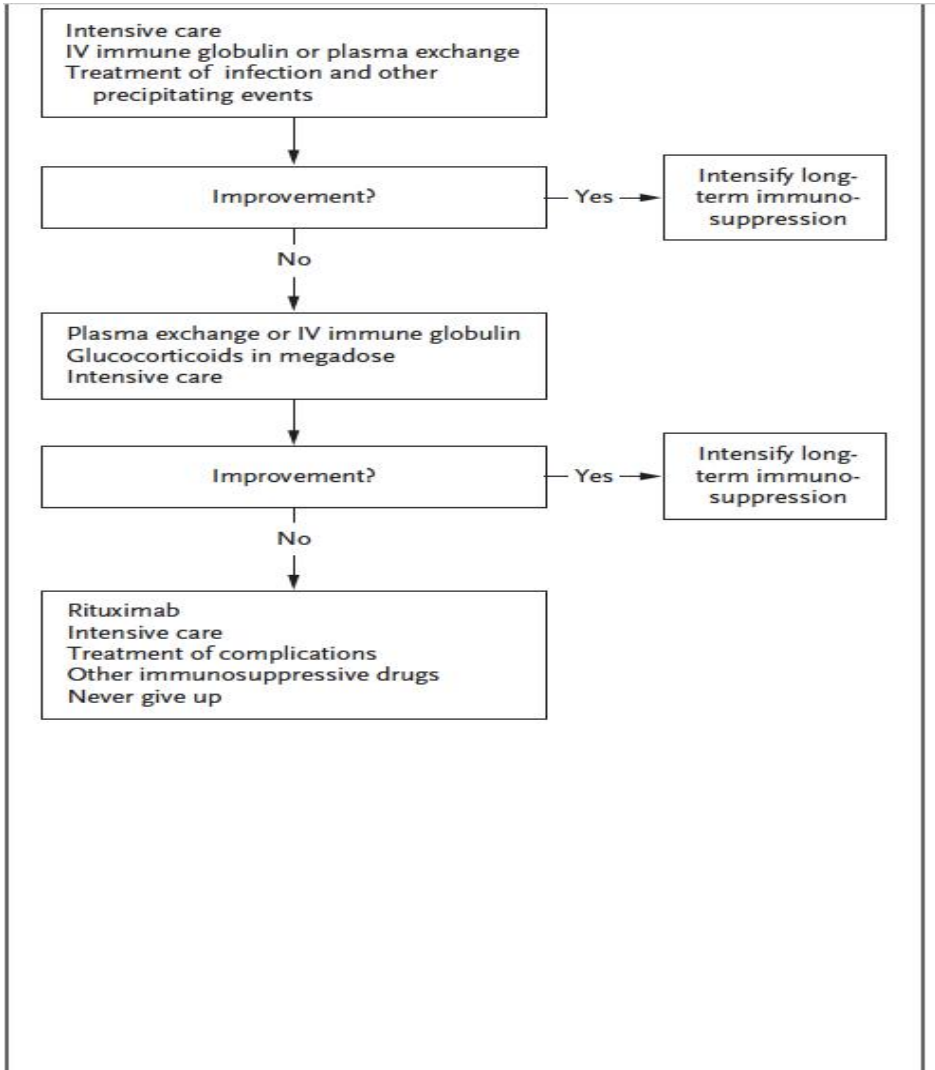
APPROACH TO THE PATIENT





TREATMENT EXCEPTIONS

- MuSK-respond well to PLEX, Rituximab.

- Pregnancy and MG-Pyridostigmine, Prednisone, IVIG and PLEX.**AVOID Mycophenolate mofetil, Methotrexate.**

PROGNOSIS AND FOLLOW UP

- Prognosis is generally good. Majority do well and achieve near normal QOL.
- Mortality 6% (70%).
- Multidisciplinary approach.
- Patient and family support, resources (www. myasthenia.org)
- Crisis plan (medic alert bracelet)

COMPLICATIONS

Crises

ICU admission (have low threshold to admit)

Mechanical ventilation

Multidisciplinary approach

THE FUTURE OF MG

IgG FcRn (Efgartigimod)

Complement inhibitors (Anti-C5) will be beneficial in the future.

KEY CLINICAL FEATURES

- A 30 year old woman presents to her televisit with ptosis and fatigue after a night shift that resolved with sufficient rest. She reports that she can no longer keep up with her children during bicycle rides. She denies SOB.
- **Physical exam:** B/L ptosis, worsens with upward gaze. DTR normal.
- **RNS:** Rt iliopsoas muscle fatigability that improves after 2 mins of rest.

- What is the most likely diagnosis? **MG.**
- What is the best test to confirm the diagnosis? **AchR Ab.**
- What is the best next step in therapy? **AchE inhibitors and IST.**

QUESTIONS

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