Name of Faculty: Dr. Amit Kumar Nayak
Designation: Professor
Department: Pharmacy
Subject: Pharmacolgy-I (BP 404T)
Unit: III
Topic: Myasthenia Gravis

LNCT SM GROUP OF COLLEGES "WORKING TOWARDS BEING THE BEST"

Outline

- Background
- Anatomy
- Pathophysiology
- Epidemiology
- Clinical Presentation
- Treatment

Background

- The word Myasthenia Gravis is derived from Latin and Greek

Myasthenia – weakness

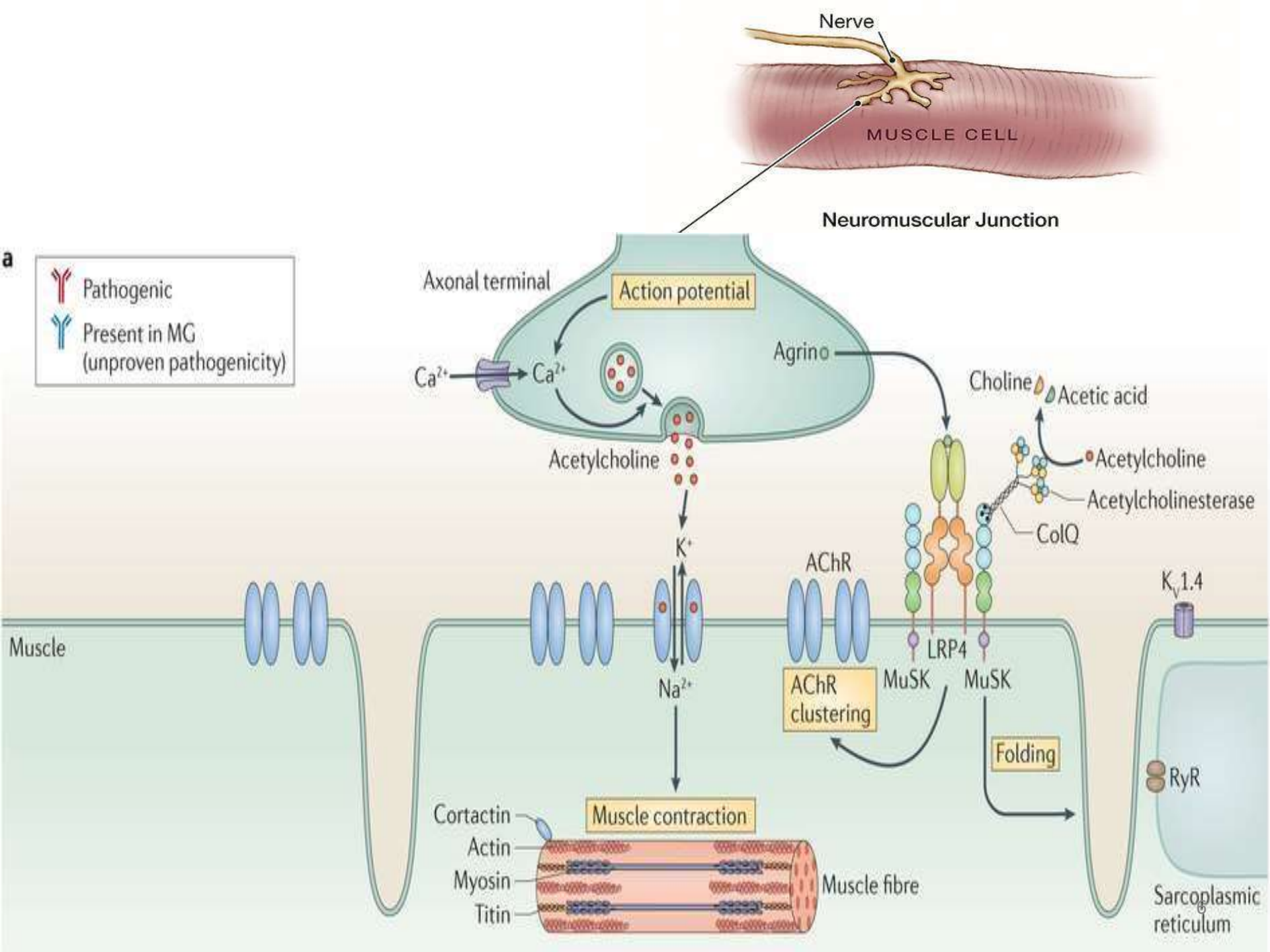
Gravis – serious

- literally means "grave muscle weakness"

- Myasthenia gravis (MG) - autoimmune disorder - antibodies against AchRs at NMJ
- these antibodies attack and destroy AchRs & postsynaptic molecules
- leads to impaired signal transduction ➡ muscle weakness and fatigability

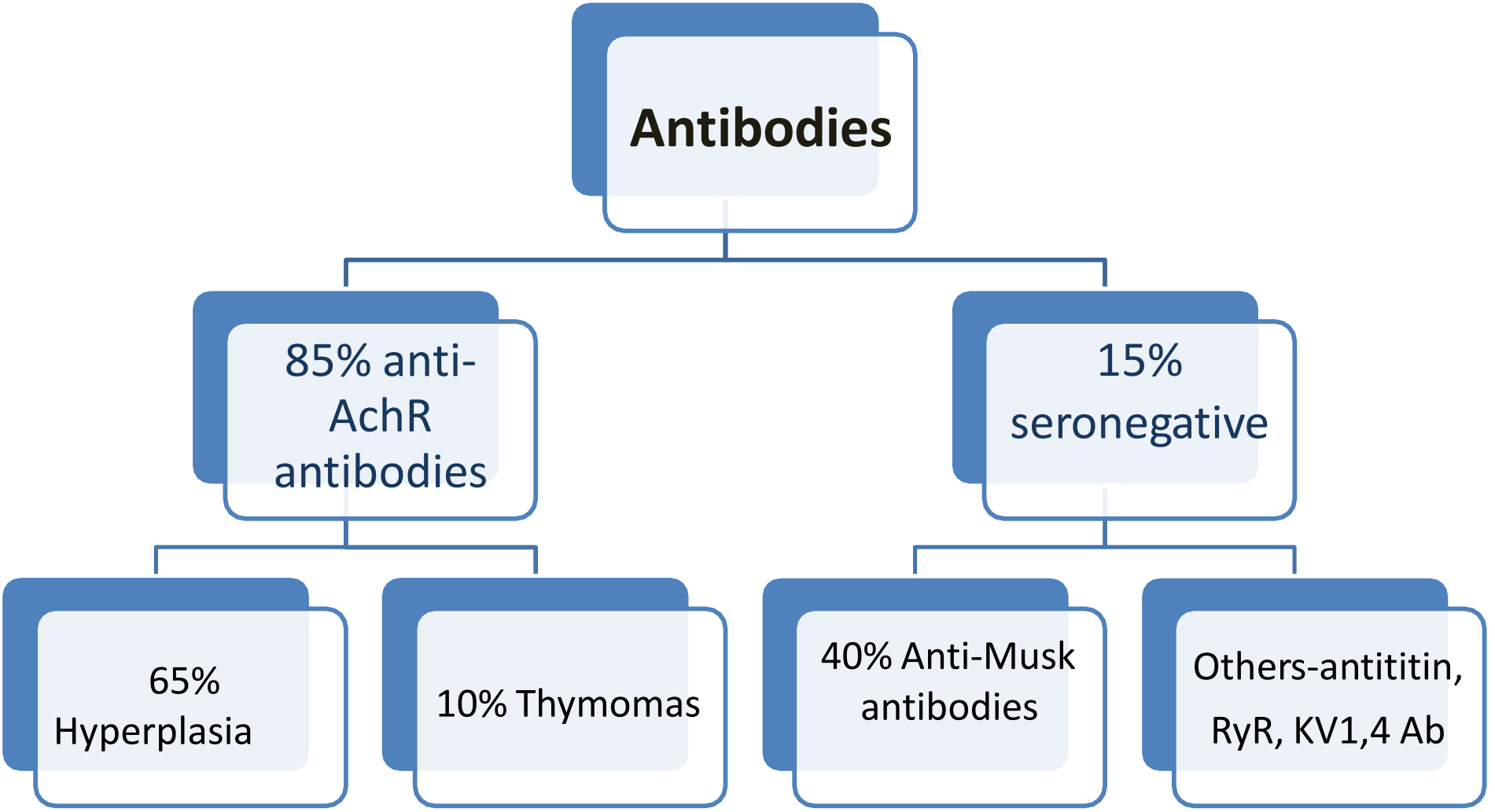
Anatomy

- Neuromuscular Junction (NMJ)
  - Components:
    - Presynaptic membrane
    - Postsynaptic membrane
    - Synaptic cleft
  - Presynaptic membrane contains Àch in vesicles
  - ACh attaches to AChR on postsynaptic membrane

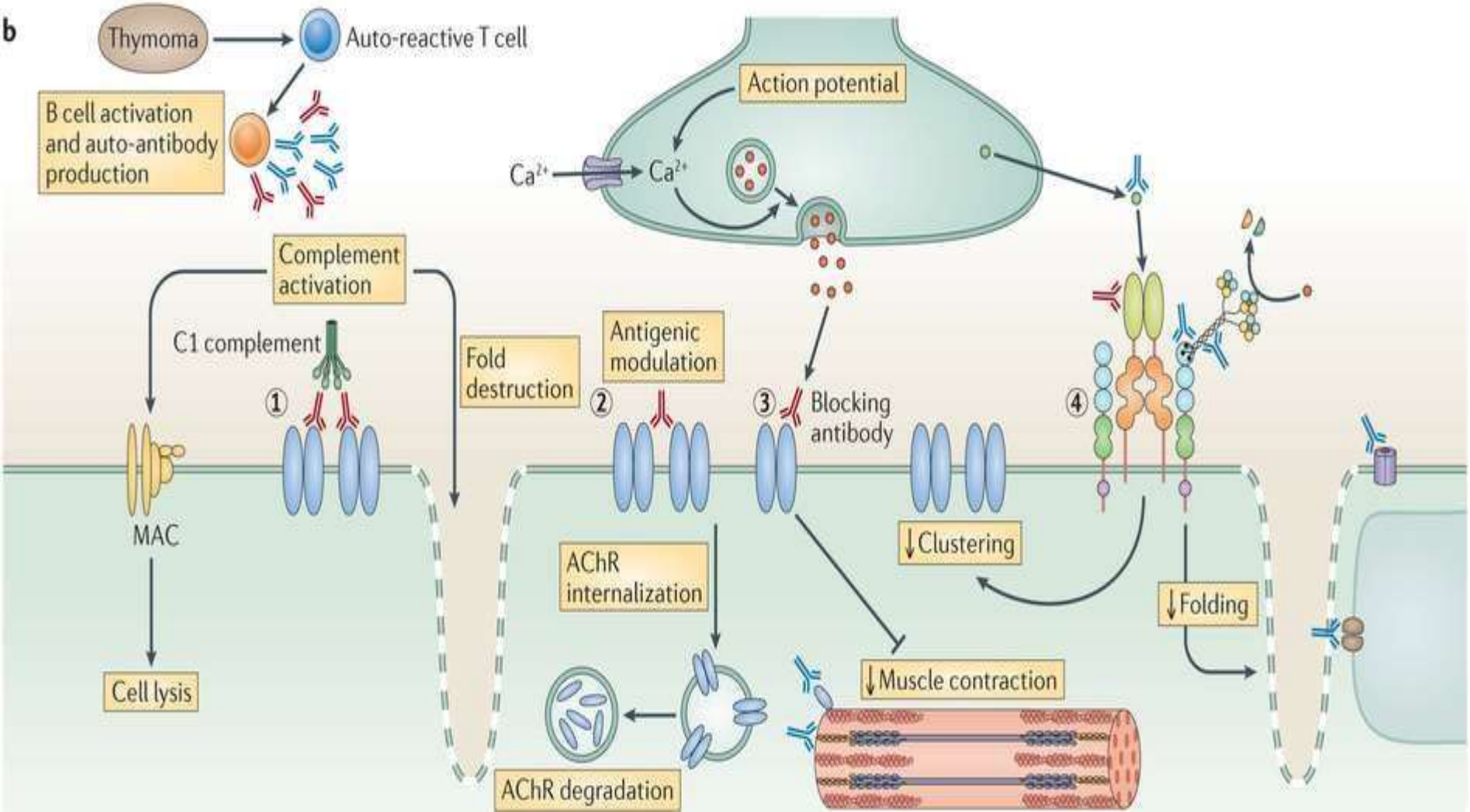

Nerve
MUSCLE CELL
Neuromuscular Junction
a
Pathogenic
Present in MG
(unproven pathogenicity)
Axonal terminal
Action potential
Ca2+
Ca2+
Agrin
Choline
Acetic acid
Acetylcholine
Acetylcholine
Acetylcholinesterase
ColQ
K+
AChR
Kv1.4
Muscle
LRP4
Na2+
AChR
clustering
MuSK
MuSK
Folding
RyR
Cortactin
Actin
Myosin
Titin
Muscle contraction
Muscle fibre
Sarcoplasmic
reticulum

Pathophysiology

In MG, antibodies are directed toward the acetylcholine receptor at the neuromuscular junction of skeletal muscles


Antibodies
85% anti-AchR antibodies
15% seronegative
65% Hyperplasia
10% Thymomas
40% Anti-Musk antibodies
Others-antititin, RyR, KV1,4 Ab

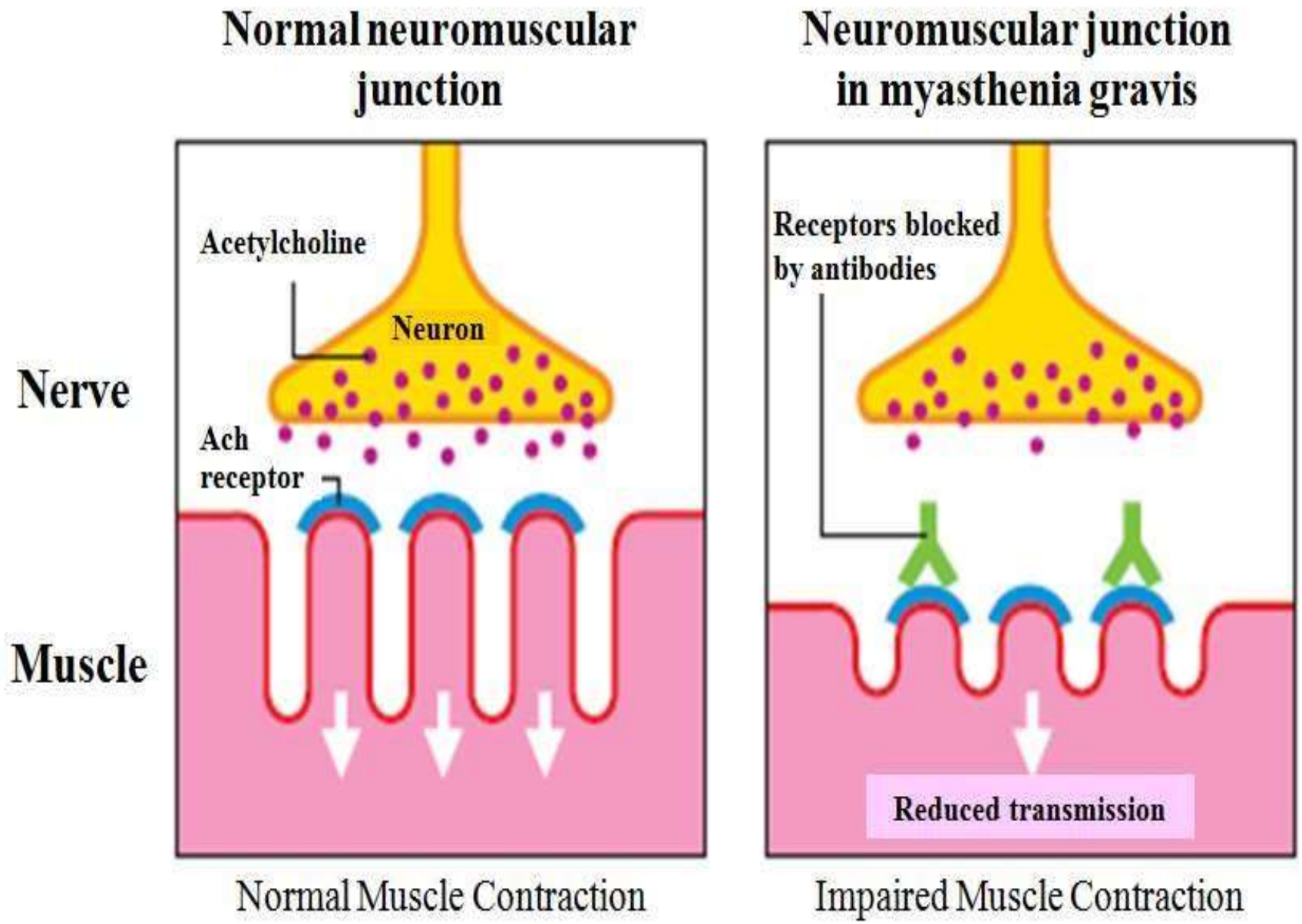
Pathophysiology



How do these antibodies act?

1. Blocks the binding of ACh to the AChR.
2. Increases the degradation rate of AChR
3. A complement-mediated destruction

- Results in:
  - ↓ nicotinic acetylcholine receptors
  - ↓ postsynaptic membrane folds
  - Widened synaptic cleft

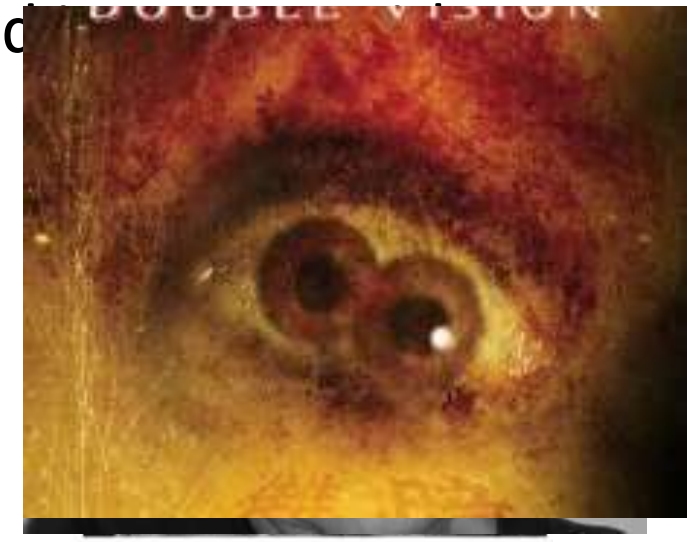

Normal neuromuscular junction
Neuromuscular junction in myasthenia gravis
Nerve
Muscle
Acetylcholine
Neuron
Ach receptor
Receptors blocked by antibodies
Reduced transmission
Normal Muscle Contraction
Impaired Muscle Contraction

Epidemiology

- Prevalence: 1-7 in 10,000
- Age: BIMODAL PEAK
- 20-30 yrs (young women), 50-60 yrs (older men)
- < 10% occur in children <10 yrs
- Overall F:M = 3:2
- More common in pts with family history of one or the other autoimmune diseases

Clinical Presentation

- Fluctuating painless weakness increased by exertion
- Worses with repetitive activities an d



  - Ocular muscle weakness

    (85%) Asymmetric

    Ptosis

    Diplopia is very common

Weakness of face and throat muscles

Dysphagia

Dysarthria

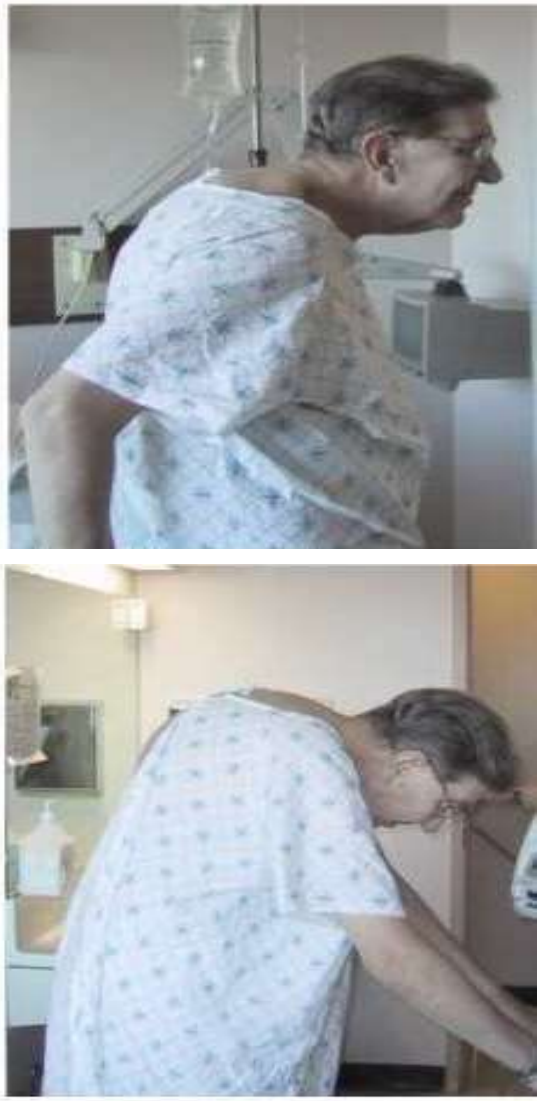
Dysphonia

normal

during attack

Myasthenic snarls

- Limb muscle weakness
  - Neck extensors > flexors
  - Upper limbs > lower limbs



Dropped head syndrome

- Respiratory weakness
  - ❑Weakness of the intercostal muscles and the diaghram
  - ❑ Collapse the upper airway
  - ❑ Neuromuscular emergency - mechanical ventilation

Progression of disease

- Mild to more severe over weeks to months
  - Usually spreads from ocular → facial → bulbar → truncal → limb muscles
  - The disease remains ocular in 16% of patients
  - Death rate reduced from 30% to <5% with pharmacotherapy and surgery

Diagnosis

History

- Diplopia, ptosis, weakness
- Weakness in characteristic distribution
- Fluctuation and fatigue: worse with repeated activity, improved by rest
- Effects of previous treatments

Physical examination

- Ptosis, diplopia
- Motor power survey: quantitative testing of muscle strength
- Forward arm abduction time (5 min)
- Vital capacity
- 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 >15% at 3 Hz: highly probable
- Single-fiber electromyography: blocking and jitter, with normal fiber density; confirmatory, but not specific
- Edrophonium chloride (Tensilon) 2 mg + 8 mg IV; highly probable diagnosis if unequivocally positive
- For ocular or cranial MG: exclude intracranial lesions by CT or MRI

Edrophonium (Tensilon test)

- Initial IV dose of 2 mg of edrophonium is given
- Observed for objective improvement in muscle weakness
- Definite improvement occurs-the test is considered positive & terminated
- If no improvement in weakness - the remainder 8mg of the drug is injected

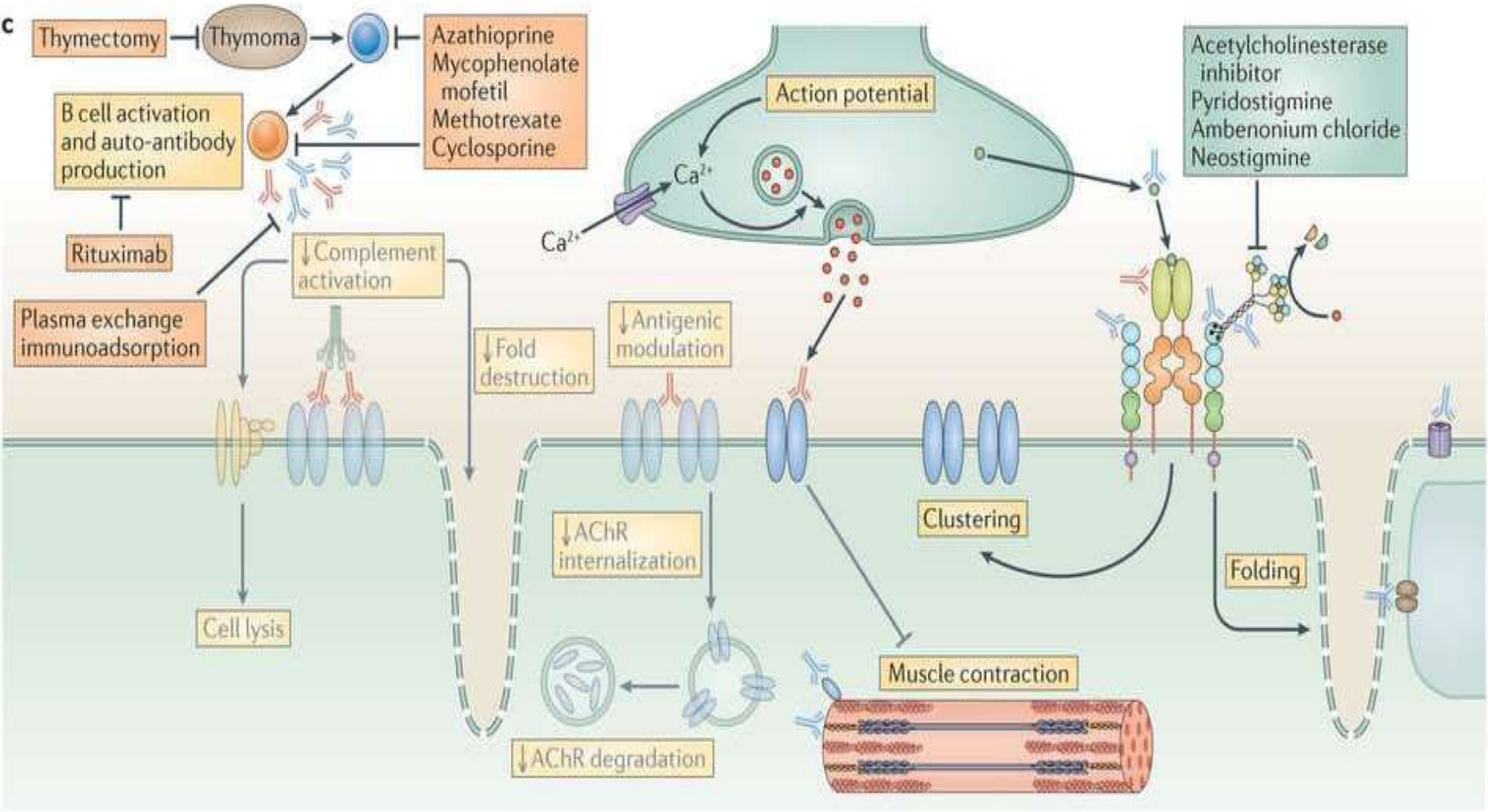
Myasthenic Crisis

- Exacerbation of weakness - endanger life
- Respiratory failure (diaphragmatic and inter costal muscle weakness)
- Cause – intercurrent infection
- Cholinergic crisis - excessive anticholinesterase medication

Treatment

There are four basic therapies:

- Symptomatic treatment - acetylcholinesterase inhibitors
- Rapid short-term - plasmapheresis and intravenous immunoglobulin
- Chronic long term - immunomodulating treatment - glucocorticoids & immunosuppressive drugs
- Surgical treatment



Nature Reviews | Neurology

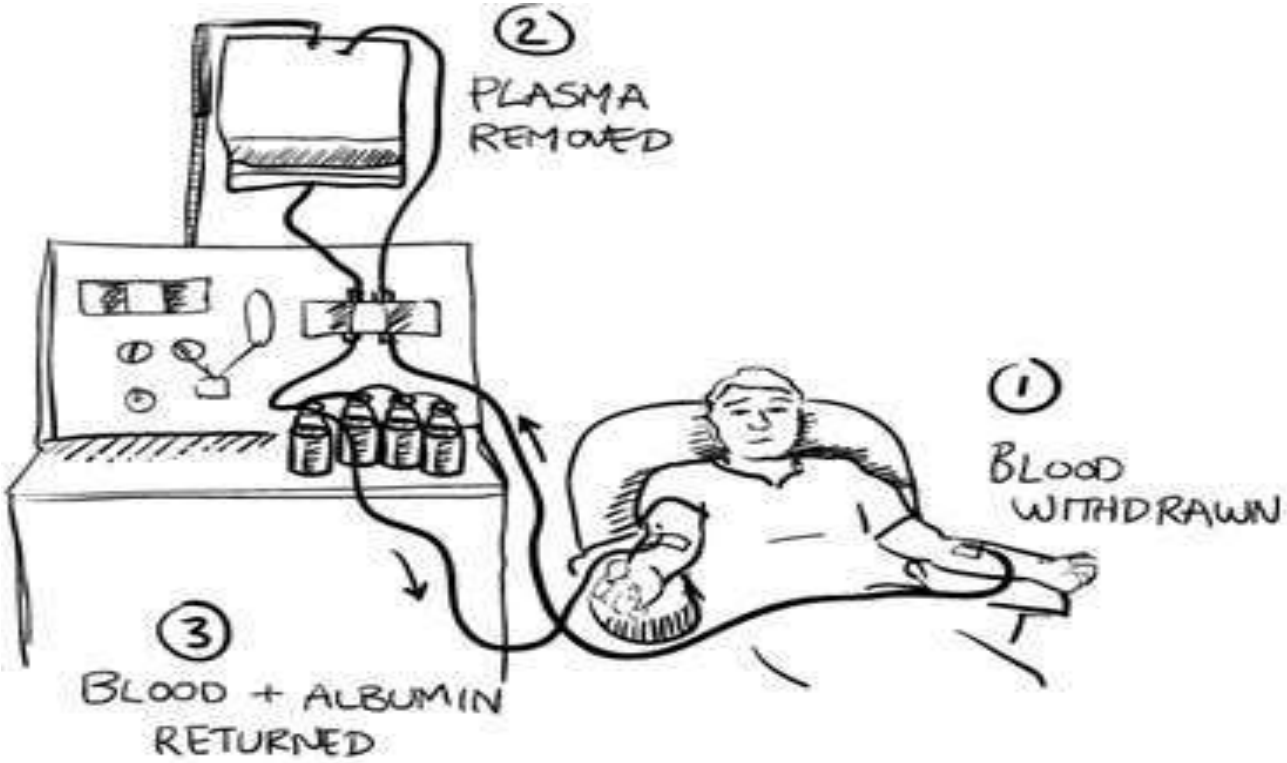
Anticholinesterase Medications

- Pyridostigmine is the most widely used
- Onset - 15–30 min and lasts for 3–4 h
- Dose - 30–60 mg three to four times daily
- Frequency of the dose should be tailored to the patient’s individual requirements throughout the day

Neostigmine

- Short-acting AChE inhibitor
- half-life - 45-60 minutes
- Poorly absorbed from the GIT
- Should be used only if pyridostigmine is unavailable

Plasmapheresis



Plasma exchange (PLEx)

Plasmapheresis

- Removes AChR Ab from the circulation

•Rapidly Improves strength

Used for

- short-term intervention
- Sudden worsening of myasthenic symptoms
- Chronic intermittent treatment for refractory cases

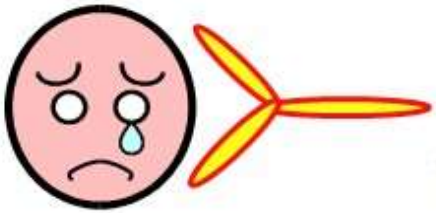
- Typically one exchange is done every other day for a total of four to six times
- Improvement is noted in a couple of days, but it does not last for more than 2 months.
- Complications – hypocalcemia, hypomagnesemia, hypothermia, hypotension & transfusion reactions

Intravenous Immunoglobulin Therapy

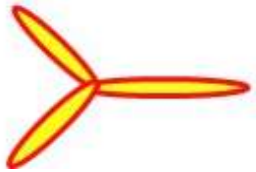
How does IVIg work in MG?

One possible mechanism

Acetylcholine receptor



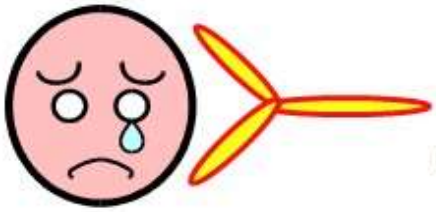
'Bad' antibody against AChR



How does IVIg work in MG?

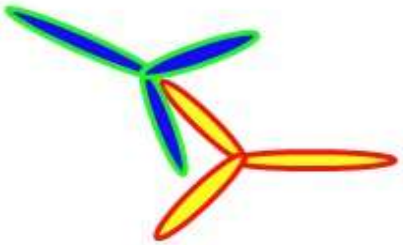
One possible mechanism

Acetylcholine receptor



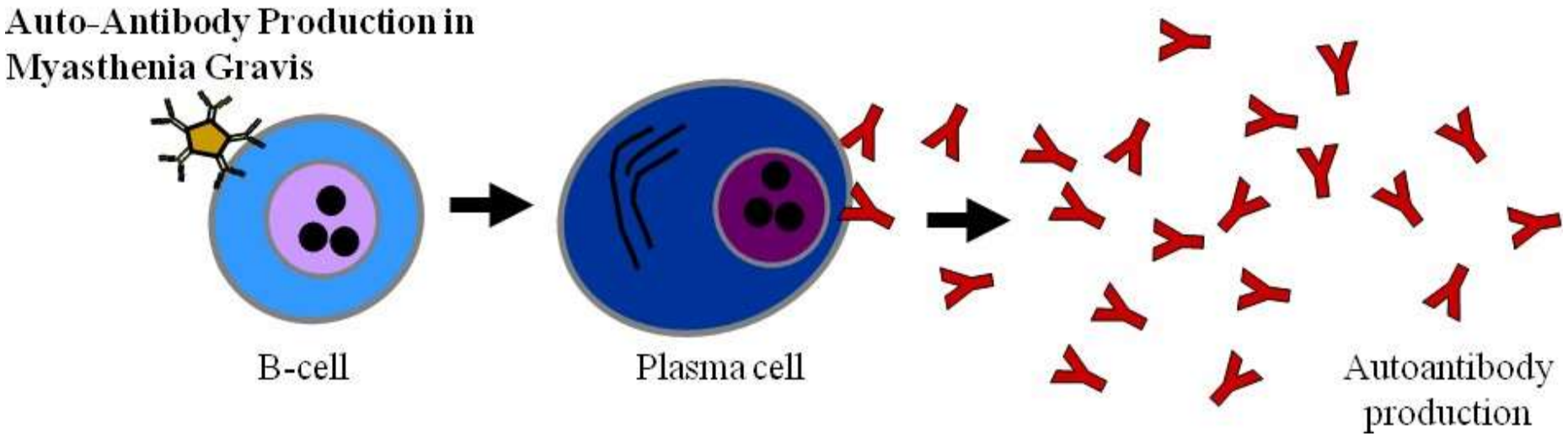
'Bad' antibody against AChR

IVIg infusion



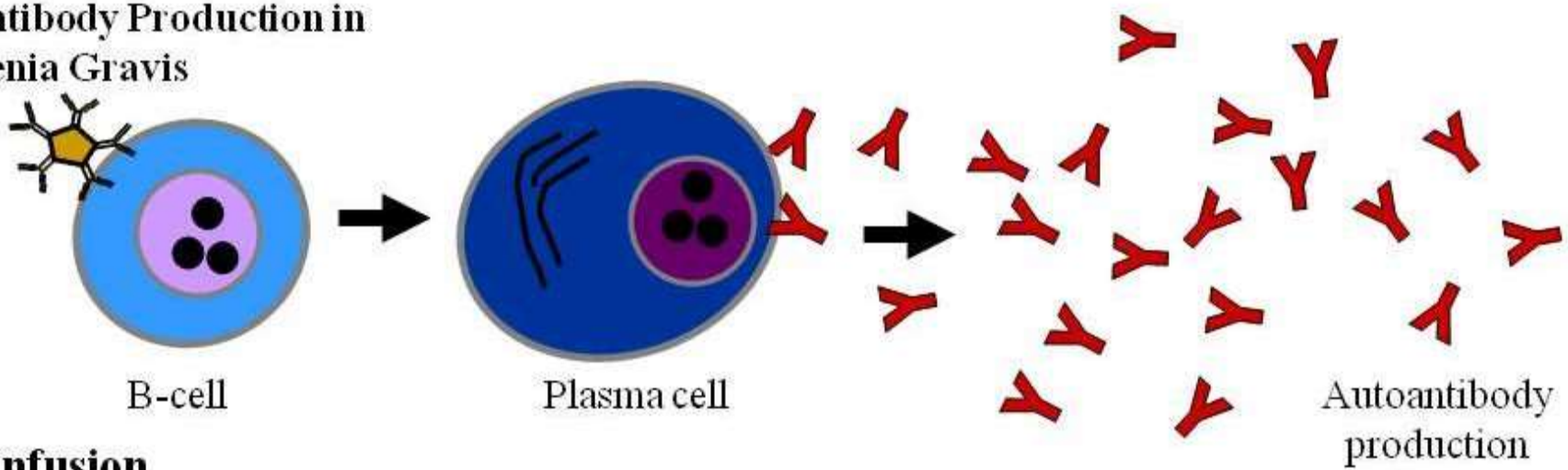
'Good' antibodies against bad antibodies

The presence of large amounts of IgG will also suppress the production of host IgG

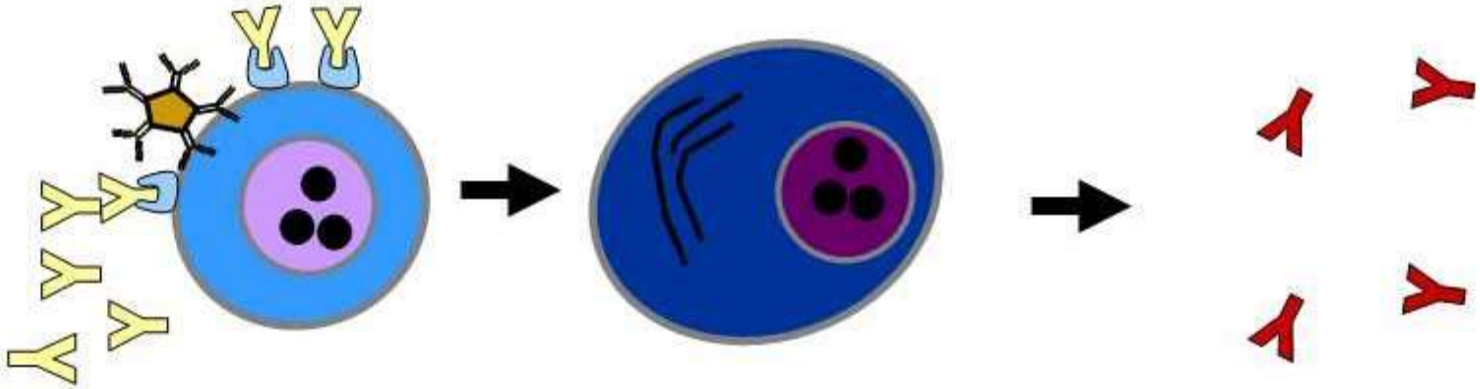


The presence of large amounts of IgG will also suppress the production of host IgG

Auto-Antibody Production in Myasthenia Gravis



IVIG Infusion



Intravenous Immunoglobulin Therapy

- Rapid improvement
- Severe myasthenic weakness
- Dose is 2 g/kg over 5 days (400 mg/kg per day)
- Improvement occurs in ~70% of patients
- Adverse reactions include headache, fluid overload, and rarely aseptic meningitis or renal failure

Immunosuppression

- Is required in nearly all pts with

  -late-onset MG

  -thymoma MG

  -MuSK-MG

- Suppress autoantibody production & its detrimental effects at NMJ

Glucocorticoids

- First & most commonly used immunosuppressant
- Used when symptoms of MG are not adequately controlled by cholinesterase inhibitors alone
- MOA - inhibits MHC expression & IL-1 production

↓ IL-2 & IFN γ production

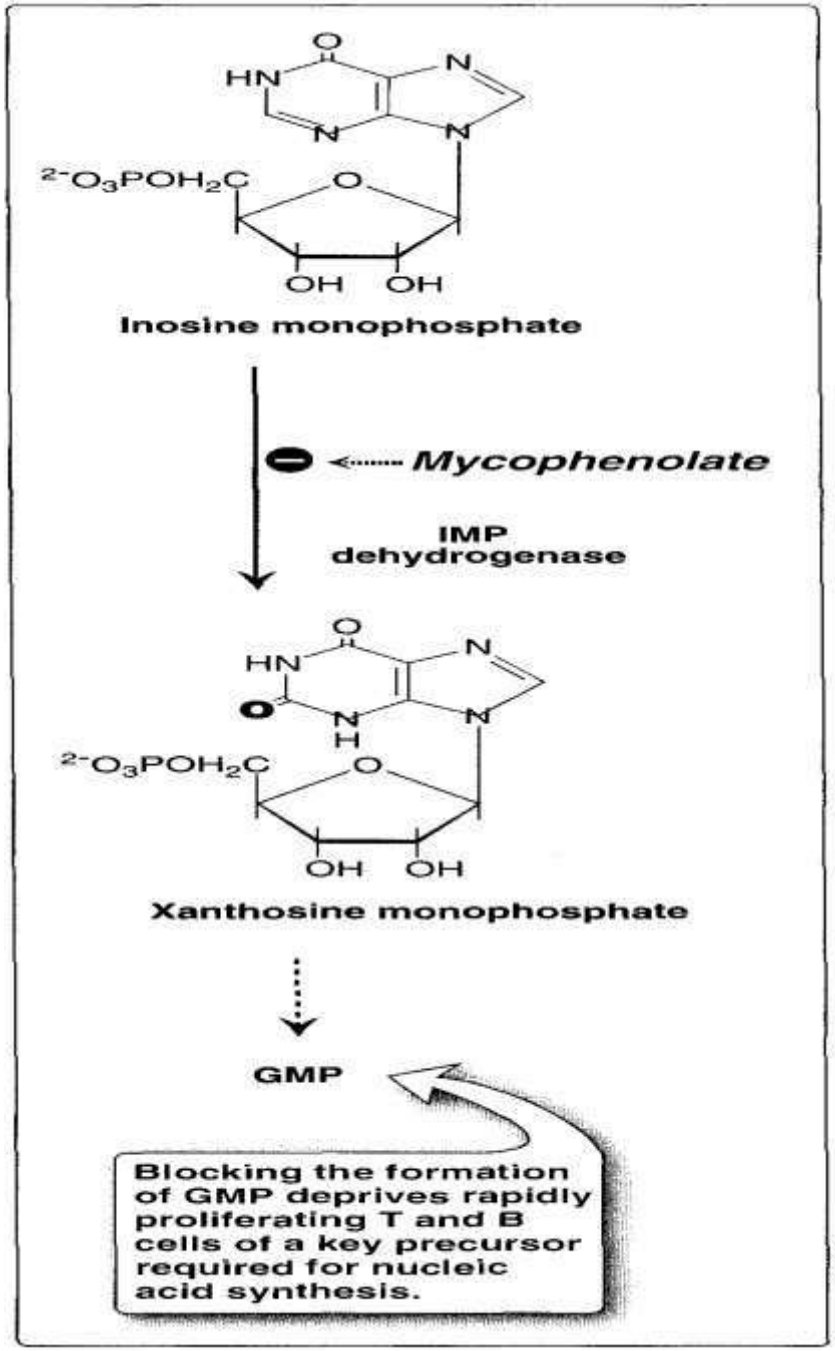
Prednisone –

- most commonly used
- Decreases the severity of MG exacerbations
- Transient worsening might occur initially
- Clinical improvement - 2-4 weeks
- marked improvement in 40%
- Remissions are noted in 30%

Mycophenolate mofetil

- Choice for long-term treatment
- MOA -prodrug of mycophenolic acid

  - Inhibits inosine monophosphate dehydrogenase
- Lymphocyte proliferation, antibody production and CMI are inhibited


Inosine monophosphate
Mycophenolate
IMP dehydrogenase
Xanthosine monophosphate
GMP
Blocking the formation of GMP deprives rapidly proliferating T and B cells of a key precursor required for nucleic acid synthesis.

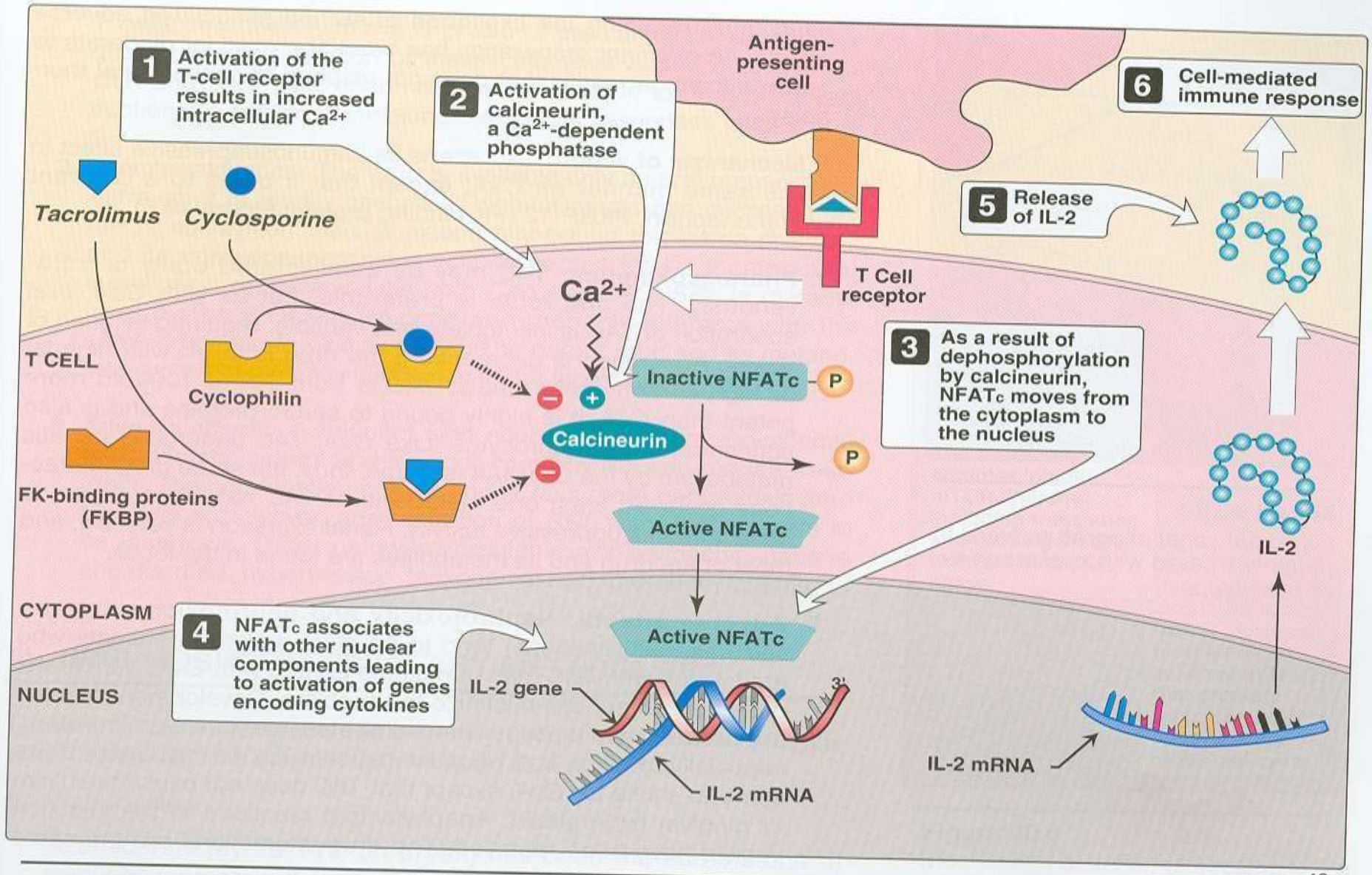
- Does not kill or eliminate preexisting autoreactive lymphocytes
- Clinical improvement may be delayed for 2-6 months
- Vomiting, diarrhoea, leucopenia and predisposition to CMV infection, g.i. bleeds are the prominent adverse effects.

Azathioprine

- It is a purine analog, reduces nucleic acid synthesis, thereby interfering with T-and B-cell proliferation
- Is effective in 70%–90% of patients with MG
- When used in combination with prednisone - more effective & better tolerated than prednisone alone
- Beneficial effect takes at least 3–6 months to begin

Calcineurin inhibitors

- **Cyclosporin -** Used mainly in patients who do not tolerate or respond to azathioprine
- Blocks synthesis of IL-2 cytokine
- Dose 4–5 mg/kg per day
- Cyclosporine can cause nephrotoxicity, neurotoxicity, hepatotoxicity, hyperlipidemia, hyperuricemia, hyperglycemia, hirsutism and


1 Activation of the T-cell receptor results in increased intracellular Ca^{2+}
2 Activation of calcineurin, a Ca^{2+}-dependent phosphatase
Antigen-presenting cell
6 Cell-mediated immune response
Tacrolimus
Cyclosporine
5 Release of IL-2
T Cell receptor
Ca^{2+}
T CELL
Cyclophilin
Inactive NFATc
P
3 As a result of dephosphorylation by calcineurin, NFATc moves from the cytoplasm to the nucleus
Calcineurin
P
FK-binding proteins (FKBP)
Active NFATc
IL-2
CYTOPLASM
4 NFATc associates with other nuclear components leading to activation of genes encoding cytokines
Active NFATc
NUCLEUS
IL-2 gene
3'
IL-2 mRNA
IL-2 mRNA

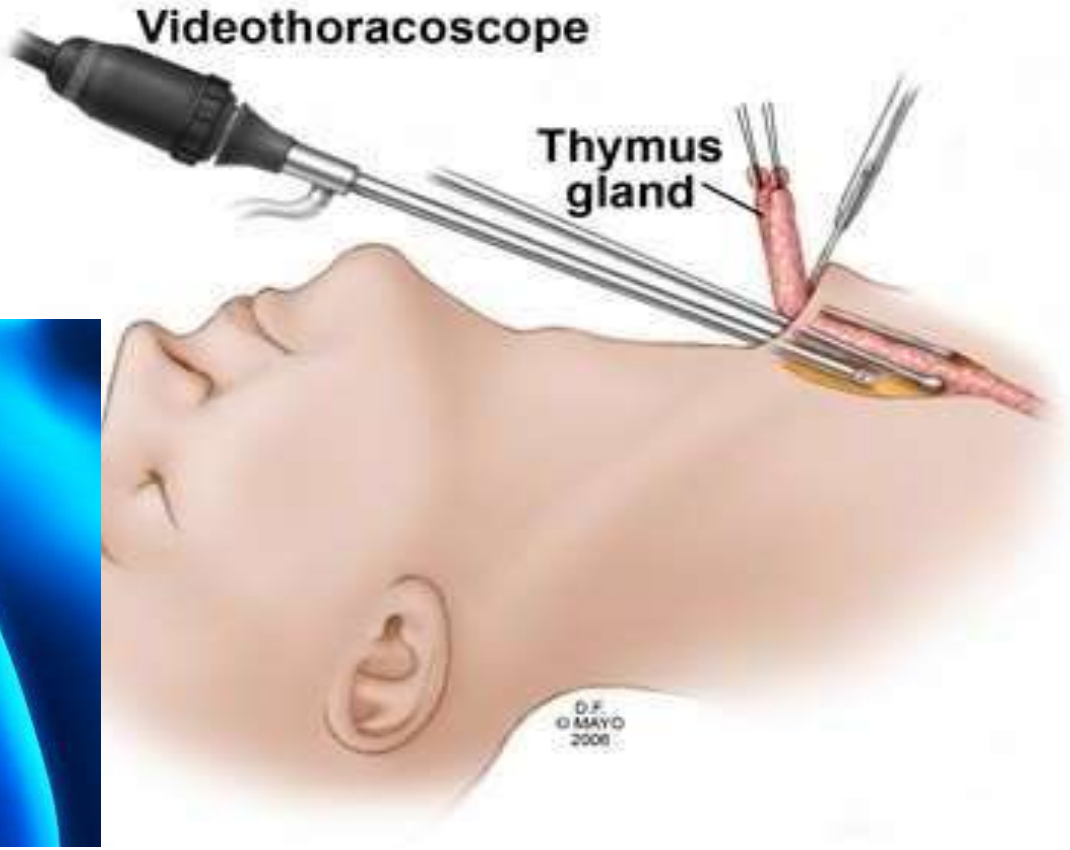
Tacrolimus

- Is ~ 100 times more potent than cyclosporin
- It binds to FK 506 binding protein (FKBP) and causes inhibition of helper T cells
- Beneficial effect appears more rapidly than that of azathioprine
- less nephrotoxicity, hirsutism, hyperlipidemia than cyclosporine
- Dose - 0.1 mg/kg per day

Treatment	Time to Clinical Effect
Pyridostigmine	10–15 minutes
Plasmapheresis	1–14 days
IVIg	1–4 weeks
Prednisone	2–8 weeks
Mycophenolate mofetil	2–6 months
Cyclosporine	2–6 months
Azathioprine	3–18 months

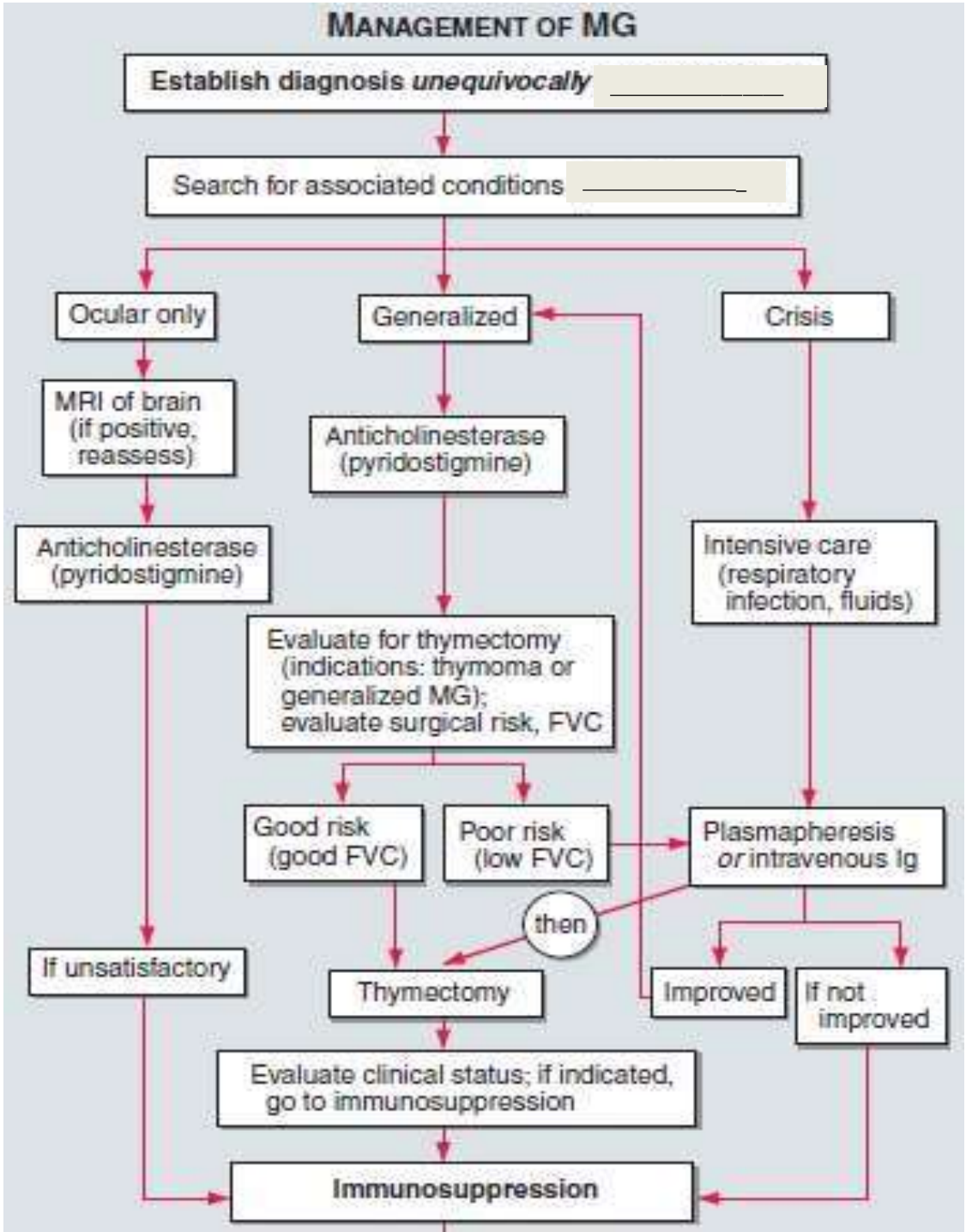
Source: Semin Neurol © 2004 Thieme Medical Publishers

Thymectomy



Thymectomy

- Carried out in all patients with generalized MG - aged between puberty and 55 years
- Thymoma - Surgical removal is a must - possibility of local tumor spread
- up to 85% of patients experience improvement after thymectomy
- of these, ~ 35% achieve drug-free remission


MANAGEMENT OF MG
Establish diagnosis unequivocally
Search for associated conditions
Ocular only
Generalized
Crisis
MRI of brain (if positive, reassess)
Anticholinesterase (pyridostigmine)
Anticholinesterase (pyridostigmine)
Intensive care (respiratory infection, fluids)
Evaluate for thymectomy (indications: thymoma or generalized MG); evaluate surgical risk, FVC
Good risk (good FVC)
Poor risk (low FVC)
Plasmapheresis or intravenous Ig
then
If unsatisfactory
Thymectomy
Improved
If not improved
Evaluate clinical status; if indicated, go to immunosuppression
Immunosuppression

Thank you