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Perioperative management of myasthenia gravis

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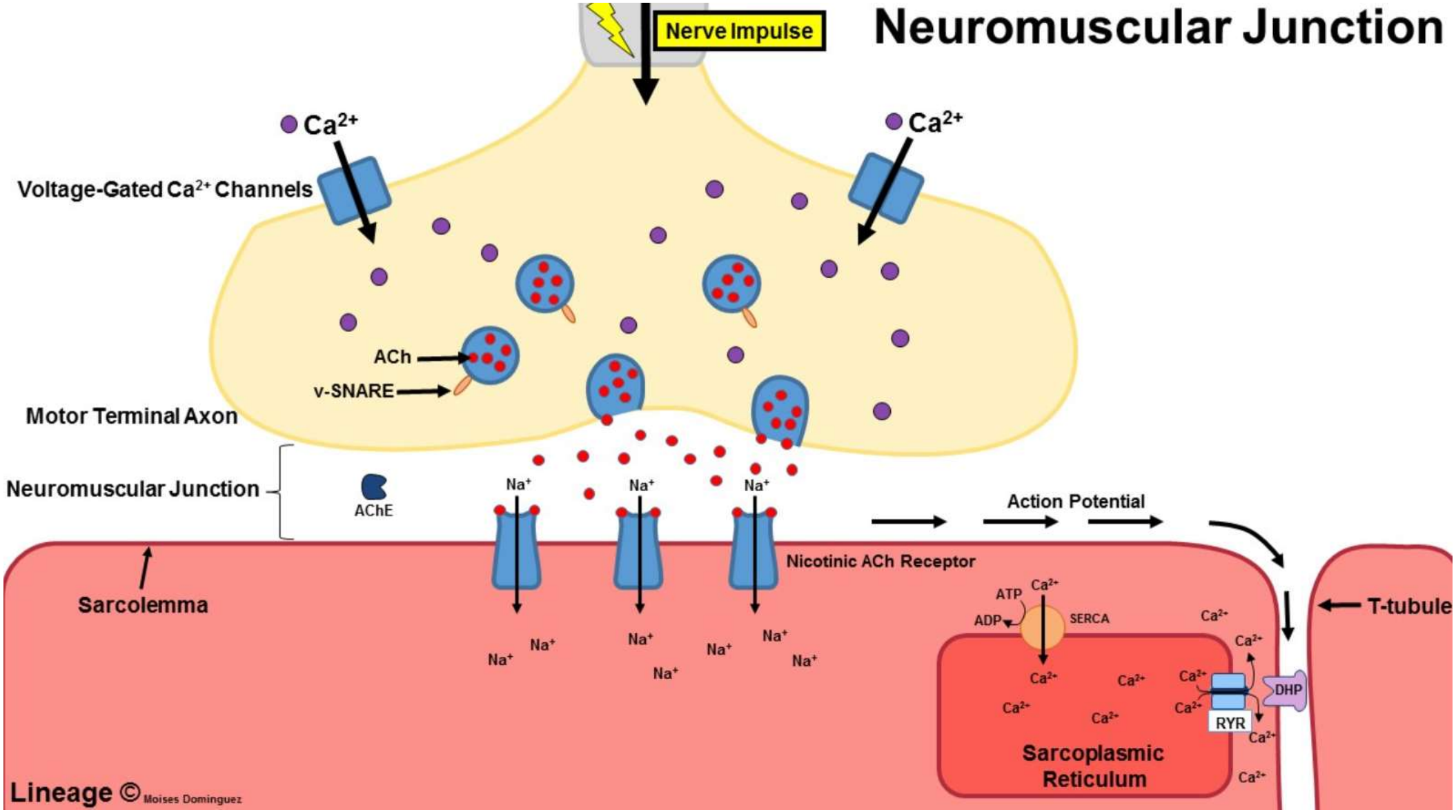
Learning objectives

- Pathophysiology
- Clinical features
- Diagnosis
- Management
- Pre op, intra op and post op management
- Myasthenic and cholinergic crisis
- Myasthenia Gravis in pregnancy

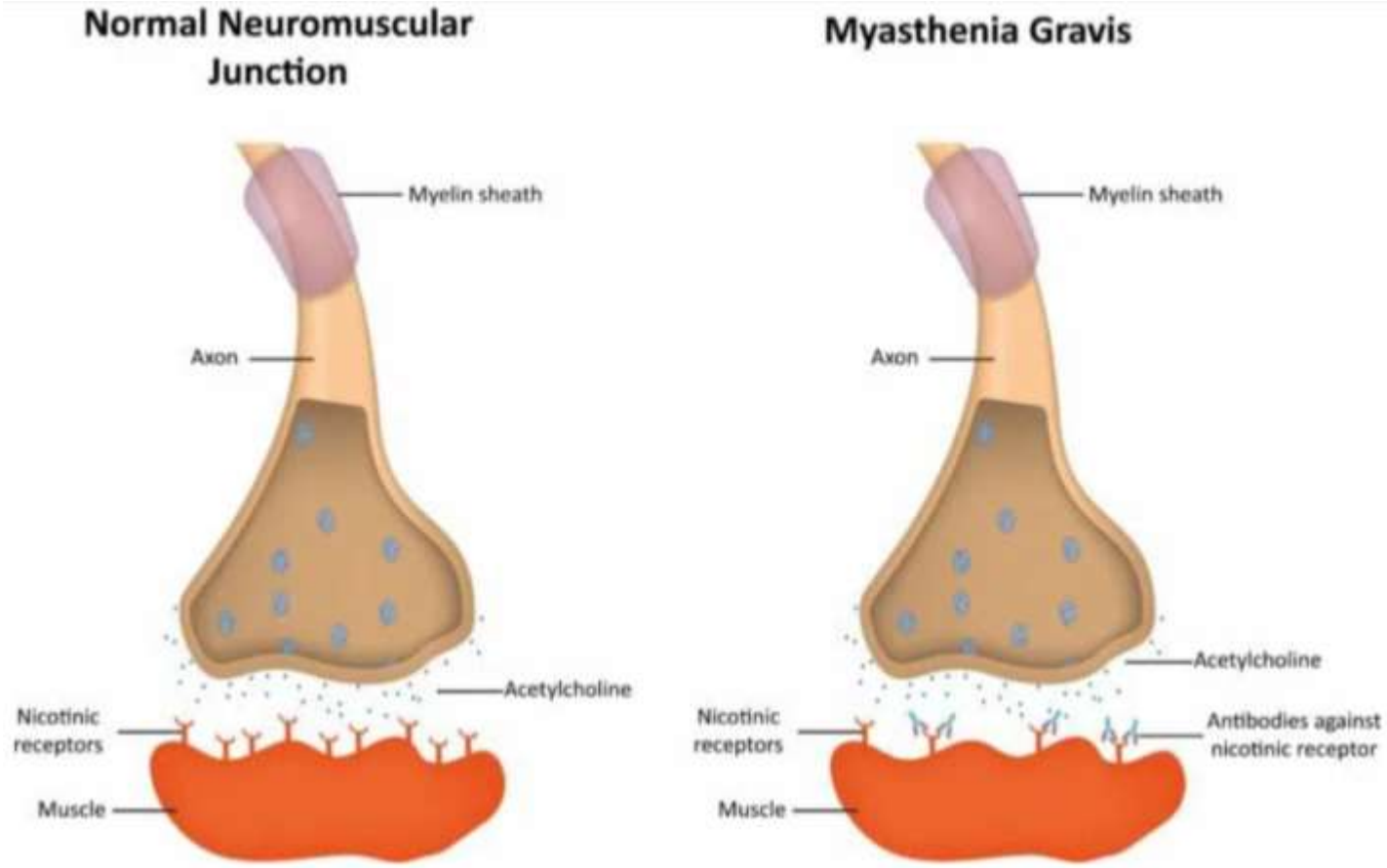
What is Myasthenia Gravis?

- Commonest NMJ disease
- B-cell-mediated AI disease
- Fatigable weakness - skeletal muscle
- UK Prevalence 15 per 100,000
- Bimodal incidence:
- Early onset (<50yrs) peaks at 30 years. Female:Male 3:1
- Late onset (>50yrs) increases with age. Men> women
- Previously - chronic disability & high mortality
- Currently improved LT prognosis


Neuromuscular Junction
Nerve Impulse
Ca2+
Ca2+
Voltage-Gated Ca2+ Channels
ACh
v-SNARE
Motor Terminal Axon
Neuromuscular Junction
AChE
Na+
Action Potential
Nicotinic ACh Receptor
Sarcolemma
T-tubule
ATP
ADP
SERCA
DHP
RYR
Sarcoplasmic Reticulum
Lineage © Moises Dominguez

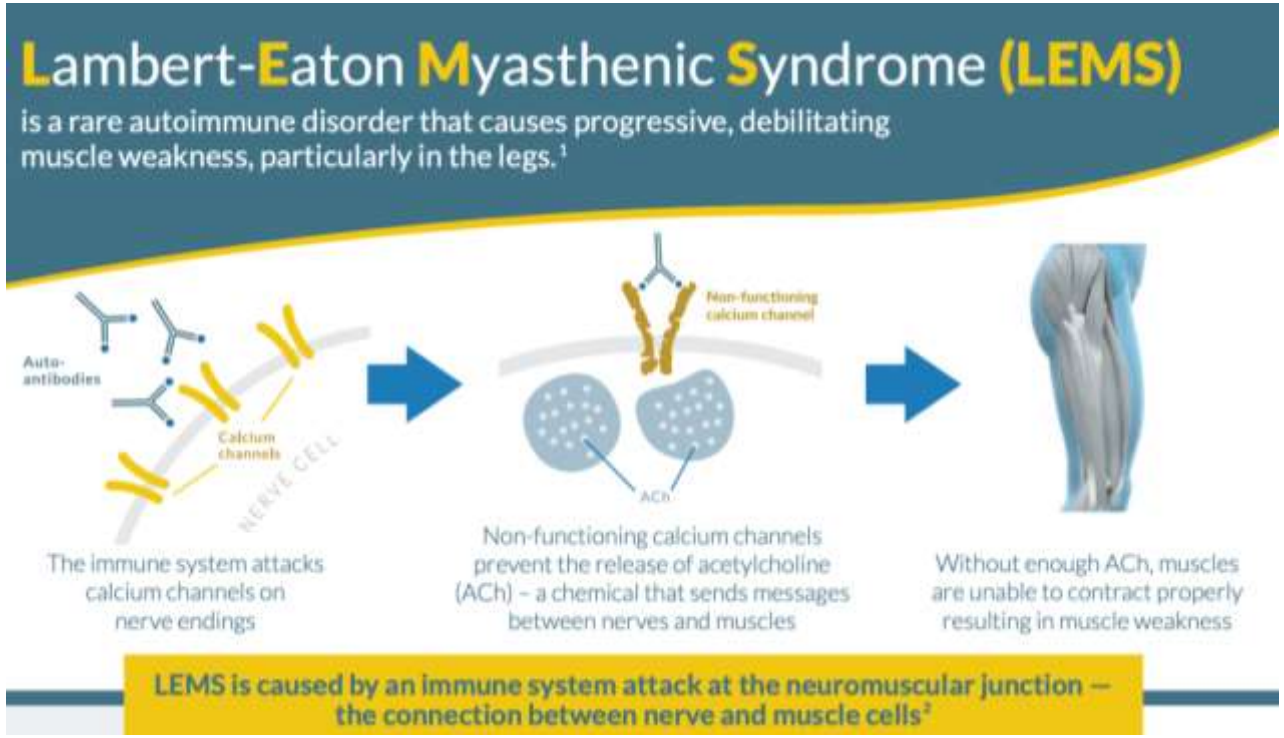
Pathophysiology

- Antibodies bind to AchR
- Receptor blockade, conformational change, complement activation, increased degradation
- Decreased motor end-plate potential amplitude
- Failure of muscle contraction



Other disorders of the NMJ

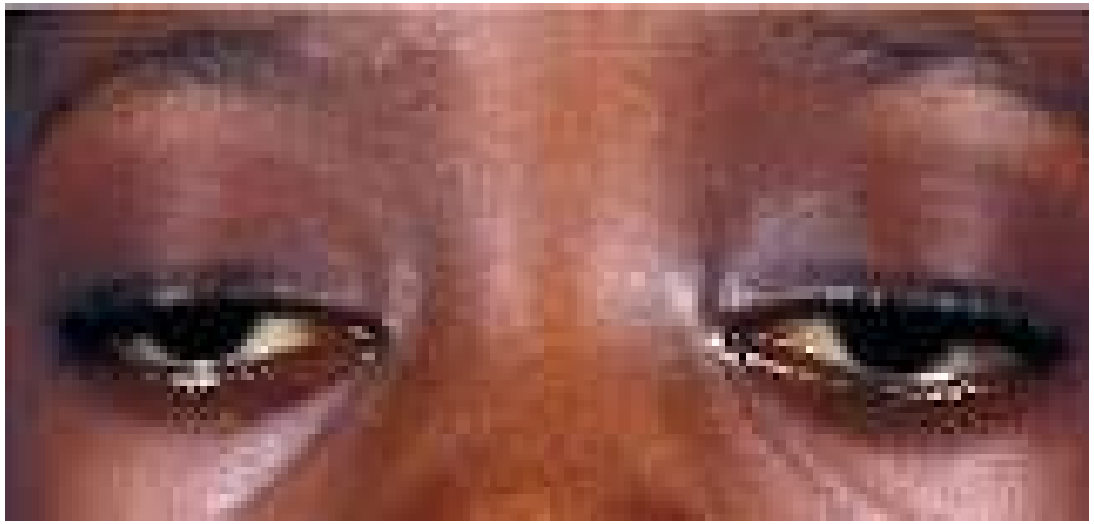
- **Rare - impaired ACh release**
- Congenital myasthenic syndromes
- Lambert Eaton Myasthenic syndrome
- Clostridium botulinum - cleaves proteins responsible for ACh release



Difference between Lambert Eaton syndrome and Myasthenia gravis

Myasthenia gravis	Lambert Eaton syndrome
Antibody against AchR antibody	Antibody against voltage gated calcium channe
Associated with Thymic tumor	Associated with Small cell lung cancer
Weakness worsen on prolonged exercise	Weakness improves on prolonged exercise
Normal Deep tendon reflex	Decreased or absent deep tendon reflex
Autonomic dysfunction is absent	Autonomic dysfunction is present
On repeated nerve stimulation, there is decremental response	On repeated nerve stimulation, there is incremental response

Clinical features



- Weakness
- Localised or generalised
- Mild to severe
- **Fatigability**
- Symptoms vary with time
- Ocular symptoms first
- Only ocular disease in 15-20%
- 75% progress to generalised disease < 3 yrs
- Generalised weakness – proximal, symmetrical
- No muscle wasting /fasciculations
- Tone, reflexes, sensation normal

Clinical features

- Second AI disease 13-22%
- Thyroid disease, SLE, RA
- Dermatopolymyositis ,Addison’s
- Cardiac involvement rare. Poor prognosis
- ECG changes, conduction disorders, myocarditis, heart failure, VT, sudden death
- Myasthenic crisis
- Precipitants– infection, surgery, residual NM block, pain, drugs, hypo- and hyperthermia, reduction /withdrawal of treatment, pregnancy, stress, sleep deprivation
- 15-20 % -crisis at least once in lifetime
- 66% - 90% crises require intubation & ventilation

Classification

Table 1 Myasthenia Gravis Foundation of America clinical classification

Class	Description
I	Any ocular muscle weakness; all other muscle strength is normal
II	Mild weakness affecting muscles other than ocular muscles A: Predominantly affecting limb, axial muscles or both B: Predominantly affecting oropharyngeal, respiratory muscles or both
III	Moderate weakness affecting muscles other than ocular muscles A: Predominantly affecting limb, axial muscles or both B: Predominantly affecting oropharyngeal, respiratory muscles or both
IV	Severe weakness affecting muscles other than ocular muscles A: Predominantly affecting limb, axial muscles or both B: Predominantly affecting oropharyngeal, respiratory muscles or both
V	Intubation with or without mechanical ventilation, except when used during routine postoperative management

Table 2 Subgroup classification of myasthenia gravis. AChR, acetylcholine receptor; LRP4, lipoprotein receptor-related peptide 4; MuSK, muscle-specific kinase

Subgroup	Common thymus pathology	Autoantibody and relative prevalence
Ocular	Variable	Variable
Early onset (<50 yrs)	Hyperplasia	AChR (80%)
Late onset (≥50 yrs)	Atrophy	AChR (80%)
Thymoma	Lymphoepithelioma	AChR (80%)
MuSK	Normal	MuSK (4%)
LRP4	Normal	LRP4 (2%)
Seronegative	Variable; normal/ hyperplasia	None detected (5%)

Diagnosis

- Clinical
- Serological - AChR Ab, anti-MuSK, anti-LRP4 Abs
- TFTs
- Seronegative -neurophysiological studies
- Repetitive nerve stimulation -progressive decline in motor action potential amplitude
- If inconclusive, EMG
- Edrophonium test -rare
- CT /MRI mediastinum

Management

- Acetylcholinesterase inhibitors
- Immunosuppression - prednisolone
- Non-steroidal immunosuppressives – azathioprine
- Mycophenolate mofetil, methotrexate, ciclosporin, rituximab
- i.v. immunoglobulin or plasma exchange + steroids
- **Thymectomy**: 1) Thymoma
  2) No thymoma + anti-AChR antibodies <45 yrs
- Reduces steroid requirements, prevents generalisation, induces remission

Thymectomy

- Experienced surgeon/anaesthetist/neurologist
- Control pre-op, even if delays procedure
- Traditionally median sternotomy
- Now minimally invasive – VATS/Robotic
- Reduced respiratory /cardiac complications, less blood loss, decreased inflammatory cytokine response, less postop pain, early removal chest drains, shorter LOS
- Remission – asymptomatic without Acetylcholinesterase inhibitors.

Preoperative

- Clinical optimisation –neurologist
- Preop IVIg or PEX
- Morning surgery -muscle function optimal
- History -bulbar symptoms, myasthenic crises
- Associated AI diseases
- Review medication- Anticholinesterases/ glucocorticoids continue periop
- Azathoprine – can stop temporarily
- Periop cover with steroids
- Check BM

Preoperative- Investigations

- FBC, U&Es, hepatic function ,TFTs
- 12-lead ECG - cardiac involvement?
- Review imaging – thymoma?
- PFTs –if NMBDs or major surgery
- FVC -Most reproducible and easily performed investigation
- VCs of 65-79%, 50-64% and <50% predicated are mild, moderate and severe respectively

RFs for post op ventilation/ Myasthenic crisis

Patient	Disease related	Surgical
COPD	Duration > 2yrs	Blood loss >1000ml
BMI>28	Bulbar/resp symptoms	Lung resection
	Generalised moderate dz	
	Previous myasthenic crisis	
	Pyridostigmine>750mg/day	
	VC<2-2.9L	
	Nerve stim decremental response >18-20%	

Intraop – avoid GA?

- Sedation - SA agents, titrate carefully
- Care with opiates
- Antimuscarinic anticholinergics eg glycopyrrolate. Minimal effects at nicotinic receptors –reduce secretions
- RA
- Neuraxial / brachial plexus blocks – caution
- Avoid ester LAs-metabolism impaired by anticholinesterases

Intra-op GA

- SA agents
- Unpredictable response to NMBDs and neostigmine
- Residual paralysis - **myasthenic crisis**
- Excess reversal - **cholinergic crisis**
- NMBDs - avoid if possible
- TIVA - propofol and remifentanil
- SA agents - opioids, lidocaine or esmolol, to facilitate intubation
- Inhalational induction- can avoid NMBDs
- Pressure support/IPPV
- Multimodal analgesia

NMBDS and reversal

- Reduced AChR density -Sux resistant
- Sensitive to nondepolarising NMBDs
- 0.1 dose, monitor NMJ
- Pyridostigmine prolongs action of sux
- Neostigmine – unpredictable. Risk cholinergic crisis
- SUGAMMADEX
- Effective and safe
- Rapid, complete reversal, successful extubation ,no postop complications
- Reduce risks periop myasthenic crises / pneumonias

Emergence

- Most safely extubated at end of surgery
- Appropriately positioned and preoxygenated, adequate return of spontaneous breathing, reflexes,muscle strength
- Monitor NMJ quantitatively
- TOFR >0.9 minimum
- Recent evidence - postop pulmonary complications reduced for TOFR >0.95 in patients without MG

Other medications

- Not complete list
- Care with antibiotics (clindamycin, vancomycin), anticonvulsants (gabapentin, phenytoin), antipsychotics (prochlorperazine) & Ca channel blockers
- Doses anticholinesterases missed during long procedures – post-op weakness
- Pyridostigmine 60 mg PO = 2 mg iv

Table 3 Drugs associated with exacerbation of myasthenia gravis (MG). MGFA, Myasthenia Gravis Foundation of America

Drug	MGFA recommendation
Aminoglycoside antibiotics	Use cautiously if no alternative treatment available
Beta blockers	Use cautiously
Botulinum toxin	Avoid
Corticosteroids	May cause transient worsening within the first 2 weeks
D-penicillamine	Strongly associated with causing MG; avoid
Desferrioxamine	May worsen MG
Fluoroquinolones	Use cautiously, if at all
Iodinated radiologic contrast agents	Use cautiously and observe for worsening; modern contrast agents appear to be safer
Ketolides (e.g. telithromycin)	Should not be used in MG
Macrolide antibiotics	Use cautiously, if at all
Magnesium	Use only if absolutely necessary and observe for worsening
Procainamide	Use with caution
Statins	Use cautiously if indicated and at the lowest dose necessary

Post op care

- Individualised
- Effective postop analgesia
- Sedation, RA or GA without NMBDs -day surgery?
- Admit if bulbar/ respiratory weakness. Consider ICU
- Routine ICU admission after thymectomy unnecessary with good perioperative preparation and management
- Myasthenic crisis - critical care admission

Myasthenic crisis

- Severe respiratory /bulbar muscle weakness
- Intubated -inadequate return of spontaneous ventilation and muscle power, weak cough, accessory muscle use
- Awake- dysphonia, dysphagia, weak cough, airway obstruction, rapid shallow breathing pattern
- VC <20-25ml/kg (30-40% predicted)
- Delay extubation or reintubate
- Consider NIV
- Neurological assessment, high-dose steroids, IVIg or PEX

Cholinergic Crisis

- Rare
- Precipitated by anticholinesterases
- Resemble OP poisoning
- Excess cholinergic activity - paradoxical weakness, bradycardia, hypotension, bronchospasm, increased secretions, sweating, vomiting and diarrhoea
- Tx -Atropine or glycopyrrolate
- Avoid further anticholinesterases
- Delay extubation. ICU

Pregnancy

- Optimise pre-pregnancy
- If controlled likely to remain stable
- MDT
- If severe weakness, manage in specialist centre
- Exacerbations - first trimester and postpartum
- Early anaesthetic assessment
- Epidural in labour
- Muscle weakness in second stage - instrumental delivery
- Supplement epidural to provide lumbosacral anaesthesia

Caesarian section

- GA advisable if significant weakness
- Consider additional RA
- Neonatal critical care access
- Transient neonatal MG up to 30%
- High autoantibodies – increased risk
- Neonates symptomatic 3-72 h after birth
- May require nutritional support, acetylcholinesterase inhibitors, IVIg mechanical ventilation

Pre-eclampsia

- Severe hypertension -methyldopa / hydralazine
- B- blockers / Ca channel blockers - avoid where possible
- Magnesium impairs NM transmission –avoid!
- Eclamptic seizure - Mg - **caution**. Tracheal intubation may be necessary
- Seizure prophylaxis - levetiracetam or valproate
- Phenytoin- refractory seizures

Summary

- Generalised weakness
- MDT approach
- Pathophysiology
- Principles - avoid exacerbation of muscle weakness and preserve respiratory function
- Optimum control pre-op
- Several factors can exacerbate weakness or precipitate myasthenic crisis
- Avoid NMBAs
- Rocuronium and sugammadex - effective
- Obstetric anaesthesia – care!