TERUMOBCT
Unlocking the Potential of Blood

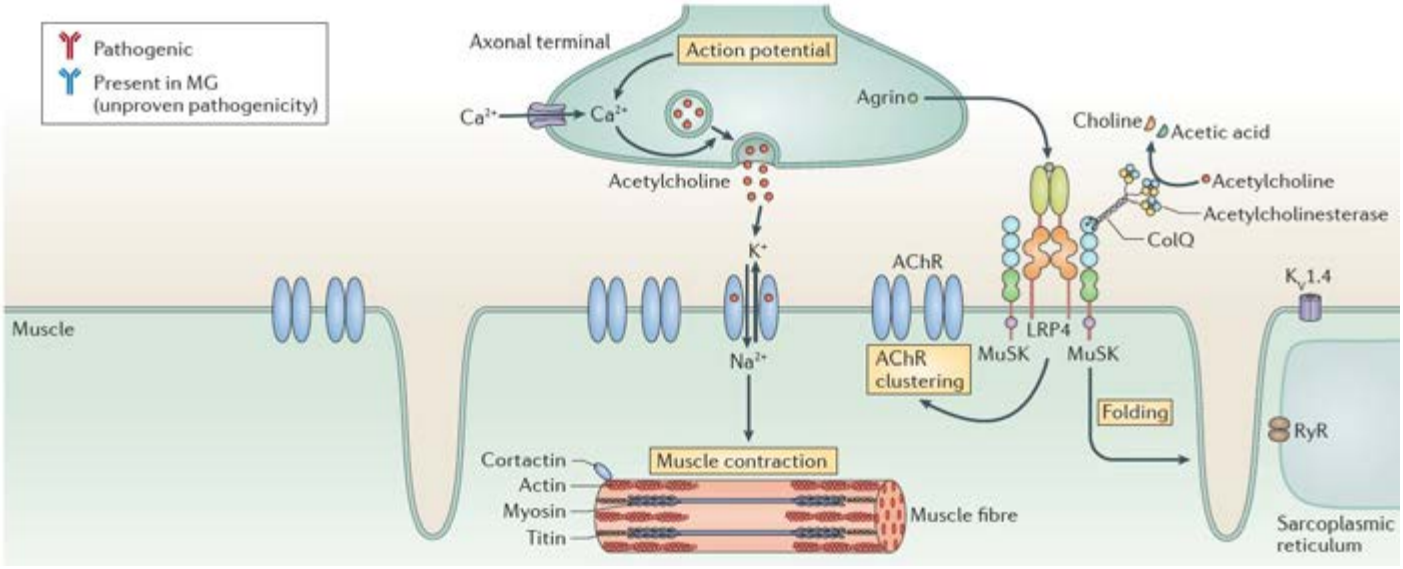
MYASTHENIA GRAVIS (MG)

CLINICAL SUMMARY SHEET

OVERVIEW

Myasthenia gravis (MG) is a rare autoimmune disease caused by antibodies directed against proteins in the postsynaptic membrane of the neuromuscular junction (NMJ: Figure 1).[1] These pathogenic antibodies result in a classic pathology,[2] translating into reduced, fatigable[3,4] muscle function.[5] A particular challenge with MG is the management of myasthenic crisis, which leads to acute respiratory failure that requires ventilatory support.[6-8] Many stressors can precipitate a myasthenic crisis,[9] and approximately 15 to 20 percent of patients with MG experience at least one episode of myasthenic crisis.[7]

Figure 1: *NMJ showing the major components implicated in MG*[10]



AChR, acetylcholine receptor; ColQ, collagen-tailed subunit of acetylcholinesterase; Kv1.4, voltage-gated potassium channel 1.4; LRP4, low-density lipoprotein receptor-related protein 4; MG, myasthenia gravis; MuSK, muscle-specific kinase; NMJ, neuromuscular junction; RyR, ryanodine receptor.

MG comprises several different conditions that are classified according to antibodies, age of onset, and accompanying thymic involvement (Table 1).[10-13]

Table 1: *Characteristics of MG subgroups*[10-13]

SUBGROUP	ANTIBODY	ADDITIONAL ANTIBODIES	AGE AT ONSET	PATIENTS (%)	AFFECTED MUSCLES	THYMUS
Early-onset	Anti-AChR	Rare	< 50 years	15–25	Generalized	Hyperplasia common
Late-onset	Anti-AChR	Common	> 50 years	35–45	Generalized	Atrophy common
Thymoma	Anti-AChR	Very common	Any	10	Ocular, bulbar, neck, generalized	Lymphoepithelioma
MuSK	Anti-MuSK	Rare	Any	1–10	Ocular, bulbar, neck, generalized	Normal
LRP4	Anti-LRP4	Rare	Any	1–5	Bulbar	Normal
Seronegative	None of the above detected	Variable	Any	10–15	Ocular, generalized	Variable
Ocular	Variable	Rare	Any	15	Ocular	Variable

AChR, acetylcholine receptor; LRP4, low-density lipoprotein receptor-related protein 4; MG, myasthenia gravis; MuSK, muscle-specific kinase.

EPIDEMIOLOGY

Worldwide prevalence of MG is 7.8 cases per 100,000 people.[14] In the United States, the incidence of MG is 1 per 100,000,[4] and the prevalence is estimated to be 20 per 100,000.[15] The disease is most common in females younger than 40 years and males older than 50 years.[1,16,17] Juvenile MG is rare.[18]

ASSOCIATIONS

Other autoimmune diseases are commonly associated with MG (Table 2), and the most common comorbidity is autoimmune thyroid disease (10%).[19]

Table 2: *MG subgroups and associated autoimmune disorders*[13]

MG SUBGROUP	ASSOCIATED AUTOIMMUNE DISORDERS
Early-onset	Autoimmune thyroid disease, systemic lupus erythematosus, type 1 diabetes mellitus, alopecia areata totalis, giant cell myocarditis, neuromyelitis optica, myositis, pure red cell aplasia, autoimmune hepatitis, Sjögren's syndrome, Addison's disease, dermatomyositis/polymyositis, Guillain-Barré syndrome
Late-onset	Hashimoto's disease, systemic lupus erythematosus, multiple sclerosis
Thymoma	Systemic lupus erythematosus, neuromyotonia, Sjögren's syndrome, autoimmune hemolytic anemia, POEMS syndrome
MuSK	Anti-MuSK
LRP4	Lambert-Eaton myasthenic syndrome, neuromyelitis optica
Seronegative	–
Ocular	Autoimmune thyroid disease

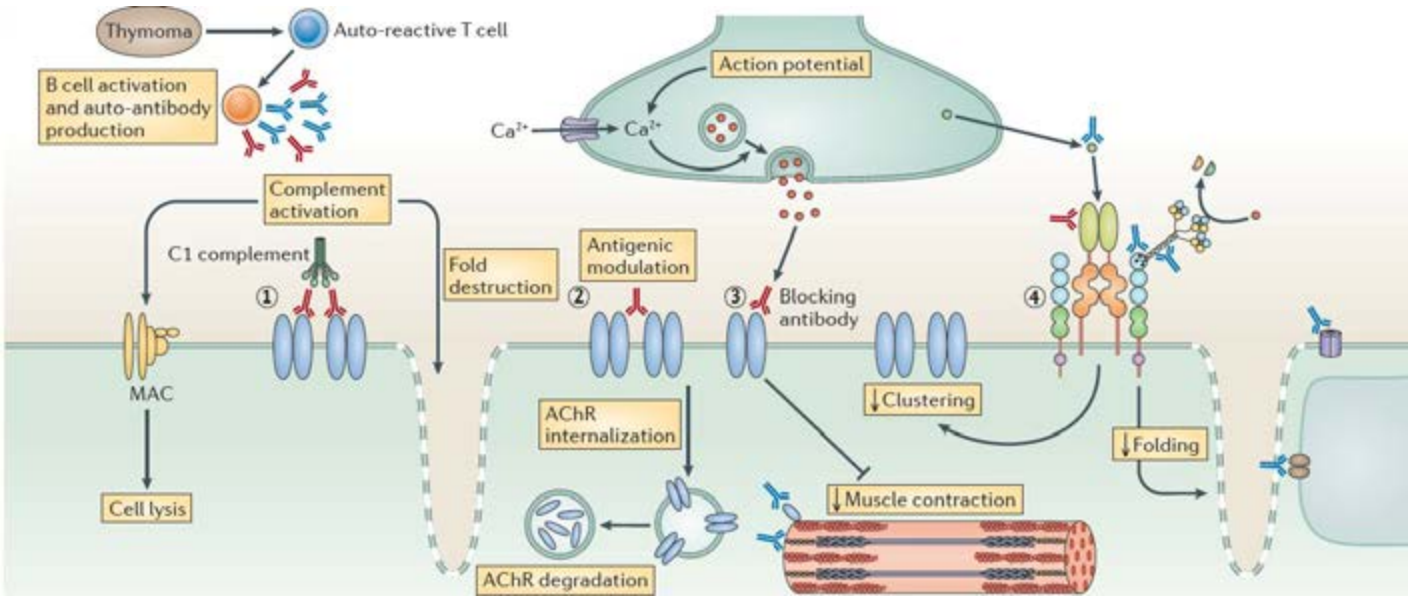
LRP4, low-density lipoprotein receptor-related protein 4; MG, myasthenia gravis; MuSK, muscle-specific kinase; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.

Prompt treatment for comorbidities is important for quality of life, performance of daily functions, short- and long-term prognosis, and survival.[11] Muscle weakness associated with MG may increase the risk of respiratory infections, osteoporosis, and weight gain. General, widespread myopathy may develop in patients with MG.[20]

PATHOGENESIS

Eighty-five percent of patients with generalized MG, as well as 50 percent with ocular MG, have pathogenic immunoglobulin G1 (IgG1) and IgG3[3] antibodies to acetylcholine receptors (AChRs; Figure 2).[21,22] Classical complement activation forms membrane attack complexes (MACs) on the muscle membrane and results in a characteristic NMJ rearrangement with internalization and degradation of surface AChRs.[10] These pathogenic processes reduce ACh function in the NMJ.[10]

Figure 2: *Major pathogenic mechanisms of the AChR antibodies in MG*[10]



1) Complement activation at NMJ; 2) Antigenic modulation; 3) Binding of AChR antibodies; 4) Normal mechanisms for maintenance of the organization of the NMJ (see Figure 1). Antibodies with known pathogenic involvement in MG are shown in red. AChR, acetylcholine receptor; MAC, membrane attack complex; MG, myasthenia gravis; NMJ, neuromuscular junction.

Other MG patients have autoantibodies that are reactive to muscle-specific kinase (MuSK), a transmembrane tyrosine receptor kinase that is required for the development and maintenance of AChR clusters at the NMJ.[12,22,23] The post-synaptic structure is disrupted when pathogenic IgG4 MuSK antibodies bind to MuSK, preventing low-density lipoprotein receptor-related protein 4 (LRP4) from binding MuSK and thereby inhibiting agrin-stimulated MuSK phosphorylation.[24] Other patients can have antibodies against LRP4 with similar deleterious effects.[12,25] Some patients with MG do not have detectable antibodies against AChR, MuSK, or LRP4 and are classified as having the seronegative form of disease.[10]

SYMPTOMS AND SIGNS

The hallmark characteristic of patients with MG is fatigable weakness,[26] often including ptosis and diplopia (Table 3).[4]

Table 3: *Clinical features of MG*[15]

CATEGORY	SIGNS AND SYMPTOMS
Ocular	1. Ptosis—asymmetric, fatigue with upgaze 2. Diplopia—the most commonly involved extraocular muscle is the medial rectus
Bulbar	1. Dysarthria—lingual, buccal, palatal (nasal speech) 2. Dysphagia—excessive clearing of the throat, recurrent pneumonias (subtle signs) 3. Dysphonia—hoarseness 4. Masticatory weakness—jaw fatigue, jaw closure more affected than jaw opening
Facial	1. Eyelid closure—inability to bury eyelashes with forced eye closure 2. Lower face—poor cheek puff, drooling
Limb muscles	1. Commonly proximal, symmetric 2. Arms more affected than legs 3. Rarely focal
Axial muscles	1. Neck flexion 2. Neck extension (head drop)
Respiratory muscles	1. Exertional dyspnea—weak sniff and cough 2. Orthopnea, tachypnea 3. Respiratory failure

Certain common prescription medications are associated with worsening MG symptoms:[1]

1. Telithromycin
2. Azithromycin
3. Ciprofloxacin/levofloxacin
4. Gentamicin/neomycin
5. Botulinum toxin
6. Corticosteroids
7. Quinine
8. Procainamide
9. Beta-adrenergic receptor blockers
10. Magnesium
11. D-penicillamine
12. Live, attenuated vaccines (shingles, nasal influenza); should be avoided in patients receiving immunosuppressants

DIAGNOSTIC CRITERIA AND TESTS

A number of tests are available to confirm a diagnosis of MG (Table 4).

Table 4: *Diagnostic tests for MG*[15]

TEST	DETAILS
Bedside Edrophonium test Ice pack test	 Reliable in patients with ptosis/extraocular weakness Used only when assessing improvement in ptosis
Electrophysiological Repetitive nerve stimulation Single-fiber electromyography	 Sensitivity is 75% in generalized MG and < 50% in ocular MG patients Highly sensitive (95%–99%), but not specific
Immunological (autoantibodies) Anti-AChR (binding) Anti-MuSK Low-affinity anti-AChR Anti-titin Anti-ryanodine receptor	 Sensitivity is 85% in generalized MG and 50% in ocular MG Detected in 40% of AChR-negative generalized MG Detected in 66% of AChR and MuSK-negative generalized MG Detected in 95% thymomatous MG and 50% late-onset non-thymomatous MG Detected in 70% of thymomatous MG (more severe disease)
Other CT scan or MRI of chest Thyroid function testing	 Obtain in all patients after diagnostic confirmation of MG –

AChR, acetylcholine receptor; CT, computed tomography; MG, myasthenia gravis; MRI, magnetic resonance imaging; MuSK, muscle-specific kinase.

Certain diseases may closely mimic MG and should be considered in the differential diagnosis (Table 5).

Table 5: *Differential diagnosis of MG*[1]

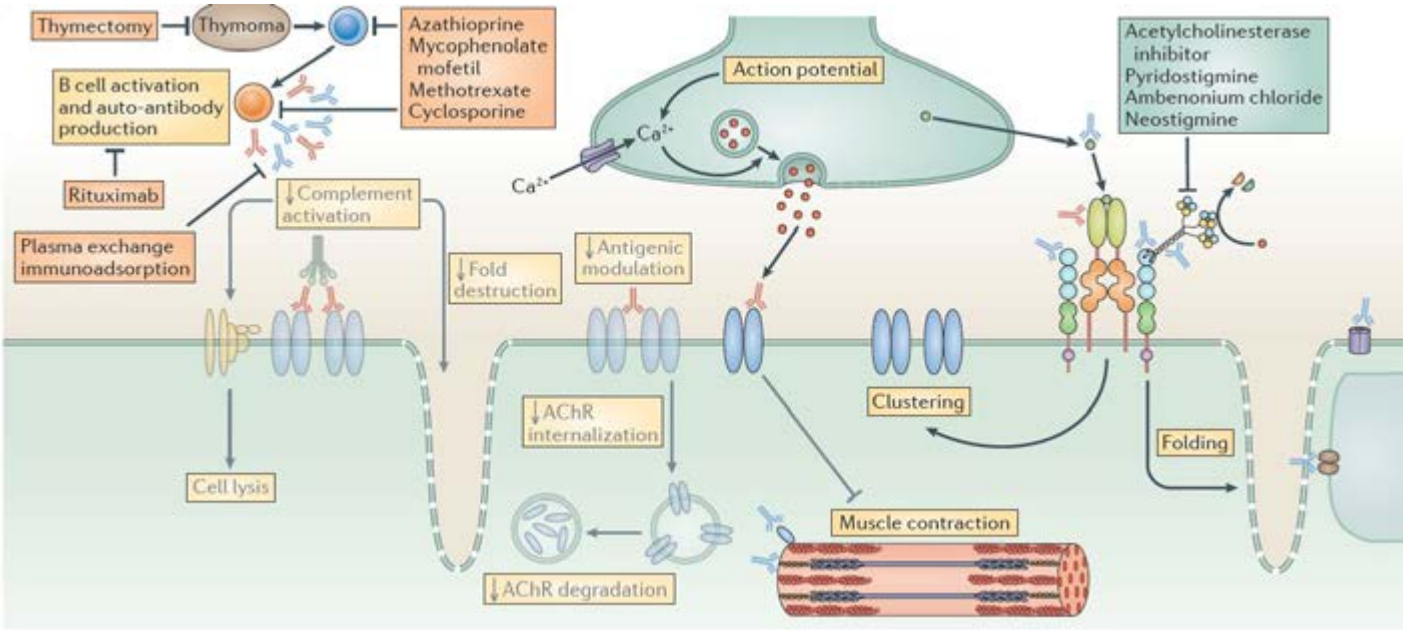
DISEASE THAT MAY CLINICALLY MIMIC MG	DIFFERENTIATING FEATURES
Lambert-Eaton myasthenic syndrome	Proximal extremity weakness Areflexia Dry mouth Voltage-gated calcium channel antibodies
Congenital myasthenic syndromes	Usually starts in infancy/childhood
Miller-Fisher syndrome	Areflexia Sensory ataxia GQ1b antibodies
Brainstem strokes	Neighborhood signs (facial numbness, Horner's syndrome) Acute onset
Mitochondrial myopathies	Progressive external ophthalmoplegia without diplopia Very gradual onset

MG, myasthenia gravis.

CURRENT MANAGEMENT

Symptomatic pharmacologic treatment, immunomodulatory treatment, plasma exchange, and thymectomy are the main therapeutic options for MG[12,27] and individualized for each MG subgroup (Figure 3).[10]

Figure 3: *Restoring the function of the NMJ*[10]



AChR, acetylcholine receptor; MG, myasthenia gravis; NMJ, neuromuscular junction.

In 2016, the Myasthenia Gravis Foundation published an international formal consensus-based guidance for the management of MG.[28] The guidance for various treatment options for MG is summarized below, along with additional supporting data.

Acetylcholinesterase (AChE) Inhibitors

First-line therapy for nearly all patients with MG should be the reversible cholinesterase inhibitor pyridostigmine.[12,28,29] Pyridostigmine[27] is most effective in patients with generalized and ocular MG[1] and less effective in those with MuSK-positive MG.[30,31] In patients who do not meet treatment goals by following a regimen of pyridostigmine, corticosteroids or immunosuppressive therapy should be considered.[28]

Common adverse events associated with AChE inhibitors include nausea; vomiting; diarrhea; abdominal cramps; increased peristalsis, salivation, and bronchial secretions; miosis; diaphoresis; muscle cramps; fasciculation; and weakness.[29]

Key Study Covering AChE Inhibitors

Table 6 summarizes data from a key study covering AChE inhibitors that was included in a systematic review of the literature through July 2014.[32]

Table 6: *Key study covering AChe inhibitors*[32]

TRIAL DETAILS	ACHE INHIBITOR	OUTCOME
Badrising 1996[33]: Randomized controlled trial. n = 10	4.5 mg intranasal neostigmine or placebo three times daily for 2 consecutive weeks preceded by a baseline observation week.	1. Improvement in generalized MG occurred in two of five participants with ocular symptoms, four of four with bulbar symptoms, and four of seven participants with impaired muscle power. 2. Dyspnea improved in two participants with this symptom. 3. One participant experienced no effect. 4. One of three participants with ocular MG had less ptosis with neostigmine. 5. None of the participants receiving a placebo showed improvement.

AChe, acetylcholinesterase; MG, myasthenia gravis.

IMMUNOSUPPRESSIVE AGENTS

Generally, corticosteroids (prednisone and prednisolone) improve muscle strength in all MG subtypes,[27] and corticosteroid administration in patients with ocular MG may prevent progression to generalized MG.[34,35] If treatment goals are reached, the dose of corticosteroid should be tapered, and a low-dose corticosteroid given long-term is often necessary.[28] When corticosteroids are contraindicated, not tolerated, ineffective, or refused, an immunosuppressant agent should be considered.[28]

Azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, and tacrolimus are used to treat MG.[28] Azathioprine is the preferred first-line non-steroid immunosuppressive agent in MG and is often co-administered with corticosteroids.[12,28] Cyclosporine is effective;[28] however, it is not typically used because of safety risks and drug-drug interactions.[28] Mycophenolate mofetil and tacrolimus are widely used to treat MG and are recommended by some national treatment guidelines.[28,36,37] Recent results of a 12-month randomized, double-blind, placebo-controlled trial of methotrexate versus placebo in patients with MG showed that methotrexate had no steroid-sparing effect.[38]

Once patients have met and maintained treatment goals for 6 months to 2 years, the non-steroidal immunosuppressive agent should be tapered to the lowest effective dose.[28] It is common for patients to require immunosuppressive drugs for many years, and sometimes for the rest of their lives.[28] Patients with MuSK-MG often have a favorable response to immunosuppressive therapy.[39]

Key Studies Covering Immunosuppressive Agents

Table 7 summarizes key studies covering immunosuppressive agents that were included in a systematic review of the literature through July 2007.[40]

Table 7: *Key studies covering immunosuppressive agents*[40]

TRIAL DETAILS	AGENT	OUTCOME
De Feo 2002[41]: Randomized, double-blind, controlled trial of cyclophosphamide plus prednisolone versus prednisolone plus placebo. n = 23; 12 in the cyclophosphamide (CP) plus corticosteroids group, 11 in the corticosteroids plus placebo group.	Intravenous cyclophosphamide (CP) 500 mg/m^2 of body surface and titrated according to response or side effects versus placebo.	1. Reductions of methylprednisone doses were noted in both groups but were more pronounced in patients receiving CP than placebo at 6 months $P < 0.05$) and at 12 months ($P < 0.03$). 2. At 12 months, 5 patients on CP had tapered off their steroids; no patient on placebo achieved further reductions ($P < 0.03$). 3. CP improved muscle strength at 3 and 6 months, and this improvement reached statistical significance compared with placebo at 12 months, mainly in the bulbar and masticatory ($P < 0.009$) and extraocular muscles ($P < 0.03$).
Gajdos 1993[42]: Randomized, unblinded, controlled trial of azathioprine plus initial prednisolone versus prednisolone. n = 41; 21 were randomized to receive prednisolone for the first month plus azathioprine, and 20 received prednisolone.	Prednisolone (1 mg/kg daily for 1 month, subsequently reduced to 0.5 mg/kg daily by 5 months and to 0.25 mg/kg daily by 10 months) versus azathioprine (3 mg/kg daily for 1 year and then 2 mg/kg daily). In the latter group, participants were also given prednisolone 1 mg/kg daily for 1 month, which was then gradually tapered and discontinued.	1. 21 patients showed deterioration: 12 in the prednisone group and 9 in the azathioprine group ($P = 0.40$) during the 30-month follow-up. 2. No differences were noted between groups in muscular score and functional grade or in tolerance. 3. Treatment failure occurred in 12 patients in the prednisone group and in 5 patients in the azathioprine group ($P = 0.02$).

TRIAL DETAILS	AGENT	OUTCOME
Meriggioli 2003[43]: Randomized, double-blind, controlled pilot study. One group received mycophenolate mofetil (MMF) plus either cyclosporine or prednisolone or no immunosuppressants; another group received placebo plus either cyclosporine or prednisolone or no immunosuppressants. n = 14; 7 in the MMF plus either cyclosporine or prednisolone or no immunosuppressants group, and 7 in the placebo plus either cyclosporine or prednisolone or no immunosuppressants group.	MMF (1 g twice daily) in one group versus placebo in the other group. Five participants in each group were also on prednisolone. One participant in each group was also on cyclosporine. Two participants in each group were on MMF monotherapy.	1. Patients who received MMF improved by 2.86 QMG points versus 0.29 points on average for placebo (P = 0.30). 2. Median change of antibody titer was 1.1 nmol/L in the MMF group and was 0.1 nmol/L in the placebo group (P = 0.52).
Nagane 2005[44]: Randomized, unblinded, non-placebo-controlled pilot trial of tacrolimus plus corticosteroids with/without plasma exchange versus no tacrolimus plus corticosteroids with/without plasma exchange. n = 34; 18 in the tacrolimus plus corticosteroids with/without plasma exchange group, 16 in the no tacrolimus plus corticosteroids with/without plasma exchange group.	Tacrolimus (FK506) was administered orally at a dose of 3 mg/day. For early-phase therapy, participants received tacrolimus or prednisolone or both. The prednisolone dose was tapered and adjusted to the minimal dose needed to maintain minimal manifestations. For the follow-up phase, participants were treated to maintain minimal manifestations for one year; plasma exchange plus high-dose intravenous methylprednisolone, high-dose intravenous methylprednisolone alone, or pyridostigmine was administered as needed to maintain minimal manifestations..	1. Low-dose FK506 reduced the duration of early-phase therapy in hospital (P < 0.05) and the need for combined therapy with plasma exchange and high-dose intravenous methylprednisolone or high-dose intravenous methylprednisolone alone (P < 0.05). 2. Low-dose FK506 reduced the daily dose of prednisolone (P < 0.05) required to maintain minimal manifestations of Myasthenia Gravis Foundation of America post-intervention status.
Palace 1998[45]: Randomized, double-blind, controlled trial of azathioprine plus prednisolone versus prednisolone plus placebo. n = 34; 15 in the azathioprine plus prednisolone group and 19 in the prednisolone plus placebo group	All participants received initial high-dose prednisolone (1.5 mg/kg or 100 mg on alternate days). Participants were also randomized to receive either azathioprine (2.5 mg/kg daily) or the equivalent dose of a matching placebo. The initial prednisolone dose was maintained until remission and then tapered to the minimum required to maintain remission.	1. No significant differences were noted between the two treatment groups in objective or subjective measurement scores at 12 months. 2. There was no significant difference between the two treatment groups in terms of number of participants experiencing treatment failure. 3. Duration of remission was significantly longer in the azathioprine plus prednisolone group compared with the prednisolone plus placebo group, giving a relative risk of 0.28 (95%, CI 0.08 to 0.94).

CI, confidence interval; QMG, quantitative myasthenia gravis score.

TRIAL DETAILS	AGENT	OUTCOME
Tindall 1987[46]: Double-blind, randomized, placebo-controlled trial of cyclosporine. n = 20	Cyclosporine 6 mg/kg was administered daily and then adjusted on the basis of assessments of blood drug levels, renal function, clinical response, and adverse events.	1. Seven of ten participants in the cyclosporine group and four of ten participants in the placebo group showed mild improvement at 6 months (relative rate of improvement was 1.75 [95%, CI 0.74 to 4.14]). 2. The cyclosporine group demonstrated a significantly greater increase in muscle strength. 3. Six participants in the cyclosporine group and five participants in the placebo group experienced treatment failure, giving a relative risk of 1.20 (95%, CI 0.54 to 2.67).
Tindall 1993[47]: Randomized placebo-controlled trial. n = 39	Cyclosporine was started at a dose of 5 mg/kg daily and adjusted on the basis of blood drug levels, renal function and adverse reactions. Corticosteroid withdrawal began at 2 months with a reduction of 10 mg if the dose was 60 mg every other day or lower, and 20 mg if the dose was 80 mg to 100 mg. From 3 to 6 months, the dose of corticosteroids was reduced by 10 mg/month. If weakness increased following reduction in corticosteroids, the dose was increased.	1. Eight of 20 participants in the cyclosporine plus prednisolone group improved. Two of the 19 participants in the prednisolone plus placebo group improved (relative rate of improvement was 5.70 [95%, CI 1.46 to 22.18]). 2. The cyclosporine group demonstrated a significantly greater increase in muscle strength than the placebo group.

CI, confidence interval; QMG, quantitative myasthenia gravis score.

Two monoclonal antibodies, rituximab and eculizumab, have shown promise for the treatment of MG. Results of a recent meta-analysis showed that rituximab was more effective in patients with MuSK antibodies versus those with AChR antibodies.[48] A retrospective analysis of patients with refractory MG (n = 14) suggests rituximab may lead to clinical improvement and reduction or discontinuation of corticosteroid use and therapeutic plasma exchange.[49] In a randomized, double-blind, placebo-controlled, crossover trial (n = 14), eculizumab was effective in treating severe, refractory MG.[50] Both of these small studies require replication.

Therapeutic Plasma Exchange (TPE)

TPE, also known as plasmapheresis, PE, PEX, or PLEX, is a procedure that removes a patient's plasma from the blood and replaces it with either fresh plasma or albumin.[4,51] Central venous catheters or peripheral veins can be used for venous access.[52] TPE may also be useful prior to beginning steroid treatment to relieve exacerbations of MG, to induce a rapid response, or to achieve a response after other treatments do not provide relief.[28] TPE is effective in patients with severe generalized MG[28] and has been shown to improve quality of life.[53] Most side effects (such as nausea, vomiting, and hypotension) associated with TPE are mild and are easily managed in patients with MG.[54] TPE is also recommended for maintenance therapy in patients with juvenile MG,[55] as well as in patients with refractory MG.[28]

Patients experiencing a myasthenic crisis should be hospitalized and monitored for respiratory and bulbar function and treated with TPE.[28] Compared with intravenous immunoglobulin (IVIg), TPE is associated with a superior ventilatory status 2 weeks post-myasthenic crisis, but TPE has higher complication rates.[56] Management guidelines published by the German Neurological Society recommend TPE in patients with myasthenic crisis.[57] Corticosteroids are often co-administered to sustain a clinical response.[28]

The American Society for Apheresis (ASFA) has published guidelines on the use of TPE for managing MG.[4] Highlights from the ASFA guidelines and key studies are outlined in Table 8.

Table 8: *Category and grade recommendation for TPE for the management of MG according to ASFA*[4]

INDICATION	CATEGORY	RECOMMENDATION	RANDOMIZED CONTROLLED TRIALS	CONTROLLED TRIALS	CASE SERIES
Moderate-severe	I	Grade 1B	8 (279)*	8 (2,837)	30 (556)†
Pre-thymectomy	I	Grade 1C	0	5 (342)	2 (51)†

*Number of trials/case series (total number of enrolled participants/patients).
†6 (405) case series contained both groups of patients; case series added anti-MuSK 110, with rippling muscle disease 2 (10).[4]
Category I: Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment.
Grade 1B: Strong recommendation with moderate-quality evidence; can apply to most patients in most circumstances without reservation.
Grade 1C: Strong recommendation with low-quality or very low-quality evidence; recommendation may change when higher-quality evidence becomes available.
ASFA, American Society for Apheresis; MG, myasthenia gravis; TPE, therapeutic plasma exchange.

Similarly, the European Federation of Neurological Societies recommends TPE for the short-term management of MG, especially in patients with severe disease or those undergoing surgery.[27] The Association of British Neurologists recommends TPE in patients with specific risk factors for IVIg.[37] The International consensus guidance for management of MG[28] suggests that TPE may be more effective than IVIg in the treatment of MuSK-MG. TPE and IVIg are used as short-term treatments for impending and manifest myasthenic crisis, as well as in patients with significant respiratory dysfunction. Although clinical trials suggest that TPE and IVIg are equally effective, this expert consensus suggests that TPE is more effective and works more quickly.

Key Studies Covering TPE

Table 9 summarizes the key studies covering TPE that were included in a systematic review of the literature through June 2002.[58]

Table 9: *Key studies covering TPE*[58]

TRIAL DETAILS	INTERVENTION	OUTCOME
Gajdos 1983[59]: Randomized controlled trial. n = 14	Group 1 received prednisone. Group 2 received prednisone and TPE.	1. Improvement in mean (SD) quantitative muscle score was not significantly greater in patients treated with TPE plus prednisone than in patients treated with prednisone alone 1 month after initiating treatment (79 [22] versus 62 [22]). 2. Mean (SD) muscle score values after 1 year were 82 (19) in the prednisone and plasma exchange group and 91 (6) in the prednisone-alone group. 3. More relapses (5) were observed in the TPE plus prednisone group in the first year compared with the prednisone-alone group (1).
Gajdos 1997[60]: Randomized controlled trial, two parallel groups. n = 87	Group 1 received 3 TPE treatments.	The mean (SD) change in the MMS score at day 15 was 16.6 (16) in the TPE group and 15.6 (15.9) in the IVIg group.
Kamel 2009[61]: Randomized controlled trial, two parallel groups. n = 35	Group 1 received 3 TPE treatments before thymectomy. Group 2 received no TPE treatments before thymectomy.	1. Duration of postoperative mechanical ventilation was 1.8 (1.3) hours in group 1 versus 2.9 (1.7) hours in group 2, with a mean difference of 1.10 hours (95% CI −2.12 to −0.08, P = 0.03). 2. Duration of ICU and hospital stay was lower in group 1 than in group 2.
Ronager 2001[62]: Randomized controlled crossover trial. n = 12	Group 1 received IVIg 0.4 g/kg for 5 days and then, 16 weeks later, received 5 TPE treatments. Group 2 received the same treatments on the opposite schedule.	1. Mean decrease in QMG from baseline to 1 week after TPE was 0.23 (P < 0.05) and after IVIg was 0.10 (NS). 2. From baseline to 4 weeks, the mean decrease in QMG after TPE was still significant and after IVIg was 0.23 (P < 0.05); change at 8 or 16 weeks was not significant in either group.

CI, confidence interval; ICU, intensive care unit; IVIg, intravenous immunoglobulin; MMS, myasthenic muscle score; NS, not significant; QMG, quantitative myasthenia gravis score; SD, standard deviation; TPE, therapeutic plasma exchange.

Intravenous Immunoglobulin (IVIg)

In a similar way to TPE, IVIg is reserved for specific situations in which acute treatment is necessary.[1,28] IVIg is effective in patients with severe generalized MG, but it may not be as efficacious in patients with milder MG or ocular MG.[28] IVIg may also not be as effective in patients with MuSK-MG.[28] IVIg may be used as maintenance therapy in patients with refractory MG or in cases in which immunosuppressive agents are contraindicated.[28] Like TPE, IVIg has been shown to improve quality of life in patients with severe MG and worsening symptoms.[53] IVIg is recommended for maintenance therapy in patients with juvenile MG, although it may not result in responses that are as consistent as those seen with TPE.[55]

Patients experiencing myasthenic crisis should be hospitalized and monitored for respiratory and bulbar function and may be treated with IVIg.[28] Corticosteroids are often also co-administered to these patients to sustain a clinical response.[28]

The AAN cautiously recommends IVIg for the treatment of MG, noting that IVIg is probably effective.[63] There is insufficient evidence to compare the efficacy of IVIg and TPE.[63]

Key Studies Covering IVIg

Table 10 contains key studies covering IVIg that were included in a systematic review of the literature through September 2011.[64]

Table 10: *Key studies covering IVIg*[64]

TRIAL DETAILS	INTERVENTION	OUTCOME
Barth 2011[65]: Randomized controlled trial, two parallel groups. n = 84	Group 1 received IVIg 2g/kg. Group 2 received five TPE treatments.	1. IVIg and TPE reduced the QMG, and IVIg was comparable to TPE in efficacy. 2. The presence of AChR antibodies and greater baseline disease severity predicted a better response to therapy. 3. Percentage of patients improved with treatment: 69% on IVIg and 65% on TPE.
Gajdos 1997[60]: Randomized controlled trial, two parallel groups. n = 87	Group 1 received three TPE treatments. Group 2a received IVIg 2 g/kg. Group 2b received IVIg 1.2 g/kg.	Myasthenic muscular score variation was similar in both groups (median value +18 in the TPE group and +15.5 in the IVIg group; (P = 0.65).
Gajdos 2005[66]: Randomized controlled trial, two parallel groups. n = 173	Group 1 received IVIg 1g/kg. Group 2 received IVIg 2 g/kg.	Mean improvements in the myasthenic muscular scores after 2 weeks were 15.49 points (95% CI, 12.09 to 18.90 points) in group 1 and 19.33 points (95% CI, 15.82 to 22.85 points) in group 2 (P = 0.12).
Ronager 2001[62]: Randomized controlled crossover trial. n = 12	Group 2b received IVIg 1.2 g/kg.	1. Mean decrease in QMG from baseline to 1 week after TPE was 0.23 (P < 0.05) and after IVIg was 0.10 (NS). 2. From baseline to 4 weeks, the mean decrease in QMG after TPE was still significant and after IVIg was 0.23 (P < 0.05); change at 8 or 16 weeks was not significant in either group.
Schuchardt 2002[64]: Randomized controlled trial, two parallel groups. n = 33*	Group 1 received methylprednisolone 1 mg/kg to 1.5 mg/kg for 14 days. Group 2 received IVIg 30 g/day for 5 days.	The mean (SD) sum of the two most pathological items of the QMG at day 0 was 3.9 (1.1) for the IVIg group and 4.2 (0.7) for the methylprednisolone group.
Wolfe 2002[67]: Randomized controlled trial, two parallel groups. n = 15	Group 1 received IVIg 1 g/kg for 2 days followed by IVIg 1 g/kg on day 22. Group 2 received 5% albumin for 2 days followed by 5% albumin on day 22.	1. At day 42, there was no significant difference between groups in terms of change in QMG. 2. The study was terminated early because of insufficient IVIg inventory.
Zinman 2007[68]: Randomized controlled trial, two parallel groups. n = 51	Group1 received IVIg 1 g/kg for 2 days. Group 2 received 5% dextrose for 2 days.	1. Clinically meaningful improvement in QMG score for disease severity was observed at day 14 and persisted at day 28 in patients who received IVIg. 2. The greatest improvement occurred in patients with more severe disease as defined by a QMG score for disease severity > 10.5.

*Unpublished data.

AChR, acetylcholine receptor; CI, confidence interval; IVIg, intravenous immunoglobulin; PE, plasma exchange; QMG score, quantitative myasthenia gravis score; SD, standard deviation; TPE, therapeutic plasma exchange.

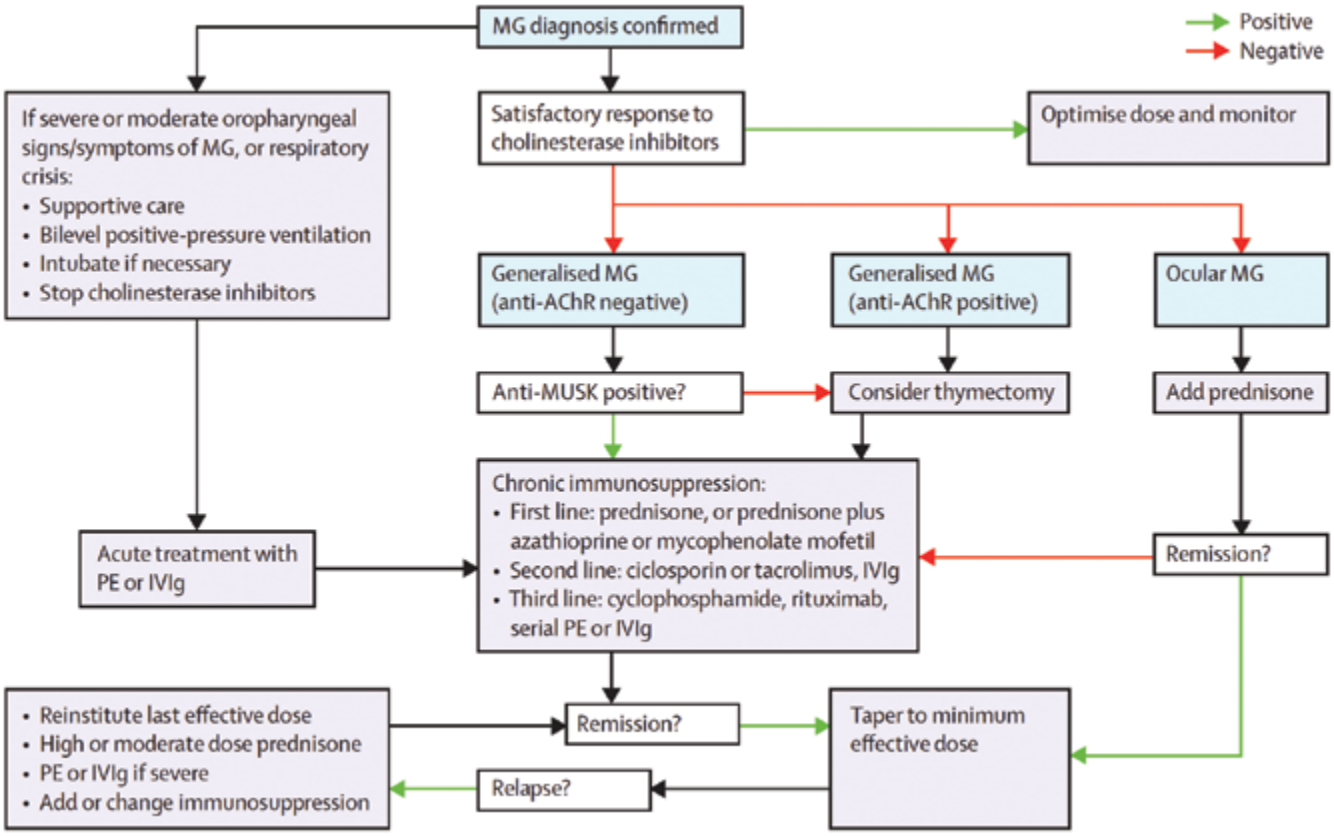
Thymectomy

In patients with thymoma, thymectomy should be performed to remove the tumor.[28] Removal of the tumor may not immediately alleviate symptoms of MG,[28] and clinical improvement may take years to achieve.[4]

Results of a recent multicenter, randomized trial indicate that thymectomy improves clinical outcomes in patients with non-thymomatous MG.[69] Patients (n = 126) were randomized to a thymectomy-plus-prednisone group and a prednisone-only group,[69] and quantitative myasthenia gravis score (QMG; scale 0 to 39, with 39 indicating more severe disease) was assessed.[69] Over a 3-year period, patients randomized to thymectomy plus prednisone had a lower-weighted mean QMG than patients who received prednisone alone (6.15 versus 8.99, P < 0.001).[69] The prednisone dose for patients in the thymectomy group was lower than that in the prednisone-only group (44 mg versus 60 mg, P < 0.001).[69] Fewer exacerbations were reported in the thymectomy group, with 9 percent of patients requiring hospitalization for exacerbations versus 37 percent in the prednisone group (P < 0.001).[69]

A proposed treatment algorithm for patients with MG is shown in Figure 4.

Figure 4: *Treatment flowchart*[15]



AChR, acetylcholine receptor; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MuSK, muscle-specific kinase; PE, plasma exchange.

PROGNOSIS

Available treatment options have decreased mortality due to MG from 30 percent to less than 5 percent.[4,12] Patients with mild to moderate symptoms often make a full recovery or at least substantial improvement.[12] However, patients with refractory MG should be referred to a physician or a medical center with expertise in the management of MG.[28] Similarly, the mortality rate due to myasthenic crisis is less than 5 percent.[70]

The MG composite scale is a validated and reliable outcome measure for MG (Table 11).[71] This scale, which can be used to assess the clinical status of patients with MG, is composed of physician- and patient-reported test items.[71]

Table 11: *The MG composite scale*[71]

Ptosis, upward gaze (physician examination)	> 45 seconds = 0	11–45 seconds = 1	1–10 seconds = 2	Immediate = 3
Double vision on lateral gaze, left or right (physician examination)	> 45 seconds = 0	11–45 seconds = 1	1–10 seconds = 3	Immediate = 4
Eye closure (physician examination)	Normal = 0	Mild weakness (can be forced open with effort) = 0	Moderate weakness (can be forced open easily) = 1	Severe weakness (unable to keep eyes closed) = 2
Talking (patient history)	Normal = 0	Intermittent slurring or nasal speech = 2	Constant slurring or nasal but can be understood = 4	Difficult to understand speech = 6
Chewing (patient history)	Normal = 0	Fatigue with solid food = 2	Fatigue with soft food = 4	Gastric tube = 6
Swallowing (patient history)	Normal = 0	Rare episode of choking or trouble swallowing = 2	Frequent trouble swallowing, e.g., necessitating changes in diet = 5	Gastric tube = 6
Breathing (thought to be caused by MG)	Normal = 0	Shortness of breath with exertion = 2	Shortness of breath at rest = 4	Ventilator dependence = 9
Neck flexion or extension (weakest) (physician examination)	Normal = 0	Mild weakness = 1	Moderate weakness (i.e., ~50% weak, ± 15%) = 3*	Severe weakness = 4
Shoulder abduction (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ± 15%) = 4*	Severe weakness = 5
Hip flexion (physician examination)	Normal = 0	Mild weakness = 2	Moderate weakness (i.e., ~50% weak, ± 15%) = 4*	Severe weakness = 5

*Moderate weakness for neck and limb items should be construed as weakness that equals roughly 50% ± 15% of expected normal strength. Any weakness milder than that would be classified as mild, and any weakness more severe than that would be classified as severe.

MG, myasthenia gravis.

SUMMARY

1. MG is an autoimmune disease of the NMJ with pathogenic antibodies targeting proteins in the postsynaptic membrane.
2. MG is characterized by fatigable weakness. There are seven main MG subgroups, which are characterized according to antibody involvement, age at onset, affected muscles, and thymus involvement.
3. Diagnostic tests include clinical, electrophysiological, and immunological tests, as well as other tests, such as CT scan or MRI and thyroid function tests.
4. Acetylcholinesterase inhibitors, immunosuppressive agents, TPE, and thymectomy are the accepted treatments for MG.
5. Prognosis is good for most patients, with mortality rates less than 5 percent.
6. TPE may be more effective than IVIg in the treatment of MuSK-MG.
7. Although clinical trials suggest that IVIg and TPE are equally effective in the treatment of impending or manifest myasthenic crisis, expert consensus suggests that TPE is more effective and works more quickly than IVIg.[28]

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