

## **A Guide to the Diagnosis & Management of Myasthenia Gravis**

Joël Oger, MD, FRCPC, FAA.

*In Memoriam*  
*Dr. John Newsom-Davis 1932-2007*

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### **Design & illustration:**

L. Waters, MFA, MScBMC, Waters Biomedical

### **Acknowledgements:**

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BIOTHERAPEUTICS

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To order your copy, please visit: < [www.myastheniagravisbooklet.com](http://www.myastheniagravisbooklet.com) >  
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## Introduction to the reader

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Dear Reader,

During my many years of following Myasthenia Gravis (MG) patients, I have noticed that physicians adhere to relatively similar therapeutic plans. Most helpful to MG patients, however, is the practitioner's attention to details that include a clear and exhaustive plan for drug titration. This detailed approach will make the patient confident that he or she has found the doctor in whom he or she can put his or her confidence.

This booklet has been written with neurology residents in mind as an easy reference document that they can access when they have to admit their first MG patient. It will also be useful to neurologists in general practice who need a refresher because one does not see a new MG patient often. It could also help other health care professionals when the time comes to counsel patients. I have often suggested to my patients to offer this type of booklet to their family doctors as soon as they have been diagnosed.

## **Section 1: Autoimmune Myasthenia Gravis (MG) — Classification**

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### **Acquired or Autoimmune Myasthenia Gravis (MG)**

- Ocular MG
- Bulbar Predominant MG
- Generalized MG

### **Classification of Autoimmune Myasthenia Gravis (MG) based on Antibodies**

- Acetylcholine Receptor Antibody positive MG
- Anti-MuSK (muscle specific kinase) Antibody Positive MG
- Antibody Negative Autoimmune MG

### **Forms of Autoimmune Myasthenia Gravis based on age at onset**

- Neonate
- Child
- Young Adult
- Elderly

## **Autoimmune Myasthenia Gravis (MG): Epidemiology and Pathophysiology**

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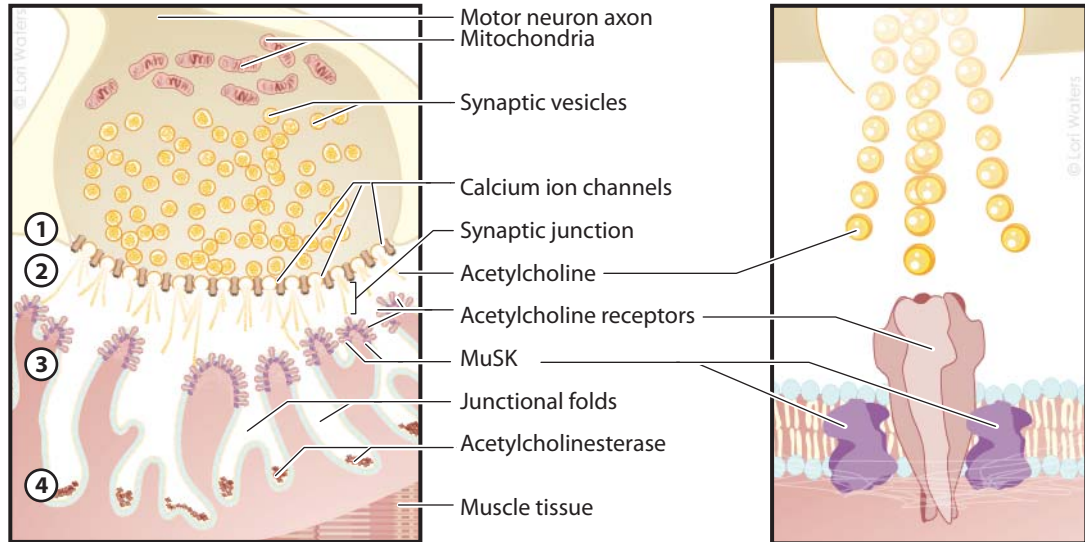
Myasthenia Gravis is a rare disease with a prevalence of 20/100,000. Most neurologists would not be expected to see more than 5 or 6 in their whole career unless they specialize in neuromuscular disorders or neuro-immunology. Similar to what is seen in other autoimmune disorders, there is evidence of a genetic predisposition and certain human leukocyte antigen (HLA) associations. There is no racial or ethnic predominance.

Two age groups have been identified as being preferentially affected: young, early onset (< 45 years of age; a group where women tend to predominate) and elderly, late onset (> 60 year of age; a group where men tend to slightly predominate).

As time passes, the disease becomes more common and is more frequently recognized among those over the age of 80, probably evidence of successful aging of the Western population and availability of testing.



**Figure 1. Physiology of the normal neuromuscular junction (NMJ)**



When the action potential reaches the NMJ, Ca<sup>++</sup> flows into (1) the voltage-gated channels releasing acetylcholine (ACh) from the presynaptic vesicles (2). ACh binds to the receptor at the top of the post junctional folds of the muscle membrane (3). Binding of ACh to the receptor results in opening of the channel pore (insert) permitting Na<sup>+</sup> influx in the muscle and initiating muscle contraction. Excess ACh is destroyed by acetylcholinesterase (4).

## Autoimmune Myasthenia Gravis: Ocular MG — Signs and Symptoms (cont'd)



① Left ptosis (Ocular MG)



② After icepack five minutes.  
(see Ice cube test — page 23).

## **Additional Tests: Staging of Disease**

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### **Osserman Classification of Myasthenia Gravis (modified from MGFA)**

#### **Class I – pure ocular**

- Any ocular weakness, may have weakness of eye closure;
- Strength of all other muscles is normal.

#### **Class II – ocular plus other deficits**

- IIa Mild weakness affecting limbs±bulbar muscles;
- IIb Predominantly affecting limbs ±oropharyngeal.

#### **Class III – moderate generalized**

- IIIa Moderate weakness Predominantly affecting limb, axial muscles, or both;
- IIIb Moderate generalized weakness predominantly affecting oropharyngeal, respiratory muscles, or both.

#### **Class IV – severe generalized**

- IVa Severe weakness affecting limbs;
- IVb Severe weakness affecting limbs. Predominantly affects bulbar muscles.

#### **Class V**

- Ventilator dependent except when used during routine postoperative management.

**Table 2 - Acetylcholinesterase Inhibitors**

<b>Pyridostigmine bromide</b>				
<b>Administration Route / Formulation</b>	<b>Dosage Form</b>	<b>Dose / Regimen (Adults)</b>	<b>Therapeutic Effect</b>	
			<b>Onset</b>	<b>Duration</b>
oral (tablet; Mestinon®)	60 mg/tablet	Initial: 60-120 mg q 3-4 hrs during waking hours	20-30 min	3-4 hrs
oral (extended-release tablet; Mestinon®-SR)**	180mg/tablet	1 tablet, 1-2 times/day (12 hrs between doses)**	30-60 min	6-12 hrs
oral (syrup; not commercially available can be made by a compounding pharmacist)	60 mg/5 mL	Up to ten 5-mL teaspoons, daily	20-30 min	3-4 hrs
IV (injection USP; Regonol®)	5 mg/mL (2 & 5 mL ampoules)	2 mg q 2-3 hrs	2-5 min	Up to 2 hrs
** poor bioavailability so should be used only at bedtime to relieve early morning symptoms				

<b>Neostigmine bromide</b>				
<b>Administration Route / Formulation</b>	<b>Dosage Form</b>	<b>Dose / Regimen (Adults)</b>	<b>Therapeutic Effect</b>	
			<b>Onset</b>	<b>Duration</b>
oral (tablet; Prostigmin®)	15 mg/tablet	Initial: 15 mg q 3-4 hrs. Maintenance: 150 mg/day (24-hr period)	45-75 min	3-6 hrs

<b>Neostigmine methylsulfate</b>				
<b>Administration Route / Formulation</b>	<b>Dosage Form</b>	<b>Dose / Regimen (Adults)</b>	<b>Therapeutic Effect</b>	
			<b>Onset</b>	<b>Duration</b>
IM, SC (injection USP; Prostigmin®)	0.5 mg/mL, 1 mg/mL, 2.5 mg/mL	0.5-2.5 mg every 1-3 hours (up to 10 mg/24 hrs max)	20-30 min	2-3 hrs

<b>Neostigmine methylsulfate</b>				
<b>Administration Route / Formulation</b>	<b>Dosage Form</b>	<b>Dose / Regimen (Adults)</b>	<b>Therapeutic Effect</b>	
			<b>Onset</b>	<b>Duration</b>
IV (injection USP; Prostigmin®)	0.5 mg/mL, 1 mg/mL, 2.5 mg / mL	0.5-2 mg administered slowly, every 1-3 hours (up to 10 mg/24 hrs maximum)	4-8 min	1 hr

## **Treatment: Corticosteroid Agents (cont'd)**

**The following treatment protocol for prednisone has been effective and safe:**

- Starting dose of 10 mg every other day.
- Increase dose by 5 to 10 mg every 4th day to reach 1 mg/kg/day every other day.
- Continue at this dose until patient reaches remission.
- Symptoms rarely worsen with this scheme. If worsening occurs, then treat with plasma exchange or IVIg.
- When the patient reaches remission, reduce and discontinue Mestinon®.  
An inability to discontinue Mestinon® indicates that patient is not well controlled.
- When remission (or a minimal symptomatic state) has been achieved, prednisone can be reduced progressively by 10 mg every 2 weeks to a dose of 50 mg every other day. Then by 5 mg every month until 25 mg e.o.d.
- Prednisone reduction is more easily achieved if an immunosuppressive drug is added.

**During the reduction in prednisone dosage:**

- The patient should be observed closely for re-appearance of signs and symptoms.
- If signs re-appear, it is necessary to increase the prednisone back to the dose at which the patient was minimally symptomatic.

## Treatment: Immunosuppressive Therapies — Azathioprine & Cyclosporin A

### Azathioprine (Imuran®) (Aza.)

- Recommended as first choice steroid-sparing medication;
- Aza. may take 12 months to be effective, but cyclosporine acts faster in a matter of a few weeks. It is still the only immunosuppressive agent shown to improve MG in an RCT (Palace et al).
- Generally well tolerated; rarely an acute idiosyncratic reaction occurs on initiation of therapy with fever and hepatitis. Treatment should be stopped immediately.
- Aza. has not been shown to be harmful to the fetus. Numerous uncomplicated pregnancies have occurred in transplant patients receiving Aza.
- Dosage with Aza. should rapidly reach 3mg/kg/day in 3 divided doses (gastric tolerance permitting) and the dose should be adjusted to the monthly blood work (CBC, WBC, Diff, platelets and ALP). See sliding scale on page 77.
- The administration of Aza. can reduce bone marrow maturation and lead to liver dysfunction with a micronodular cirrhosis.

## **Treatment: Intravenous Immunoglobulins (IVIg)**

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### **Mechanism of Action**

- In Myasthenia Gravis autoantibodies are pathogenic and are of the IgG class.
- IVIg reduces the amount of antibodies bound at the neuromuscular junction by increasing the total concentration of IgG circulating in serum and extra-cellular fluids. IVIg also modulates regulatory cells by binding to Fc receptors & anti-idiotypes.

### **Indication**

- IVIg is useful in myasthenic crisis, in preparing MG patients for surgery, and aiding diagnosis of seronegative MG.
- Available in areas without plasmapheresis centres. Its single draw back compared to use of plasma exchange is that it may act slightly more slowly.
- It is important to stress that IVIg does not stimulate the immune response so that it can be used chronically in very resistant cases.
- IVIg is expensive with a cycle of 2mg/kg/day costing in excess of \$10,000.

### **Side Effects**

- Allergic reactions, headache, occasional lymphocytes meningitis, clotting problems;
- Some premedicate patients with anti-histamine (Benadryl®).

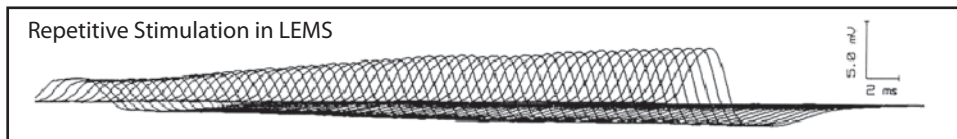


**Table 4: Intravenous Immunoglobulin (IVIg) versus Plasma Exchange (Plex)**

	<b>Intravenous Immunoglobulin (IVIg)</b>	<b>Plasma Exchange (Plex)</b>
<b>Mechanism of Action</b>	Downregulates production of anti-AChR antibodies; modulates T-cell function	Removes anti-AChR antibodies from extra-cellular space
<b>Indications</b>	Exacerbations of MG; myasthenic crisis; preparation for surgery; long term use in refractory MG	Exacerbations of MG; myasthenic crisis; preparation for surgery
<b>Treatment Regimen</b>	2 g/kg divided over 2-5 days	3 to 5 exchanges, daily or every second day
<b>Response Rate</b>	IVIg = Plex	IVIg = Plex
<b>Onset of Action</b>	≥ 3-4 days	Within 1-2 days
<b>Duration of Effect</b>	1-2 months (IVIg = Plex)	1-2 months (IVIg = Plex)
<b>Efficacy</b>	IVIg = Plex	IVIg = Plex
<b>Side Effects</b>	Platelet aggregation problems, Allergic reactions, Lymphocytic meningitis (rare)	BP variations, venous access problems, duration of procedure= 3-5 hours,
<b>Cost</b>	\$9,800 / 1 gram	\$5,120 + indirect costs / sitting
<b>Availability</b>	Widely available - infused in outpatient clinics	Requires special equipment & expertise; available in very few tertiary care centres

## MG Variants — Lambert Eaton Myasthenic Syndrome (LEMS) (cont'd)

- Presence of voltage-gated calcium channel antibodies in >90% of patients.
- Surgical removal of the primary neoplasm may greatly improve LEMS symptoms.
- Symptomatic treatment includes 3, 4-diaminopyridine (10-20mg four times/day-risk of seizure with higher doses.), quinidine, or 4-aminopyridine. Mestinon® by itself is not effective but can work synergistically with 3, 4-diaminopyridine.
- Immune directed treatment can be added when tumour removal is insufficient; it will be the sole treatment for the autoimmune form: dosage of Azathioprine is same as in MG (see page 53).
- IVIg (2 g/kg, divided over 2-5 days) as an adjunct to immunosuppressive therapy.
- Plasmapheresis would only be used as induction.



## Appendix 1: Medications Contra-indicated in Myasthenia Gravis

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1. **CURARE Derivatives** but also  
Methoxyflurane (Penthrane®)

### 2. ANTIBIOTICS

(mostly aminoglycosides)

- **Neomycin, Streptomycin, Gentamicin**
- Kanamycin, Tobramycin, Amikacin
- Polymyxin B, Colistins
- Tetracyclines,
- Erythromycin
- Azithromycin
- Lincomycin
- Clindamycin
- Ampicillin
- Vancomycin
- Viomycin
- Ketek (Telithromycin)

### 3. CARDIOVASCULAR DRUGS

- Bretylium
- **Quinidine**
- **Procaine, Procainamide**, Lidocaine
- Labetalol chlorhydrate (Trandate®)

- Propranolol, Oxprenolol, Practolol &  
other beta blockers
- Accupril® & other ACE inhibitors
- Verapamil and Calcium Channel  
Blockers

### 4. CNS ACTIVE DRUGS

- Chlorpromazine and Promazine
- Lithium
- Diphenylhydantoin &  
Trimethadione
- Trihexyphenidyl (Artane®)

### 5. OTHERS:

- Trimethaphan (antitussif  
in many cough preps.)
- Chloroquine
- D-Penicillamine
- Emetine
- Quinine
- Magnesium

Medications  
in **bold** are  
**dangerous**  
in MG

## Appendix 4: Further Reading

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Evaluation of diagnostic tests: A systematic review of diagnostic studies in MG  
Michael Benatar *Neuromuscular disorders* 2006;16:459-467.

Seronegative generalized myasthenia gravis: Clinical features, antibodies and their targets A. Vincent, J. Bowen, J. Newsom-Davis and J. McConville *Lancet* 2003 ii: 99-102

The single report of RCT in immunosuppression of MG: J. Palace, J. Newsom-Davis, B Leaky and the MG study group RCT of prednisolone alone or with azathioprine in Myasthenia Gravis *Neurology* 1998;50: 1778-1783

Myasthenia Gravis Foundation of America's: Recommendations for Clinical Research Standards A. Jaretski III, R. Barohn et al. *Ann Thor Surg* 2000, 70:327-334  
Sharshar et.al. *J.Neurol.*2000; 247: 286-290.

Congenital Myasthenic syndromes: progress over the last decade A. Engel, K. Ohno and SM Sine: *Muscle nerve* 2003 (27): 4-25

Medications to avoid in MG: Z. Argov and I Wirguin: *Drugs and the neuromuscular junction in Handbook of Myasthenia Gravis and Myasthenic Syndromes* pp 295-315 R.P.Lisak Ed 1 vol.Marcel Dekker New York, Basel Hong Kong 1994) Look for regular updates under Z. Argov

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