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Portuguese Consensus Guidelines for the Diagnosis and Treatment of Myasthenia Gravis

Recomendações Nacionais de Consenso para o Diagnóstico e Tratamento da Miastenia Gravis

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ABSTRACT

Myasthenia *gravis* is an autoimmune disease that affects the neuromuscular junction, mainly through the action of pathogenic antibodies such as those directed against the nicotinic acetylcholine receptor or, more infrequently, against the muscle specific kinase. Other important components of the autoimmune process include the complement pathway and B and T cell populations. Diagnosis is based on the finding of fatigable muscle weakness, which can affect several muscle groups, either in isolation or in variable combinations. Neurophysiological techniques and/or the detection of pathogenic antibodies in serum are also essential for the diagnosis of myasthenia *gravis*. Maintenance treatment was traditionally based on corticosteroids and non-steroidal immunosuppressants. Recently approved drugs, such as the terminal complement pathway inhibitors and the neonatal Fc receptor antagonists, are reshaping the treatment landscape, supported by robust evidence of an excellent combination of efficacy and safety. Although several international guidelines have been published in the last decade, some key questions remain without precise guidance. Hence, a group of nine experts from the Portuguese Neuromuscular Society has elaborated consensus guidelines that aim to provide detailed guidance on diagnostic workup and treatment, grounded both in published evidence and in clinical experience. Key novel aspects include step-by-step instructions for diagnostic workup, a set of diagnostic criteria, guidance on the use of complement inhibitors and neonatal Fc receptor antagonists, and tailored treatment algorithms according to antibody subgroup and clinical severity.
Keywords: Consensus; Myasthenia Gravis/diagnosis; Myasthenia Gravis/drug therapy

RESUMO

A miastenia *gravis* é uma doença autoimune da junção neuromuscular, cuja fisiopatologia consiste na produção de anticorpos patogénicos, mais frequentemente dirigidos contra o recetor nicotínico da acetilcolina e, mais raramente, contra a cinase específica do músculo. Outros elementos fisiopatológicos importantes incluem a cascata do complemento e as linhagens linfocitárias B e T. O diagnóstico assenta em fraqueza muscular fatigável, que pode afetar diversos grupos musculares, de forma isolada ou em combinações variáveis. A deteção sérica de anticorpos patogénicos e/ou a realização de estudos neurofisiológicos são também essenciais para o diagnóstico. O tratamento de manutenção baseia-se tradicionalmente na corticoterapia e em imunossupressores não esteroides. Recentemente, têm surgido várias opções terapêuticas promissoras, como os inibidores da porção terminal do complemento ou os antagonistas do recetor Fc neonatal, que estão a transformar o cenário terapêutico da miastenia *gravis*, apoiados por evidência robusta de eficácia e segurança. Apesar da publicação de diversas recomendações internacionais ao longo da última década, existem várias questões importantes que carecem de orientações detalhadas. As presentes recomendações foram elaboradas por um grupo de nove especialistas da Sociedade Portuguesa de Estudos de Doenças Neuromusculares e são as primeiras recomendações portuguesas dirigidas à miastenia *gravis*. Nestas recomendações, produzidas por consenso e baseadas na evidência e na prática clínica, procura-se uniformizar a avaliação dos doentes com miastenia *gravis*, fornecer orientações concretas para a investigação diagnóstica dos casos suspeitos de miastenia *gravis* e apoiar as decisões referentes ao tratamento. Entre as principais novidades destas recomendações destacam-se: propostas de marcha diagnóstica e de critérios de diagnóstico, recomendações sobre instrumentos de avaliação da resposta terapêutica, posicionamento dos novos imunossupressores e algoritmos terapêuticos adaptados ao serogrupo e à gravidade clínica.
Palavras-chave: Consenso; Miastenia Gravis/diagnóstico; Miastenia Gravis/tratamento farmacológico

INTRODUCTION

Myasthenia *gravis* (MG) is the most common primary neuromuscular junction disease and is mediated by pathogenic antibodies, with particular emphasis on antibodies directed against the acetylcholine receptor (AChR), present in up to 90%

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of cases, and antibodies against muscle-specific kinase (MuSK), in up to 5%.[1-3] The essential element of the diagnosis of MG is the presence of fatigable muscle weakness, but the detection of pathogenic antibodies in serum and the neurophysiological demonstration of neuromuscular junction dysfunction help to confirm the diagnosis.[3]

Traditionally, the treatment of MG included pyridostigmine, oral corticosteroids, and conventional non-steroidal immunosuppressants, widely used in other neurological and systemic autoimmune diseases. Their use in MG is mainly supported by extensive clinical experience and expert recommendations, since available data derive largely from low-quality studies.[2,3] In recent years, the treatment landscape of MG has changed substantially with the emergence of new drugs, such as neonatal Fc receptor antagonists (aFcRn) and complement cascade factor C5 inhibitors (C5i), which act through selective mechanisms and, in randomized double-blind controlled clinical trials, have demonstrated robust efficacy and safety profile.[4,5]

Over the last decade, national guidelines from several countries have been published, as well as an international consensus guidance document and its updated version. However, these documents focus exclusively on therapeutic aspects and do not address diagnostic issues.[4-11]

The main objective of these recommendations was to standardize clinical practice regarding the diagnosis and treatment of MG in Portugal and to provide detailed guidelines with practical applicability. In addition, we sought to fill some of the main gaps in the 2016 and 2021 international consensus guidance,[10,11] namely: 1) to establish diagnostic criteria to improve reliability, particularly in seronegative MG; 2) to increase objectivity in clinical severity classification and define parameters to guide therapeutic decisions; 3) to provide practical recommendations for the use of conventional therapies with established benefit; and 4) to specify the role of rituximab and novel selective immunosuppressants.

METHODS

Members of the Portuguese Society for the Study of Neuromuscular Disease began developing these recommendations in September 2023. A working group was composed of nine neurologists with extensive experience in the care of MG patients and a deep knowledge of the geographical area where they develop their clinical activity. These experts were considered representative of the diversity of diagnostic and therapeutic practices across Portuguese healthcare institutions.

The scarcity of high-quality evidence regarding MG diagnosis and treatment precluded the use of strictly evidence-based methodologies. Thus, to produce these guidelines, a consensus-based methodology was chosen, using the RAND/UCLA Appropriateness Method,[12] a variant of the Delphi method used, for example, in the preparation of the 2016 and 2021 versions of the international consensus guidance.[10,11]

Eight main topics were initially defined by the working group and, within these, the issues targeted by the guidance statements. The initial drafting of the recommendations for each topic was carried out by two members of the working group. The statements and their rationale were then individually shared with the other members, who were asked to rate each statement from 1 to 9 for appropriateness: a score between 1 and 3 would mean that the recommendation was inappropriate (i.e., the risks implied would clearly outweigh the benefits); a score of 4 to 6 would mean that the appropriateness was uncertain (i.e., the risk/benefit balance was unclear or there were no conditions to give an opinion on the topic under consideration); a score of 7 to 9 would mean that the recommendation was appropriate. For the scores below 9, comments and suggestions were provided to improve the content. The liaison element received individual appraisals of the other elements of the group, which were assessed by the drafting team, who analyzed the suggestions and prepared proposals for rewording or argued in favor of the initial text. The revised text was then shared again individually with the group members, and the evaluation process was repeated. Consensus was defined as a median score between 7 and 9, with no more than two votes below 7.

RECOMMENDATIONS

This section summarizes the main topics of these guidelines, all of which reached consensus as predefined. A full version is available in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15824) and includes: full guidance statements, literature summaries and lines of argumentation, and treatment algorithms. Median and range of ratings assigned by consensus group members to each guidance statement are also provided in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15824).

Topic 1: Diagnostic workup

1.1. Initial diagnostic workup

Diagnostic workup should follow a stepwise approach, adapted to the available resources of each healthcare institution. Recommended strategies for suspected ocular or generalized MG are depicted in Figs. 1 and 2.

1.2. Utility of repeating antibody screening when initially negative

If the initial screening for AChR and MuSK antibodies is negative, and if a live cell-based assay (L-CBA) in an international reference laboratory is not feasible, the antibody testing should be repeated, preferably after at least six months.

1.3. Utility of screening for titin or striational antibodies

- Testing for titin or striational antibodies may be considered in all AChR antibody-positive patients with early symptom onset (before the age of 50), given the high predictive value for thymoma in this age group. This should not replace imaging screening.
- In late-onset patients, these antibodies provide no additional diagnostic or prognostic value.

1.4. Thymoma screening

- Chest computed tomography (CT) scan is the preferred imaging modality for thymoma screening.
- Thymoma screening should be performed at diagnosis in all AChR antibody-positive patients.
- In seronegative MG, screening for thymoma should be considered.
- In MuSK antibody-positive MG, thymic abnormalities, including thymoma, are extremely rare: screening may nonetheless be considered.
- In AChR antibody-positive patients, initially without thymoma on CT or histology, repeat chest CT should be considered if a clinical exacerbation occurs that cannot be explained by well-established aggravating factors (listed in section 6.6).

Topic 2: Diagnostic criteria

2.1. Clinical manifestations with diagnostic utility

The cardinal clinical manifestation of MG is fatigable muscle weakness, which consists of the appearance or worsening of muscle weakness as a result of prolonged or repetitive exertion, and its improvement with rest. The clinical expression of this phenomenon is extremely varied and depends on the muscle groups that are affected in each patient. To determine the diagnostic certainty, the clinical signs of MG were divided into two groups (Tables 1 and 2), according to their diagnostic specificity.

2.2. Definition of ocular MG

The term 'ocular MG' designates any pattern of muscle weakness that exclusively affects the external eye muscles (resulting in diplopia, with or without overt ocular movement paresis) or the eyelid levator muscle (resulting in eyelid ptosis). Concomitant weakness of the eyelid closure does not exclude this designation, but muscle strength in the remaining facial muscles, masticatory, oropharyngeal/laryngeal, respiratory, axial and limb muscles should be normal. This concept does not depend on disease duration.[10]

2.3. Diagnostic criteria for MG

Diagnostic criteria include one core, one confirmatory and four supportive criteria (Table 3). Depending on AChR or MuSK antibody status, the specificity of the clinical signs, and the presence of supportive criteria, MG diagnosis can be classified into three levels of certainty: definitive (seropositive or seronegative), probable, and possible (Fig. 3). Probable and, especially, possible MG should be regarded as working diagnoses and should prompt a thorough reassessment of differential diagnoses as well as an active search for elements to upgrade the level of certainty. Invasive, high-risk or costly treatments must be avoided in possible MG and should be selected carefully in probable MG cases.

Topic 3: Important concepts and assessment of treatment response

3.1. Post-intervention status

Among the several concepts developed by the Myasthenia Gravis Foundation of America (MGFA) to designate the clinical status after a therapeutic intervention,[13] three stand out as the most useful:

- Complete stable remission: absence of MG symptoms and signs for at least one year, in the absence of any treatment for the disease in this period.
- Pharmacological remission: identical to complete stable remission but with ongoing MG treatment. Pyridostigmine is excluded as its use indicates residual muscle weakness.
- Minimal manifestations (MM): no symptoms or functional limitations due to MG but examination reveals muscle weakness, other than isolated eyelid closure weakness.

3.2. Clinical classification

The MGFA clinical classification, developed with the aim of standardizing the grading of clinical severity, establishes five classes of increasing severity.[13] Despite the usefulness of this classification, even in clinical practice, its main limitation is the unclear distinction between the three intermediate classes, corresponding to mild, moderate and severe generalized MG. Therefore, these guidelines propose complementary definitions based on the functional impact of non-ocular myasthenic symptoms [Appendix 2, Table 1 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15825)].

3.3. Therapeutic goals

- The goal of MG treatment is to achieve 'remission' or a 'minimal manifestations' status, with no side effects or only with mild side effects (mild symptoms, not requiring a targeted intervention), as proposed by the 2016 international consensus guidance.[10]
- In addition to the previous statement, we recommend that after achieving 'remission' or 'minimal manifestation', corticosteroid maintenance dose should ideally not exceed 5 mg/day of prednisolone (or equivalent), although 7.5 mg/day might be reasonable if reaggravation occurs with a lower dose.

3.4 Instruments for the evaluation of therapeutic response in clinical practice

- During the follow-up of patients with MG, specific symptoms and signs of the disease should be evaluated regularly. For this purpose, we recommend routine application of the Activities of Daily Living scale (MG-ADL), ideally combined with another scale incorporating physical examination findings (e.g., MG composite).
- During follow-up, patients should be regularly asked about their quality of life and overall satisfaction with disease control.

3.5. Serial AChR or MuSK antibody testing

- Therapeutic decisions in AChR antibody-positive MG should not be based on antibody titers. Serial testing is not recommended for monitoring treatment response.
- In MuSK antibody-positive MG, serial titers may support interpretation in suspected relapses or when response to treatment remains uncertain after clinical evaluation.

Topic 4: Symptomatic treatment

4.1. Indications for initiating pyridostigmine

Pyridostigmine should be used in the initial treatment phase for all patients with symptomatic MG, regardless of severity and serological subgroup.

4.2. Initial dose and titration

- We recommend starting with 30 mg (half tablet) administered three or four times daily during periods of the day when the patient expects to be physically active. There is no benefit in administration at bedtime or during nocturnal sleep period.
- If the drug is well tolerated but symptoms persist, it may be increased after three to four days to a dose of 60 mg (one tablet) four times daily. If required and well tolerated, it may be increased up to six daily doses of 60 mg or up to a maximum dose of 90 mg in four or five daily doses.
- In MuSK antibody-positive MG, titration should be slower and with close monitoring for clinical worsening or adverse effects.

4.3. Indications for discontinuation of pyridostigmine

- Generally, in patients who are concomitantly receiving immunosuppressive drugs, discontinuation of these drugs should be preceded by successful withdrawal of pyridostigmine, as tolerance of its discontinuation without clinical worsening indicates that treatment goals have been achieved.
- In persistently asymptomatic patients, pyridostigmine tapering (e.g., reducing by 30 to 60 mg per week) should be considered until complete withdrawal.
- In patients in myasthenic crisis requiring invasive mechanical ventilation (IMV), pyridostigmine should be temporarily stopped due to the risk of increased bronchial secretions and bronchospasm.

4.4. Other symptomatic treatments

No other drugs are recommended for symptomatic treatment of MG.

Topic 5: Maintenance immunosuppressive treatment

5.1. Indications for initiating immunosuppressive treatments

- Immunosuppression should be offered to patients with mild but bothersome clinical manifestations, including ocular MG, when therapeutic goals are not achieved with pyridostigmine monotherapy.
- Immunosuppression should be started upfront in patients with moderate (class III) or severe (class IV) generalized manifestations or in myasthenic crisis (MGFA class V), as sustained control is unlikely with pyridostigmine and traditional fast-acting immunomodulatory therapies alone.

5.2. Chronic corticosteroid therapy

5.2.1. Indications as a first line

- Corticosteroids are the most effective oral immunosuppressive agent in MG and should be the first-line treatment in eligible patients meeting the criteria in section 5.1. Caution should be observed with chronic use in patients at risk for serious adverse effects (e.g., glaucoma, osteoporosis, diabetes mellitus with poor glycemic control).

5.2.2. Titration, maintenance and weaning schemes

- Ocular MG, mild generalized MG, and moderate generalized nonbulbar MG (MGFA classes I, IIa, IIb, and IIIa)
  - Start prednisolone at a dose of 10 mg/day (or equivalent) and increase by 5 to 10 mg every five to seven days until symptoms resolve or a maximum 1 mg/kg/day (or 100 mg/day) dose is reached.
  - Maintain maximum dose, or the one that allowed resolution of symptoms, for at least four weeks and no longer than eight weeks, to prevent serious adverse effects and poor compliance.
  - Tapering schedule depends on compliance, comorbidities (notably diabetes *mellitus* with poor glycemic control) and clinical context. Full suggestions of tapering schedules can be found in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15824).
- Moderate generalized bulbar MG, severe generalized MG and myasthenic crisis (MGFA classes IIIb, IV and V).
  - Induction schedule will depend on severity and context:
    - Patients with MG classes IIIb or IV should ideally be admitted to the hospital. After starting treatment with intravenous immunoglobulins (IVIg) or plasmapheresis, begin oral prednisolone at a dose of 1 to 1.5 mg/kg/day. If admission, or at least a course of IVIg / plasmapheresis as outpatient, are not feasible, follow the ascending titration schedule suggested above to prevent steroid-induced exacerbation.
    - Patients with myasthenic crisis should be admitted to an Intensive Care Unit (ICU). Concomitantly with a course of plasmapheresis or IVIg, start oral prednisolone at a dose of 1 to 1.5 mg/kg/day (maximum 100 mg/day).
  - Maintain maximum dose for at least four weeks and no longer than eight weeks, to prevent serious adverse effects and poor compliance.
  - Tapering schedule depends on compliance, comorbidities (notably diabetes mellitus with poor glycemic control) and clinical context. Full suggestions of weaning schedules can be found in Appendix 1

(Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15824).

5.2.3. Surveillance and prevention of corticosteroid adverse effects

See Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15824).

5.3. Traditional nonsteroidal immunosuppressants (NSI)

5.3.1. Indications for its use in MG

- Using a traditional NSI alone:
  - If corticosteroid therapy is contraindicated or refused by the patient.
- Using a traditional NSI upfront, combined with corticosteroids:
  - If there is a high risk of steroid-related adverse effects, based on the patient's comorbidities (e.g., diabetes *mellitus*, osteoporosis, glaucoma).
  - If the treating neurologist finds that adequate control with prednisolone monotherapy at a safe dose is unlikely.
- Using a traditional NSI as add-on drug in patients under corticosteroid therapy:
  - If adverse effects of corticosteroid therapy appear and are considered relevant by the patient and/or the treating physician.
  - If clinical response has been insufficient after a period of corticosteroid therapy of adequate duration and dose (dose up to 1 mg/kg/day for at least six to eight weeks).
  - If relapse occurs when tapering prednisolone to 7.5 mg/day or below.

5.3.2. Choice of drug to use

- Traditional NSIs are, in MG, mainly an adjuvant therapy aimed essentially at maintaining the effect of highly effective therapies whose long-term use is limited by safety (corticosteroids) or logistics (new immunosuppressants, IVIg, and plasmapheresis).
- There is no foreseeable added benefit in the sequential use of more than two traditional NSIs if each of them has been stopped for inefficacy, despite adequate dose and duration.
- Azathioprine and mycophenolate mofetil are first-line options among traditional NSIs, either in ocular or generalized MG. Methotrexate can be an alternative option.
- Drug choice should be individualized, based on comorbidities, possible drug interactions and required speed of effect.
- In the current treatment landscape, cyclophosphamide, cyclosporine, and tacrolimus should not be used in the treatment of MG.

5.3.3. Titration and maintenance dose

See Appendix 2, Table 2 (Appendix 2: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15825).

5.3.4. Surveillance and prevention of NSI adverse effects

See Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15824).

5.4. Rituximab

5.4.1. Indications for its use in MG

- MuSK antibody-positive MG – rituximab is recommended in all cases for whom corticosteroids are ineffective, not tolerated or refused.
- AChR antibody-positive MG – rituximab may be considered in the following scenarios:
  - In mild generalized MG (MGFA class II)
    - As add-on if corticosteroid therapy is insufficiently effective.
    - In place of corticosteroids (if refusal or non-compliance), when the first-line treatment, an adequate trial with pyridostigmine and a traditional NSI, is not effective.

- In moderate generalized bulbar MG (MGFA class IIIb) or severe (IVa and b), as possible first-line if refusal or non-compliance to corticosteroids.
- In myasthenic crisis (MGFA class V), as possible first-line treatment if there's refusal or non-compliance to corticosteroids, after initial response to IVIg or plasmapheresis. In this setting, IgG levels should be near normal before starting rituximab.

5.4.2. Dosage regimens

- Dose: the choice of a high-dose schedule (option A: two administrations of 1000 mg, two weeks apart; option B: 375 mg/m^2, weekly for four consecutive weeks) or a reduced-dose schedule (e.g., 2 x 500 mg administrations two weeks apart; 375 mg/m^2 in two administrations two weeks apart) depends on disease duration, prior treatment response or refractoriness, and the patient's infectious risk profile.
- Treatment should be repeated in the following situations:
  - When the clinical response is considered sufficient, consideration may be given to resuming only in case of a clinical relapse, although this implies a careful clinical follow-up and facilitated access to the healthcare team as soon as first symptoms reappear.
  - If the initial clinical response is partial, treatment may be repeated when clinical worsening is observed, ensuring that a minimum interval of approximately 6 months has elapsed since the last dose.
  - If the clinical response is not considered significant, a second cycle, eventually with a higher dose, may be attempted in mild generalized (MGFA classes IIa or b) or moderate nonbulbar MG (IIIa). In more severe cases, switching to therapies with higher expected efficacy (i.e., C5 inhibitors or neonatal Fc receptor antagonists) is preferable.

5.4.3. Surveillance and prophylaxis

See Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15824).

5.5. Neonatal Fc receptor antagonists and complement C5 inhibitors

5.5.1. Indications for its use in MG

- Complement C5 factor inhibitors (C5i) and neonatal Fc receptor antagonists (aFcRn) should be used mainly in clinical situations requiring high efficacy and rapid improvement.
- The use of these drugs is recommended – ideally as a bridging therapy – in the following indications:
  - In mild generalized MG (MGFA classes IIa or b) or moderate nonbulbar (IIIa) without significant clinical improvement (i.e., ≥ 2-point reduction on the MG-ADL scale or ≥ 3-point reduction on MG composite) after at least 2 cycles of rituximab, regardless of previously used therapies.
  - In moderate bulbar (MGFA class IIIb) or severe MG (IVa and b), without significant clinical improvement after corticosteroid therapy with adequate dose and duration.
  - In moderate bulbar (MGFA class IIIb) or severe MG (IVa and b), without significant clinical improvement after a single cycle of rituximab, in the event of steroid refusal or non-compliance.
  - In moderate bulbar (MGFA class IIIb) or severe MG (classes IVa and b), with relapse when tapering prednisolone to ≤ 7.5 mg/day, despite adequate trials with two traditional NSIs.
  - In myasthenic crisis (MGFA class V), with failure of ventilatory weaning and nasogastric or gastrostomy tube removal after an initial course of one of the traditional fast-acting immunomodulatory treatments (IVIg or plasmapheresis) plus an additional course of the other not initially used traditional fast-acting treatment (performed one to two weeks after completion of initial treatment) plus oral prednisolone at a dose of 1 mg/kg/day for at least four weeks (in parallel with IVIg and/or plasmapheresis trials).

5.5.2. Choice of drug to use

- C5i can only be used in generalized AChR antibody-positive MG. aFcRn can be used in AChR antibody-positive MG and in the other serogroups.
- Based on the available evidence, aFcRn and C5i should be considered equally effective in AChR antibody-positive MG. Safety profile and dosing schedules should guide the choice between these two pharmacological groups.

- Within the aFcRn group, the choice between efgartigimod (intravenous or subcutaneous) and rozanolixizumab (subcutaneous) should be individualized and based on criteria such as patient preference for route and frequency of administration, and patient's adherence.
- Within the C5i group, due to its dosing advantage, ravulizumab should be used preferentially over eculizumab. Zilucoplan may be a suitable alternative in selected cases, depending on the patient's preference and compliance profile.

5.5.3. Dosing schedules

- Eculizumab (intravenous): induction at 900 mg weekly for four weeks; maintenance starts at 1200 mg at week five, then 1200 mg 2/2 weeks.
- Ravulizumab (intravenous): induction with 2400 mg (40 - 59 kg), 2700 mg (60 - 99 kg), or 3000 mg (≥ 100 kg) as a single dose; maintenance with 3000 mg (40 - 59 kg), 3300 mg (60 - 99 kg), or 3600 mg (≥ 100 kg) after two weeks, then 8/8 weeks.
- Zilucoplan (subcutaneous): a daily administration of a weight-adjusted dose [16.6 mg (< 56 kg), 23 mg (≥ 56 and < 77 kg) or 32.4 mg (≥ 77 kg)].
- Efgartigimod (intravenous): each cycle consists of a weekly administration of 10 mg/kg for four consecutive weeks.
- Efgartigimod (subcutaneous): each cycle consists of a weekly administration of 1000 mg for four consecutive weeks.
- Rozanolixizumab (subcutaneous): each cycle consists of a weekly administration of a weight-adjusted dose [280 mg (≥ 35 and < 50 kg), 420 mg (≥ 50 and < 70 kg), 560 mg (≥ 70 and < 100 kg) or 840 mg (≥ 100 kg)] for six consecutive weeks.

5.5.4. Treatment duration

- C5i and aFcRn should ideally be used transiently, as bridging therapy until the expected onset of therapeutic effect of a traditional NSI used concomitantly. However, if significant clinical improvement has occurred (i.e., ≥ 2-point reduction on the MG-ADL scale or ≥ 3 points on the MG composite) with a C5i or an aFcRn, and this benefit has been lost upon taper or discontinuation of this drug, treatment should be resumed, and concomitant traditional NSI dose adjustment or replacement should be considered.
- For C5i tapering, we recommend to gradually reduce the dose and frequency of administration until withdrawal, once maximum sustained clinical benefit is achieved and concomitant NSI effect is expected to be already fully established, based on what is known about the maximum time required for the onset of action of each NSI.
- Regarding efgartigimod:
  - If after the first cycle there is no significant improvement or if the total score on the MG-ADL scale remains ≥ 5 points (> 50% attributable to non-ocular items), the second cycle should be performed four weeks after the last infusion.
  - If significant improvement occurs after the first cycle and if the total score on the MG-ADL scale is < 5 points, a second cycle should be performed only if the initial improvement has been lost. In this case, repeat treatment should occur only when reaggravation begins and at least four weeks after completion of the previous cycle. This interval should determine the periodicity of subsequent cycles.
- For rozanolixizumab, data on repeated cycles are insufficient to issue recommendations.

5.5.5. Prophylaxis

- Treatment with C5i carries a high risk of infection by encapsulated bacteria, especially Neisseria meningitidis. Therefore, vaccination and some prophylactic measures are mandatory [see Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15824)].
- FcRn antagonists do not require prior or regular blood tests or specific vaccinations.

5.6. Immunoglobulins and plasmapheresis in maintenance treatment

5.6.1. Indications

- IVIg as maintenance treatment should be restricted to selected cases of generalized MG (especially with

AChR antibody-positive) that remain moderate or severe despite adequate trials with prednisolone, rituximab, and an aFcRn or C5i.
- Plasmapheresis as maintenance treatment should be restricted to selected cases of generalized AChR or MuSK antibody-positive MG that remain moderate or severe despite adequate trials with prednisolone, rituximab, an aFcRn, IVIg, and a C5i (in case of AChR antibody-positive MG).
- Both IVIg and plasmapheresis should ideally be used as a bridging therapy, until the effect of a traditional NSI is expected to be fully established.

5.6.2. Dose and frequency of treatments

- IVIg: induction cycle with a dose of 2 g/kg over two to five days, followed by maintenance cycles with a lower dose (e.g., 0.4 to 1 g/kg). Maintenance cycles should be tailored to the duration of each patient's clinical response: most commonly the interval is around four weeks, although a few patients might require more frequent dosing.
- Plasmapheresis: induction cycle with three to five sessions every other day; maintenance cycles with one to three sessions on alternate days, with approximately monthly periodicity.

Topic 6: Myasthenic crisis

6.1. Definitions

- We recommend using the definitions proposed in the 2016 international consensus guidance[10]:
  - Manifest myasthenic crisis is defined as worsening of myasthenic weakness requiring invasive mechanical ventilation (IMV) or non-invasive ventilation (NIV) to avoid intubation.
  - Imminent myasthenic crisis is defined as rapid clinical worsening which, in the opinion of the treating physician, is likely to progress to manifest myasthenic crisis in the short term (days or weeks).
  - Exacerbation is a term that should be applied to patients who previously met the definition of remission or minimal manifestations but have recurrence of symptoms exceeding those allowed by these definitions, i.e. they are no longer asymptomatic.

6.2. Red flags

- The following clinical signs should prompt suspicion of respiratory muscle involvement and consideration of a myasthenic crisis:
  - Staccato speech at rest.
  - Use of accessory respiratory muscles (e.g., scalenes, sternocleidomastoids).
  - Intolerance to supine position due to orthopnea.
  - Paradoxical breathing pattern (abdominal retraction on inhalation and expansion during exhalation).
  - Inability to take a deep breath and count aloud at least to 20 on one single breath (this sign should only be considered if adequate patient cooperation is ensured).
  - Weak and ineffective cough.

6.3. Indications for hospital admission

- We recommend that all patients who meet the definition of manifest or imminent myasthenic crisis, or severe exacerbation (MGFA classes IVa or b) be admitted to hospital.
- Admission should also be considered in the event of moderate bulbar exacerbation (MGFA class IIIb).
- In manifest or imminent myasthenic crisis, the possibility of ICU admission should be promptly discussed.
- Arterial blood gas abnormalities appear late in the evolution of ventilatory dysfunction caused by myasthenic weakness and should not outweigh clinical signs when deciding ICU admission or ventilatory support (invasive or non-invasive).

6.4. Supportive treatment considerations in exacerbations with severe oropharyngeal and respiratory muscle involvement

- In MG patients with respiratory distress, early initiation of bilevel positive pressure (BiPAP) NIV, with airway clearance measures, may prevent the need for IMV.
  - In these patients, NIV should be initiated before hypercapnia develops.

    - The existence of overt weakness of facial muscles and difficulty managing secretions should not be considered contraindications to NIV.
- Pyridostigmine should be stopped after tracheal intubation to decrease oropharyngeal and respiratory secretions. However, pyridostigmine does not need to be stopped when the patient is on NIV and should be restarted at appropriate doses when weaning from IMV is planned.
- After extubation, early use of NIV should be considered, as it might increase the likelihood of success and decrease the risk of reintubation.

6.5. Fast-acting immunomodulatory treatments

- All patients who meet the indications for admission listed above should receive treatment with IVIg or plasmapheresis.
- Choice between IVIg and plasmapheresis depends on availability, comorbidities and current clinical status.
- Factors favoring plasmapheresis over IVIg, in hospitals where both options are available:
    - Manifest myasthenic crisis.
    - MuSK antibody-positive MG.
    - Chronic kidney disease.
    - Hypercoagulable states.
    - Severe arterial disease.
- In patients who do not have any of the factors listed above, the following factors may favor the choice of IVIg over plasmapheresis:
    - Active sepsis.
    - Advanced age.
    - Significant cardiac comorbidities (namely, heart failure).
    - Hemorrhagic diathesis or recent major bleeding.
- Plasmapheresis can preferably be performed via peripheral venous access when feasible.
- In the treatment of manifest or imminent myasthenic crisis, the number of plasmapheresis sessions to be performed should be guided by clinical response, but usually it is not necessary to exceed a total of five to eight sessions.
- For patients receiving ventilatory support (invasive or non-invasive), daily plasmapheresis sessions may be considered and discussed with the medical team to promote faster clinical improvement.
- Treatment of myasthenic crisis with IVIg should use a total dose of 2 g/kg over two to five days.

6.6. Precipitating factors

- In the face of an exacerbation of the clinical manifestations of MG, the most common precipitating factors should be considered, namely:
    - Suboptimal dose or rapid tapering of immunosuppressive drugs.
    - Acute infection.
    - Recent surgery.
    - Pregnancy, childbirth, or puerperium.
- If these precipitating factors are absent, concurrent medications should be reviewed in order to assess whether there is a plausible causal association.
    - Although in most cases the evidence for causal association is limited, the following pharmacological groups have been especially associated with the onset or exacerbation of clinical manifestations of MG:
        - Immune checkpoint inhibitors.
        - D-Penicillamine.
        - Chloroquine and hydroxychloroquine.
        - Classes Ia and Ic antiarrhythmics (especially propafenone).
        - Aminoglycoside antibiotics (except tobramycin), macrolides and fluoroquinolones.
        - Botulinum toxin.
        - Magnesium (especially intravenous).
        - Potentially respiratory center depressant drugs, namely opioids and benzodiazepines (especially intravenous and at high doses).

  - Statins.
  - Beta-adrenergic blockers and calcium channel blockers.
- None of these drugs are absolutely contraindicated in MG nor should they be discontinued if they were already in chronic use at the time of the onset of symptoms of the disease. However, de novo use should be avoided if equivalent and presumably safer therapeutic alternatives exist.

Topic 7: Thymectomy

7.1. Indications (based in 2016 international consensus guidance[10]):

- Thymectomy is indicated in all patients with thymoma.
- In MG without thymoma, thymectomy may be considered in the following situations:
  - Early in the course of generalized AChR antibody-positive MG, if age of onset between 18 and 50 years.
  - It should be strongly considered in patients with AChR antibody-positive MG with poor response or intolerable adverse effects from initial immunotherapy in an appropriate regimen.
  - It may be considered in patients with seronegative generalized MG if response to immunosuppressants is unsatisfactory or to minimize adverse effects.
  - It may be considered in patients with ocular AChR antibody-positive MG if response to pyridostigmine is inadequate and if immunosuppressants are refused, not tolerated or ineffective.
- Current evidence does not support thymectomy in MuSK or LRP4 antibody-positive MG (without concomitant AChR antibody).
- Thymectomy in the context of MG is an elective procedure and should ideally be performed when the patient is stable and surgery is considered safe.

7.2. Use of fast-acting immunomodulatory treatments before thymectomy and other surgeries

- In patients who are about to undergo thymectomy or other surgical procedure and who are in remission or in a state of minimal manifestations, a pre-surgical treatment, namely with IVIg or plasmapheresis, is not recommended.
- Preoperative treatment may be used to prevent severe exacerbation or myasthenic crisis in patients with persistent moderate or severe MG (MGFA classes III or IV).
- The choice between IVIg and plasmapheresis should follow the criteria listed in 6.5.
- The use of oral corticosteroids at the time of thymectomy, even at high doses, is not contraindicated nor deleterious.

Topic 8: Pregnancy, childbirth and breastfeeding [see full version in Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15824)**]**

8.1. Family planning and MG treatment in women of reproductive age

- Pregnancy in women with MG should be planned and ideally should occur during a stable phase of the disease.
- Regarding the treatments used in MG:
  - Pyridostigmine, prednisolone and azathioprine are generally considered safe in pregnancy.
  - Mycophenolate mofetil and methotrexate should not be prescribed to women of reproductive potential.
  - Rituximab can be used in women of childbearing age, but conception should ideally occur at least four months after the last infusion.
  - Complement inhibitors and FcRn antagonists may be used in women of reproductive potential if indispensable, but their use should be accompanied by effective contraception. However, if conception occurs while on C5i or aFcRn, the risks of newborn immunosuppression must be weighed against the benefits on maternal disease control when considering the continuation of treatment.
  - IVIg and plasmapheresis can be used without restrictions in women of reproductive potential.
  - Thymectomy, even in the absence of suspected thymoma, is recommended in this age group (per criteria in 7.1.) and probably decreases the risk of neonatal MG. However, it should not be performed during pregnancy.

8.2. Precautions in the treatment of MG during pregnancy

- Regardless of the regular medication that the patient is taking, it should never be abruptly suspended at the time

of pregnancy detection.
- Thymectomy should not be performed during pregnancy.
- Although the introduction of NSIs during pregnancy should be avoided, azathioprine is considered safe and can be maintained during this period if it is considered important to maintain disease control.
- Magnesium sulfate should be avoided in the prophylaxis of eclampsia. If the patient develops eclampsia, namely with seizures, IV magnesium sulfate can be used although with extreme caution and with supervision by anesthesiology. Nonetheless, in the context of seizures, anti-seizure medications (e.g., levetiracetam) should preferably be used.

8.3. Childbirth issues

- Delivery and anesthetic approach should be planned.
- General anesthesia should be avoided but, if indispensable, neuromuscular blockers must not be used.
- In epidural anesthesia, drugs of the amide group (e.g., ropivacaine, bupivacaine) should preferably be used.
- Vaginal delivery should be the goal and should be actively encouraged. Cesarean section should be reserved for obstetric indications, including prolonged labor due to maternal exhaustion.
- Women with moderate or severe generalized MG near term may benefit from IVIg or plasmapheresis prior to delivery, to reduce the risk of worsening during labor and in the puerperium.
- Delivery should occur in a hospital with neonatology support and neonatal ICU, due to the risk of transient neonatal MG with possible need for ventilatory and nutritional support to the newborn.
- For the same reason, and because transient neonatal MG can develop a few hours or even days after delivery, the newborn should remain under observation for at least two days.

8.4. Breastfeeding issues

- Generally, breastfeeding should be encouraged among mothers with MG, as well as in the general population. However, in women receiving mycophenolate mofetil and methotrexate, breastfeeding should be discouraged.
- Treatments for MG that are considered safe during breastfeeding include: pyridostigmine, prednisolone, azathioprine, rituximab, IVIg, and plasmapheresis.

THERAPEUTIC ALGORITHMS

See Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/24089/15824).

CONCLUSION

To the best of our knowledge, these guidelines are the first to include formal diagnostic criteria for MG, designed to differentiate highly specific from non-specific clinical manifestations, and to clarify the role of ancillary diagnostic tools. They are also the first to provide detailed indications for the use of novel immunosuppressants in MG, together with comprehensive therapeutic algorithms tailored to serogroup and clinical severity. The working group believes that these recommendations will contribute to improving the care of patients with MG and to a greater consistency and standardization of concepts and of diagnostic and therapeutic strategies.

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AUTHOR CONTRIBUTIONS

SC: Literature review, writing of the manuscript.

AM: Literature review, writing and critical review of the manuscript.

LB, CFC, JC, LM, ES, LS, AV: Critical review of the manuscript.

All authors approved the final version to be published.

CONFLICTS OF INTEREST

SC participated on advisory boards for Argenx and UCB Pharma; received speaker's honoraria from CSL Behring;

performed medical writing for CSL Behring and Argenx; received support for attending meetings from CSL Behring, Kedrion and Takeda.

AM participated on advisory boards for Argenx and UCB Pharma.

LB participated on the advisory board for Argenx; performed medical writing for Argenx.

CFC acted as subinvestigator in a randomized controlled trial for Argenx; received speaker's honoraria from Argenx.

LM participated on advisory boards for Argenx and UCB Pharma; performed medical writing for argenx; received support for attending meetings from Argenx, CSL Behring and Kedrion.

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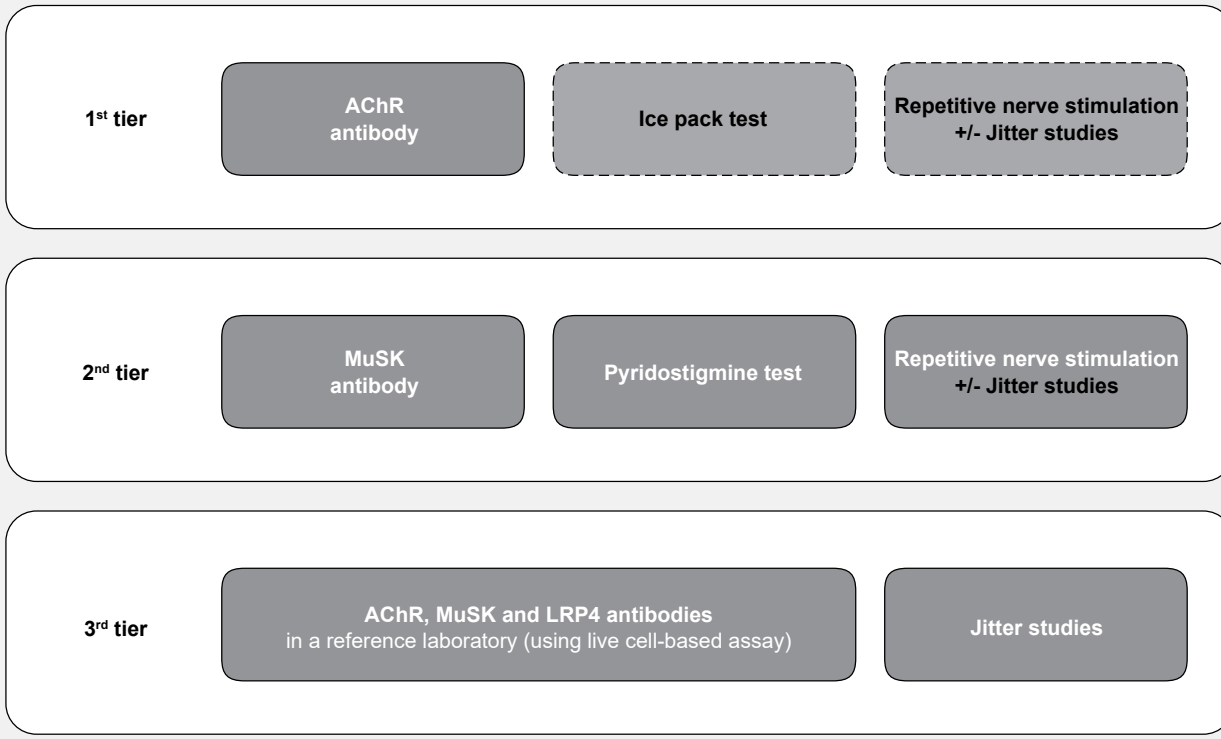

Figure 1 – Diagnostic workup of suspected cases of ocular MG. The gray background boxes with dashed outline and dark letters indicate that a particular test can be used at an earlier stage if it is easily accessible. Each tier should only take place if the previous tier was negative.

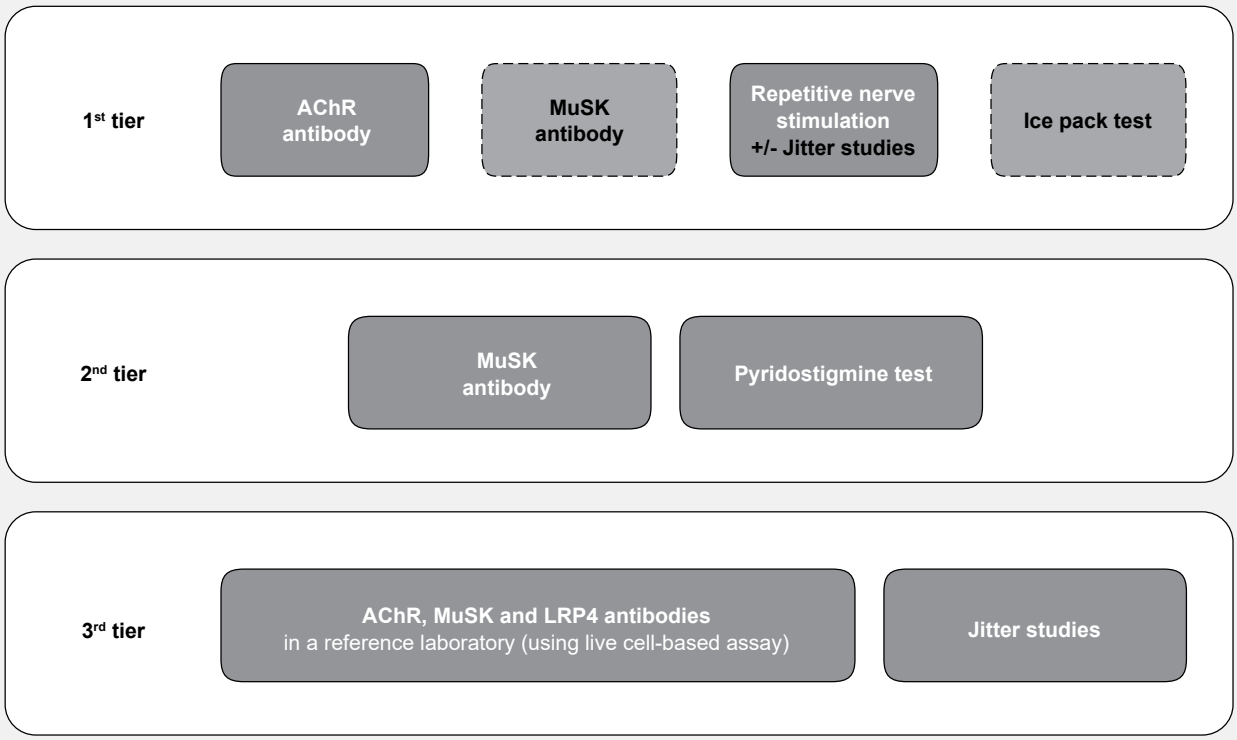

Figure 2 – Diagnostic workup of suspected cases of generalized MG. The gray background boxes with dashed outline and dark letters indicate that a particular test can be used at an earlier stage. Each tier should only take place if the previous tier was negative.

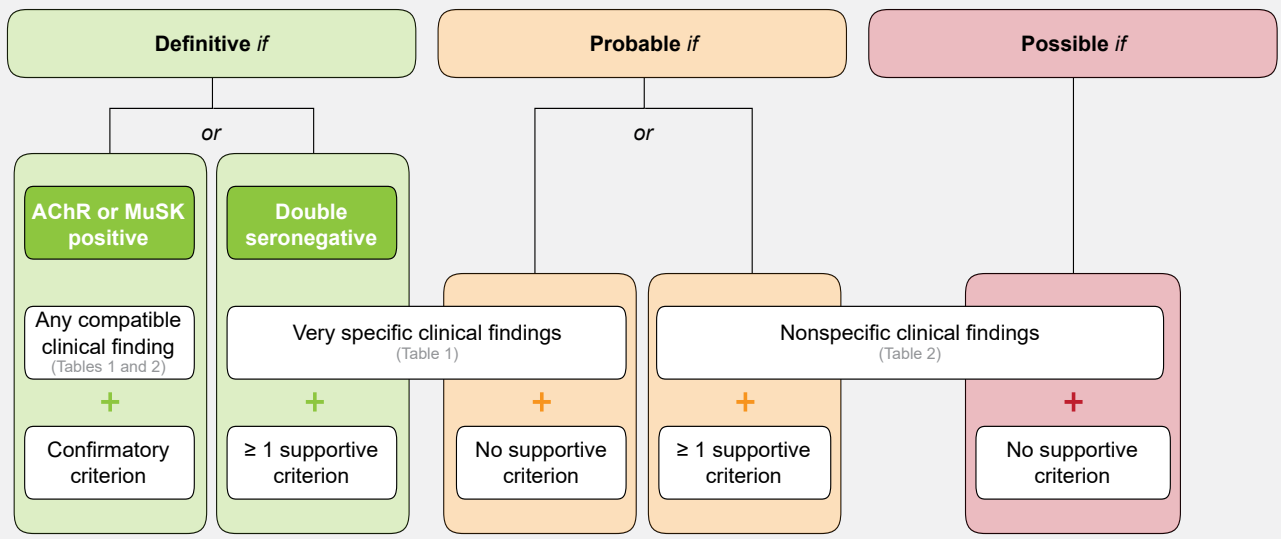

Figure 3 – Degrees of certainty of the diagnosis of MG. In double seronegative (AChR and MuSK antibodies) patients, it is essential to exclude, as far as possible, plausible differential diagnoses.

Table 1 – Clinical signs compatible with and very specific to the diagnosis of MG

• Fatigable muscle weakness: unequivocal appearance or worsening (ideally measurable or quantifiable) of weakness in any muscle group during physical examination
• Unilateral or asymmetric eyelid ptosis with variable side and severity between observations
• Eyelid ptosis with Cogan's sign and/or curtain sign
• Variable pattern of ocular movement paresis between observations
• Ocular movement paresis not consistent with a single cranial nerve or central nervous system lesion, or with an orbital myopathy
• Painless weakness on chewing and involuntary jaw opening after 20 seconds of maintained pressure over the mentum

Table 2 – Clinical signs compatible with but nonspecific to the diagnosis of MG

• Eyelid ptosis with concomitant weakness of eyelid closure
• Symmetrical bilateral eyelid ptosis or unilateral ptosis without variability of side or severity between observations
• Diplopia without clinically evident ocular movement paresis, particularly if intermittent
• Any pattern of ocular movement paresis compatible with an isolated lesion of cranial nerves (without pupillary dysfunction) or of a central nervous system location
• Symmetrical facial weakness, affecting both the upper and the lower face or only the eyelid closure
• Flaccid dysarthria and/or nasal dysphonia
• Vocal cord paralysis, with or without clinically audible stridor
• Oropharyngeal dysphagia
• Tongue weakness
• Weak and ineffective cough
• Orthopnea and paradoxical breathing pattern
• Head drop
• Neck flexion weakness
• Limb-girdle muscle weakness

Table 3 – Diagnostic criteria for MG

Core criterion: at least one clinical sign compatible with the diagnosis of MG, regardless of whether it is very specific or nonspecific
Confirmatory criterion: AChR or MuSK antibodies
Supportive criteria: • Low frequency repetitive nerve stimulation compatible with a postsynaptic dysfunction of neuromuscular transmission • Abnormal *jitter* studies consistent with neuromuscular junction dysfunction, after excluding muscle, peripheral/cranial nerve, nerve root, or lower motor neuron disease • Clear improvement of myasthenic signs on physical examination after pyridostigmine intake • Positive ice pack test (in cases with overt eyelid ptosis) • Positive LRP4 antibody