LSN MS Guidelines for the Management of Multiple Sclerosis

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Preface

To be well judged, medical decision-making should foster mutual agreement of different principals (patients, physicians and community). This agreement cannot be achieved without clinical ethics; defined as, the judgment of value of the medical decision and action. Therefore, Clinical ethics becomes the guide for quality improvement and its measurement. High quality care is hence represented by the adoption of criteria indispensable to declare an action as conforming to a particular reference or guideline.

The Lebanese Society of Neurology (LSN) has adhered to the concept of guidelines that have become standard to protect every science and emerging technique. The establishment of such guidelines is at the heart of the concept of “quality of care” that increasingly incorporates the processes of continuous evaluation and improvement.

The LSN, that is the National Scientific Community of Lebanese Neurologists, has developed consensus guidelines to help measure and improve the care of patients with multiple sclerosis (MS). This reference, developed by the LSN, has been reviewed by prominent and independent MS experts in Lebanon and Europe. The aim is to document that the care provided is evidence-based, improves health outcomes for patients, promotes quality improvement and standardizes Lebanese Neurological practice and performance.

Our wish is that this standard of care be adopted by national institutions - the healthcare system, in particular - so that the concept of quality care will become part of the process of continuing education and a tool for continuous evaluation and improvement.

Thanking the LSN MS team and the LSN Board of administration for their dedication, patience, achievements and mainly for their “fidelity and faithfulness in this troubled and irregular world” as described by Amine Maalouf.

While the LSN MS guidelines are here to better serve the vulnerable Lebanese community and to protect, I’d like to emphasize that truth and quality work are paramount!

Fadi ABOU-MRAD MD, PhD
President, Lebanese Society of Neurology
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LSN MS Guidelines for the Management of Multiple Sclerosis

I. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system (CNS), involving the brain, the spinal cord and the optic nerves. It starts in early adult life and has an impact on social, financial and professional life. There is no biomarker for diagnostic certainty, especially at presentation. Diagnosis should be established as early as possible, as disease modifying drugs (DMDs) have higher efficacy when initiated early and may change the natural history of the disease.

The aim of the conference is to:

1. Establish guidelines for diagnosis, treatment, follow-up and management of patients with MS in Lebanon.
2. Discuss and participate in research projects based on epidemiology, clinical trials and more fundamental aspects of the disease in the future.

A guideline may be defined as a developed statement that assists clinicians in making decisions. MS guidelines are aimed at helping health care professionals provide optimal ways to diagnose, treat and follow-up patients with MS. It is an evidence-based guideline which takes into consideration the resources available locally.

In Lebanon, the number of MS patients is estimated to be between 1500 to 2000 from unofficial sources, as there are no available or reliable epidemiological studies to date. Diagnosis is usually made between the ages of 20 and 50 years, however, patients often realize that the condition has been present for many years. It affects women more than men in a 3:1 ratio. The cause is unknown, but it is thought to be a combination of genetic background (genetic susceptibility) and environmental factors. This combination of factors triggers an inappropriate immune reaction (dysimmune disease), responsible for inflammation through the CNS, mediated by reactive T and B cells with a secondary demyelination, axonal damage and degeneration. Remyelination and repair is common in the early phases of the disease, but repeated episodes lead to accumulation of degeneration which is supposed to underlie the progressive secondary phase of MS. Key responsibilities for the medical team include making the correct diagnosis, reducing the intensity of symptoms, prevent exacerbations, slowing disease progression, and trying to help the patient adjust to the psychosocial difficulties that may occur. The challenges are related to the polymorphic presentations of MS and the unpredictable prognosis of the disease for an individual patient. All of these features mean that MS patients should be diagnosed, treated
and followed by neurologists, in coordination with other members of the interdisciplinary MS team.

There is no data regarding economic burden (DMDs cost, hospitalizations) nor is there data regarding psychosocial burden.

A-Methodology

Under the authority of the Lebanese society of Neurology (LSN), a group of neurologists took the initiative to participate in this LSN MS committee with the purpose of establishing a consensus for the management of patients with MS, under the supervision of a Coordinator designed by the LSN board. The coordinator sent a proposal of contents, and chapters were distributed among the committee. A first meeting with an elected committee was held in Paris on April 27th, 2011. The second meeting was in Beirut from the 27-29 May 2011. The coordinator sent additional information by email on the 30th and 31st of May.

All points were discussed and approved by the members present at the meeting. The discussed documents were reviewed by the coordinator who proposed a synthesis to the members of the committee. Two other meetings (July and September 2011) allowed to discuss final details and to propose future actions. The consensus committee presented the guidelines on July 15th at the Franco-Lebanese meeting in Beirut and on September 24th at the 3rd International Congress of the Lebanese Society of Neurology Brumana. The final document was sent for approval to all members of the MS group in October 2011. It will be presented to the officials after its approval by the LSN board and members.

B. Epidemiology of MS in Lebanon

There is no available epidemiological studies that have been done in Lebanon. Thus, data from third party payers, MOH, Security and Armed forces institutions are the only sources of information. These sources are focused primarily on the number of treated MS patients, most of whom are those who are being treated with interferons.

A study published in 2008 estimated the number of patients with MS to be between 1200 and 1700, however this is only an approximation. In the same paper, authors described the characteristics of 202 patients fulfilling the McDonald criteria. Data reported in this paper are questionable. There is a need to establish a national registry that would include all MS patients to accurately define the disease incidence and prevalence in Lebanon. This will require financial support from the MOH.
C. Perspectives

This consensus working group looked forward to assessing the basic and updated criteria to optimize management of MS in Lebanon. This will allow Lebanese neurologists to collaborate with each other and to initiate clinical trials regarding therapeutics and pathophysiology of MS.

As several new drugs will be proposed in MS treatment in the coming years, this consensus statement may serve as a basis for discussions with official health authorities and help to establish future common research programs. Regular updates will be necessary.

Chapters below have been written by members of the committee, discussed and approved by all members present at the May 2012 meeting.
II. Diagnosis

A- Clinical aspects

Four principal clinical evolutionary modes of MS have been proposed:

a. Relapsing-remitting (RR-MS)
b. Secondary progressive (SP-MS)
c. Primary progressive (PP-MS)
d. Progressive relapsing (PR-MS)

1- Clinical Presentations

RR-MS is the most frequent presentation, initially occurring in more than 80% of individuals with MS with a clear gender difference. Women are affected more than men with a ratio of 2.7:1. Clinically, RR-MS is characterized by relapses, with full or partial recovery, followed by interval periods of clinical stability and absence of disease progression.

Clinically Isolated Syndrome (CIS) is described as a first neurological episode that lasts at least 24 hours and is caused by either inflammation or demyelination confined to the CNS. Patients with CIS may be at high risk for future attacks and development of MS based on the initial MRI and not on CSF results according to McDonald criteria 2010. When CIS is accompanied by MRI lesions that are similar to MS lesions, the affected individual has a higher risk of developing a second neurologic event and progressing to clinically definite MS (CDMS) within several years. The first symptoms are not recognized as changing the risk of a CIS. If they meet radiological criteria of dissemination in space (DS), disease is defined as possible MS. If both DS and dissemination in time (DT) are met, the disease is MS. If only two lesions located in the same strategic region are present on brain MRI, CSF may be helpful in defining MS (according to the New McDonald criteria 2010)

Radiologically isolated syndrome (RIS) is subclinical MS with lesions on brain and or spinal cord MRI showing the dissemination of the disease in time and space during the preclinical phase. The patient's history and neurological examination are non-relevant.
**PP-MS** is the other common presentation, occurring in 10-20% of cases. PP-MS manifests with disease progression from the onset, occasional disease activity plateaus and temporary minimal improvement. Unlike RR-MS, females and males with PP-MS are affected equally. Patients are usually older and there is no gender difference. The disease process usually manifests with myelopathy with less brain lesions and progresses more rapidly.

2- **Clinical Evolution**

After several years, patients with RR-MS may progress into SP-MS, which is characterized by disease progression with or without occasional relapses, minor remissions and plateaus. About 50% of people with RR-MS develop SP-MS during the first 20 years of their illness. **PR-MS** (a rare form) is characterized by a progressive course from the beginning, acute relapses with or without recovery, and intervals between attacks which demonstrate disease progression. **Transitional progressive MS** is a form of MS characterized by an initial relapse, followed by progression after several years of clinical stability.

The most accepted definition of **benign MS** is when patients remain fully functional in all neurologic systems (EDSS < 3) 15 years. Lower disability and longer duration (20 years) would be better, but this is still controversial.

**Malignant Form:** disease with a rapid progressive course, leading to significant disability in multiple neurologic systems or death in a relatively short time after disease onset. Marburg variant of MS is an acute and clinically fulminant form of the disease that can lead to coma or death within days. Balo type is another mainly neuropathologically defined variant.

3- **Definitions**

**Relapses:** A relapse is defined as an episode of neurological disturbance (new symptoms, or exacerbation or recurrence of pre-existing symptoms) for which causative lesions are likely to be inflammatory and demyelinating in nature independent from increase of body temperature. New occurrence of paroxysmal symptoms fulfills also the definition. There should be a subjective report (supported by objective findings) or objective observation that the event lasts for at least 24 hours. Each relapse of MS should be
separated from the last relapse by at least one month of clinical stability. The beginning of a new relapse is separated from the beginning of the previous one by at least one month.

**Progression:** Progression is defined by a worsening of disability over a minimum of six months. Usually it is measured by an increase of EDSS by 1 point after 3 months, confirmed 3 months later.

**Possible MS:** Dissemination in space is reached but not dissemination in time.

**MS:** All criteria for MS are present.

**Non MS:** There is evidence for another diagnosis.

**B- MRI Aspects**

MR imaging has played an increasing role in the diagnosis and management of MS. It provides three main advantages in MS.

- First, it helps diagnosing MS at the first attack
- Second, it can detect 5 to 10 times more activity than clinical evaluation in RR-MS.
- Third, it contributes to understanding of the pathophysiology of MS and how pathophysiological changes relate to clinical manifestations of disease.
- Fourth, it is a good surrogate marker to assess response to therapy.

**1-Diagnosis**

Several criteria have been developed to integrate MR imaging with clinical evaluation and other diagnostic methods to achieve earlier and more accurate diagnosis, including the revised McDonald criteria.

The McDonald criteria were the first to incorporate the brain and spinal cord lesions visualized on MR imaging into traditional diagnostic approaches, including history, examination, and laboratory tests. Specifically, these revisions were designed to help demonstrate lesion dissemination in time, clarify the evaluation of spinal cord lesions, and simplify the diagnosis of primary-progressive disease.
2- Pathogenesis

MS is a complex immune disease in which self-reactive T and B-cells and monocytes mediate inflammation of the CNS white matter and demyelination of axons and secondary degeneration, leading typically to cumulative neurologic disability. MR imaging by using gadolinium-containing contrast agents has helped identify the pivotal role of the blood brain barrier (BBB). Demonstrating BBB disruption on MR imaging may represent one of the earliest indications for a dissemination in time and the diagnosis of MS.

3- Prognosis

An important objective in management is predicting the disease course in individual patients. For patients with a first clinical event, the objectives are to predict the occurrence of a second episode, and later the risk of disability and its progression. In patients presenting with a first clinical event suggestive of an MS attack and lesions on MR imaging, the likelihood of developing clinically definite MS is 88% over the next 14 years. In established disease, the objectives of management are to predict relapse in the short-term and predict disability and sustained disease progression in the long-term. A relapsing course is followed by sustained progression within 2 decades in 50% of cases. The relapse rate within the first years, the initial lesion load and the accumulation of lesions in the first 5 years, seem predictive of disability and SP-MS 10, 14 and 20 years later.

Conventional MR imaging measures, including T2 lesion load, correlate poorly with clinical outcomes in MS, and correlations tend to weaken further in later stages of disease. Meta-analysis of the predictive value of gadolinium-enhanced MR imaging similarly indicates a low ability to predict relapses and development of impairment and disability.

A number of explanations have been suggested for why MR imaging assessments are dissociated from clinical status and the development of disability-the so-called “clinicoradiologic paradox”:

- Deficiencies in clinical and MR imaging assessments.
- The presence of strategic-versus-nonstrategic lesions.
- The dual role of the immune system, both in destroying and promoting repair.
- The role of neurodegenerative processes that gain importance as the disease progresses.
- Abnormalities of apparently normal white and gray matter.
- The role of adaptation and reorganization in compensating disease-related damage.
In conclusion, prognosis in individual patients cannot be based on MRI findings alone.

4-Monitoring Therapy

MR imaging is widely used to investigate the anti-inflammatory effects of therapies. In this setting, the most widely adopted MR imaging assessments are T2 (for lesion load and new and enlarging lesions) and gadolinium-enhanced T1 (for, new and enlarging lesions).

Early initiation of treatment is beneficial on MRI and clinical activity of the disease especially to patients at high risk. MR imaging helps to identify patients at risk of high clinical activity.

Techniques and Protocols for MR Imaging in MS

MR imaging is widely recognized as superior to other imaging modalities, including CT, for the visualization of lesions, particularly smaller lesions, and has largely replaced alternative imaging techniques in practice.

MS plaques can be characterized at MR imaging by their location, morphology, signal intensity, and the presence of gadolinium enhancement.

Acute-phase plaques appear as rounded areas of high-signal intensity on T2 sequences. Gadolinium enhancement on T1 sequences is related to BBB damage associated with inflammation. There are two patterns of enhancement: uniform enhancement, reflecting the onset of a new lesion, and ring like enhancement, indicating reactivation of an older lesion. Non-enhancing lesions are the result of earlier episodes of disease. T2-weighted MR imaging is considered the most sensitive diagnostic test for demonstrating disease dissemination, but with moderate specificity. T1-weighted gadolinium-enhanced imaging offers increased specificity by differentiating enhancing from non-enhancing lesions. Use of both of these imaging techniques provides optimal specificity. The amount and intensity of gadolinium enhancing lesions depends on the dosage and the time between application and examination.

Optic neuritis is present in around 50% of patients with MS and is frequently the first sign (20-25%). Gadolinium enhancement can be a sensitive method for visualizing optic neuritis and has an important role, along with brain MR imaging and symptoms, in establishing a definitive diagnosis.

The spinal cord is also frequently involved in MS and for most patients both spinal cord and the brain are affected during the course of the disease. In < 25% of patients, however, lesions are present in the spinal cord alone. Most spinal lesions are localized to the cervical
rather than the thoracic cord and tend to be multifocal and asymmetric. At MR imaging, spinal lesions show increased T2 signal intensity and during a spinal attack, frequently, gadolinium enhancement.

In general, findings at spinal MR imaging are less definitive compared with brain MR imaging for diagnosing MS.

Contrast enhancement in MS increases the reliability of MR imaging to depict active lesions and has a pivotal role in demonstrating dissemination in time, as defined in the revised McDonald criteria. Contrast enhancement also assists in excluding confounding diagnoses, including other inflammatory conditions and tumors.

For these reasons, gadolinium enhancement is widely recommended for the diagnosis and initial evaluation of MS.

- Optional dual-echo or FLAIR, sagittal midline (to detect corpus callosum lesions)
- Dual-echo and FLAIR, axial whole brain (to detect gray matter lesions)
- Unenhanced T1 is important to detect spontaneous hypersignal and to compare the aspect before and after GD
- Contrast-enhanced T1 scan: 0.2 ml/kg, 5 min after Gd infusion in 1 to 2 min.

**Recommendation: Brain-Versus-Spinal Cord MR Imaging**

- For non spinal cord presentation, brain MR imaging should be performed. MR imaging investigation may be stopped if there are sufficient lesions to support dissemination in space and time. If that is not the case, additional spinal MR imaging may be diagnostically helpful, also concerning the follow up.
- For spinal cord presentation, start investigations with spinal cord MR imaging, mainly to exclude alternative conditions. If MS remains suspected, perform brain MR imaging to identify additional lesions. Use if possible STIR sequences in addition to spin echo, and sagittal and axial planes.

In summary, MRI has become the corner stone in demonstrating ongoing lesion formation in patients suspected of having MS. MRI may thus act as a surrogate for a clinical relapse when the followings are present:

- Lesions of different ages on the T2 MRI of the brain and/or on the MRI of the spinal cord with at least one silent lesion other than the clinical related lesion
- At least one gadolinium enhanced lesion on the MRI of the brain and/or of the spinal cord
- At least three out of the four Barkhof criteria
- With the new MAGNIMS criteria, dissemination in time and/or space is clearly established at any time of the disease whenever a new brain/spinal cord should be performed and MS diagnosis confirmed. Typical MRI lesions suggestive of MS in the brain and spinal cord, performed by the approved protocol, including, at least, T2, T1 with and without Gadolinium injection.

The recommended MRI technique include the following:

<table>
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<tr>
<th>MRI technique</th>
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<tbody>
<tr>
<td>High field; 1 tesla and more</td>
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<tr>
<td>Identical sequences</td>
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<tr>
<td>Axial planes (bicallosal)</td>
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<tr>
<td><strong>Thin (3mm); interleaved</strong></td>
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<tr>
<td>1-Sagittal FLAIR</td>
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<tr>
<td>2-Axial spT2 with double ET</td>
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<tr>
<td>3-Axial T1 before gadolinium</td>
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<tr>
<td>4-Gadolinium infusion</td>
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<tr>
<td>– After 5 min.</td>
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<tr>
<td>– 0.2ml/Kg</td>
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<tr>
<td>– Distant from MPIV (&gt; 4 weeks)</td>
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<tr>
<td>5- Axial FLAIR may be acquired in the mean time</td>
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<tr>
<td>6-Axial T1 post-gadolinium</td>
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<tr>
<td>*A T13D sequence is optional</td>
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</table>

C- CSF

The CSF examination is looking for immune-inflammatory indicators of intrathecal origin. The immunologic abnormalities measured in CSF reflect activation of the humoral immune response and are not specific for MS. Examination of the CSF is frequently used to confirm the diagnosis of MS and to exclude other possibilities.
Typical CSF findings that would suggest MS:

a. Cell count: A few cells (usually ≤ 20 lymphocytes) may be found. However a cell count > 50 should raise a red flag.

b. Total protein is usually normal. A protein level >100 mg% should raise doubt about the diagnosis of MS. The albumine quotient is mainly normal. Do not use the total protein content alone to get information of the blood brain barrier.

c. IgG level and IgG index: The % of CSF IgG is normally 3-5% of total CSF protein. In MS IgG levels > 13% of total CSF protein is considered diagnostic. An IgG index > 0.77 is considered abnormal.

\[
\text{IgG index} = \frac{\text{CSF IgG}}{\text{CSF albumin}} \div \frac{\text{Serum IgG}}{\text{Serum albumin}}
\]

d. Oligoclonal bands within the CSF This is the most sensitive test for MS. Immunofixation electrophoresis is considered to be the method of choice. Two or more bands only present in CSF are necessary for the diagnosis. One single band does not confirm the diagnosis. Although OCBs have been found in a variety of diseases, their presence in the CSF of patients presenting a clinical picture compatible with MS reinforces the diagnosis (Table 1).

D- Electrophysiology

Evoked Potentials measure the response of the brain to stimulation of various sensory pathways (auditory, visual, somatosensory, etc.). Of these various types the visual evoked responses were found to be the most helpful in the diagnosis of MS.

However, with the recent advances in MR imaging the role of Visual Evoked Potential (VEPs) in the diagnosis of MS has become limited (McDonald criteria 2010).

E- Atypical MS

MS in children and adolescents (younger than 18 years of age) accounts for 3–10% of the whole MS population. It is characterized by a relapsing course in almost all cases as inflammation is highly active compared to adult onset forms; consequently, relapses are more frequent, at least in the first year of evolution. Overall, childhood clinical forms are not different from those of the adult form; however, multifocal with cerebellar and brainstem involvement with disseminated encephalomyelitis-like onset are more frequently reported.
Potentially, higher EDSS scores with mild to severe disability and progression could be reached at a younger age than in adult onset (Banwell et al. 2007; Ghezzi A. 2010).

F. Differential diagnosis

I. Monofocal

a. Optic Neuritis and diseases that include ophthalmological diseases and retinal disturbances.
b. Infectious Myelopathy: viral, bacterial, parasitic. Usually one single lesion is present with abnormal CSF findings.
c. Transverse myelitis: This term is usually used for idiopathic inflammatory myelopathy. Cord swelling and enhancement may be present; often involving a longer segment than in MS. MRI of the brain may be helpful for showing additional lesions in case of MS or Acute disseminating encephalomyelitis (ADEM). This process is typically monophasic.
d. Infarct: This is more common at the thoracic level. Usually, only a single lesion is present. Contrast may be present, although this is not the dominant feature. Signal alteration usually initially involves the anterior gray matter (anterior spinal artery distribution). The patient's clinical presentation will be acute. Especially consider this diagnosis if the patient is older and/or has a history of aortic/vascular surgery.
e. Devic Neuromyelitis Optica (NMO): There is usually an extensive lesion that involves at least 3 segments of the spinal cord with usually normal brain MRI with or without optic nerve involvement. Small MRI lesions did not exclude Devic Syndrome. The NMO antibodies are positive in blood and CSF in 50 %.
f. Radiation myelitis: Generally, doses higher than 4000 cGy are required to cause this condition. The latency period is 1-3 years. Chemotherapy may be synergistic. Images may show some peripheral enhancement.

II- Multifocal

a. ADEM: The concomitant presence of active brain lesions is the rule. It runs a monophasic course, rather than the relapsing course of MS. A history of viral infection or vaccination within the previous 3-4 weeks should alert the clinician.
b. Vasculitis: Processes such as systemic lupus erythematosus or Sjögren Syndrome can result in spinal lesions that mimic MS. Often, multiple lesions are present. However, the clinical history and the laboratory data will help to establish the correct diagnosis.

c. Sarcoidosis: This involves the CNS in approximately 5% of cases. Concomitant pial involvement is frequently encountered. Enhancement is usually the rule.

d. Non specific leukoencephalopathy

G. How to diagnose MS: (Mac Donald Criteria 2001, 2005, 2010)

Making the diagnosis of MS remains a challenging problem for clinicians; the foundation of diagnosis rests on demonstrating 3 main statements:

a. Dissemination in space
b. Dissemination in time
c. No better explanation than MS

Basic principles of diagnosis mean that the treating physician (the neurologist) should demonstrate that there is dissemination in space and time. At each diagnostic step, any other possible disease or pathology that could explain the clinical findings, should be ruled out, by applying clinical, radiologic, and laboratory evidence to secure the diagnosis. All these points are reached clinically and/or with MRI, CSF analysis and occasionally electrophysiology and other tests (biomarkers, biopsies, etc.) are necessary.

1. RR-MS
a) Dissemination in space:
   - clinically: 2 different locations or
   - clinically and with MRI: one clinical location + positive MRI
   - clinically and with MRI and CSF: one clinical location + abnormal MRI showing lesions (at least two) in the same strategic locations + positive CSF

b) Dissemination in time: clinically (2 relapses) or clinically and with MRI (lesions of different ages, or active lesions)

c) Other possible etiologies should be ruled out. Some tests are systematic. In Lebanon, it is important to consider infectious diseases (HIV, Brucella, Syphilis,
etc.), immunologic diseases (clinical examination, ANA, etc.). See chapter regarding differential diagnosis.

2- PP-MS

These patients do not experience clear attacks like patients with relapsing-remitting onset, and MRI activity is usually lacking. Separate criteria have been developed to diagnose MS in patients with progressive onset. CSF analysis is recommended for this category of patients. Dissemination in time relies on clinical evolution over at least one year (retro or prospectively). Dissemination in space is proved clinically or with CSF, brain MRI, spinal cord MRI and VEPs.
III. Therapy

A- Relapses

Relapses are treated with high doses of methylprednisolone (MPIV). A total of 3-5 gr is usually given for 3 to 7 days. Sometimes, no treatment is required. The use of oral corticosteroids in the treatment of relapses is not recommended. If not sufficient efficacy try it again with MPIV (2g per day for 3-7 days). Six sessions every other day of plasmapheresis may be given in disabling relapses not responding to corticosteroid pulse therapies within 4 weeks.

B- Symptomatic Treatment

Patient education is particularly important in the management of symptoms.

I. Spasticity

Oral Agents

**Baclofen** should be started at a very low dose with gradual increases in the dosage by 5 to 10 mg until the desired effect is achieved and/or side effects such as drowsiness, fatigue, and muscle weakness become unacceptable, usually reaching a dose of between 40–80 mg a day.

**Tizanidine** should be started at a low dose, 2 mg three times a day, and gradually increased up to a maximum of between 18–36 mgs. The most frequent side effects are tiredness, drowsiness, and dry mouth. Liver function tests must be checked before and after treatment because hepatotoxicity may occur.

**Dantrolene**: Side effects include drowsiness, weakness, fatigue, and occasionally hepatotoxicity, which may be irreversible.

**Benzodiazepines** may be used as additional therapy in resistant cases of spasticity. Its role is limited by side effects, including drowsiness and dependence.

**Cannabinoids**: There is meanwhile strong evidence of the efficacy of oral cannabinoids in spasticity of MS. A cannabinoid now is licensed in different countries for patients with unsufficient response to first line drugs. **Other Drugs were tried like** clonazepam, memantine, glycine, L-threonine, vigabatrin, and gabapentin.
**Surgery**

*Posterior rhizotomy* may have a role.

**Other treatment**

**Botulinum toxine**

Is licensed for spasticity and is the choice in disabling focal spasticity. Furthermore in patients where you cannot reach sufficient efficacy with orally given drugs botulinum toxine is helpful to reduce severe flexor or adductor spasticity. The dosages recommended depend on the kind of botulinum toxine you will apply. The duration of the effect differs individually and the pattern of spasticity can change.

**Baclofen pump**

In very severe spasticity a last line therapy are, intrathecally applied drugs via a subcutaneously placed infusion pump. The effect is initially tested by bolus injection of 25 to 100 mcg baclofen given via a lumbar puncture before considering continuous drug application through an electronically programmed drug delivery system. It is contraindicated in patients with decubitus ulcers.

**II. Ataxia and Tremor**

The treatments effects are limited. There are no licensed drugs. *Isoniazid* (with pyridoxine) for postural tremor with an intention component, up to 1200 mg a day in divided doses. It is not well tolerated and causes gastrointestinal disturbance. Other drugs have been less evaluated: carbamazepine, clonazepam, and buspirone, propranolol. Thalamotomy may be proposed. Thalamic stimulation has not yet proved its efficacy in MS.

**III. Fatigue**

Amantadine seems to be effective over placebo in the MS Specific Fatigue Scale but not pemoline. Modafinil may be effective in patients with fatigue and hypersomnia, with a beneficial effect observed with both the 200 mg and the 400 mg doses with no added benefit from the higher dose and no serious side effects.

Motor fatigability may be treated with a potassium channel blocker 3-4-diaminopyridine. Epileptic seizures can also result from this therapy. More recently, fampridine was shown to be effective and well tolerated.
IV. Bladder Dysfunction
The management of bladder dysfunction in MS includes two key components: the use of clean intermittent self-catheterization (CISC) to manage incomplete emptying, and anticholinergic agents such as oxybutynin to reduce the hyperreflexia that results in inadequate storage. Treatment for detrusor hyperreflexia include the anticholinergic agent oxybutynin as first-line treatment, started at 2.5 mg twice daily, with a maximum recommended dose of 5 mg three times daily. Desmopressin may be considered, particularly for nocturia or in special personal situations. It is administered by nasal spray, 1-2 puffs (10–20 μg) at bedtime or during the day, reducing urine output for 6 to 8 hours. Other procedures are needed in more severe cases. Permanent catheterization may be necessary in many patients with severe disease as medical treatments become ineffective or impractical. A long-term urethral catheter is rarely advisable. The preferred alternative is a suprapubic catheter, which should be inserted by a urological surgeon and subsequently changed every 2 months.

V. Bowel Dysfunction
Constipation and incontinence are treated symptomatically.

VI. Sexual Dysfunction
Decreased vaginal lubrication can be treated with water-soluble lubricants, and dysesthesias may be relieved with carbamazepine or phenytoin. There are attempts to treat also women with sildafinil or similar drugs. In male patients erectile difficulties are treated with Sildenafil (Viagra®) or similar agents which differ mainly in side effect profile and duration of the effect.

VII. Cognitive Symptoms
Neuropsychological training may be tried.

VIII. Pain
Pain is treated with carbamazepine for trigeminal neuralgia, or phenytoin, gabapentin, lamotrigine and amitriptyline. Surgical intervention may be required in chronic pain. Painful RLS-like syndrome has been described and may respond to dopamine agonists.
IX. Other Paroxysmal Symptoms

Dysarthria, ataxia, tonic spasms, and paroxysmal sensory symptoms are sensitive to carbamazepine, and a low dose gabapentin. Epilepsy is treated with anticonvulsants.

X. Psychiatric and Psychological Dysfunction

The treatment of depression is similar to that for people who do not have MS. SSRIs remain the mainstay of treatment. Psychological disturbances are common in MS, and many patients have difficulty coping from the time of initial diagnosis. This may be compounded by the subsequent development of disability.

XI. Other Symptoms

Visual Dysfunction: Involuntary eye movement disorders, such as nystagmus and oscillopsia, also cause distressing visual disturbance and may be helped by the use of prisms. There is anecdotal evidence to suggest the use of a number of medications including baclofen, gabapentin, and isoniazid for this symptom.

Vertigo: Prochlorperazine may be helpful in acute vertigo, while physiotherapy together with cinnarizine, may be helpful when symptoms are chronic.

Swallowing, Speech, and Respiratory Dysfunction: Dysphagia is not uncommon in MS, and suggestive symptoms have been reported in up to 43 percent of the MS population. These symptoms included coughing when eating, choking, anxiety about swallowing, and change in swallowing function. Such symptoms are often overlooked until the patient has a severe choking episode. Mild dysphagia usually is easily managed with assessment and advice from a speech therapist. There is an unquantified risk of aspiration pneumonia in more severe cases, and investigation may include videofluoroscopy. Percutaneous gastrostomy may be required if swallowing is unsafe or intake is inadequate. Speech disturbance in MS usually is due to dysarthria, although dysphasia does occasionally occur, usually in patients with severe cognitive deficits. Again, assessment and management by a speech therapist is helpful, and a communication aid may be useful in very severe dysarthria.
Temperature Sensitivity and fatigability of gait: 3-4-diaminopyridine has been reported to be particularly beneficial in patients with temperature sensitivity. Meanwhile fampridine (Fampyra) may be given to patients with abnormal restriction of gait due to fatigability. This medication is still not licensed in Lebanon.

Neurorehabilitation

The philosophy of rehabilitation, which emphasizes patient education and self-management, is ideally suited to meet the complex and variable needs of MS. Rehabilitation aims to improve independence and quality of life by maximizing ability and participation.

C- Disease Modifying Drugs in RRMS

Prevention or at least delay of disease progression is a key target in the management of MS. Drugs are divided in two groups, immunomodulatory and immunosuppressive agents. Only patients with MS are treated. CIS (normal MRI) or possible MS need diagnosis confirmation and risk evaluation.

1- Immunomodulatory agents

This group includes interferon beta and glatiramer Acetate. It has been shown that they reduce relapse rate, delay the occurrence of a second relapse and may reduce the severity of relapses. The efficacy regarding progression of disease is still under debate. They have been used for more than 15 years as first line therapy in RR-MS. Thus, they are more active in the inflammatory phase of the disease.

Interferon β (IFNβ)

- IFNβ are immunomodulators that switch Th1 lymphocytes to Th2 lymphocytes.
- In various clinical trials, IFNβ have been shown to have efficacy in MS. IFNβ exhibit consistent effects by reducing the clinical and MRI attack rate in patients with RR-MS (Class I):
  - They diminish the frequency of relapses between 30-45%.
  - They diminish the accumulation of MRI lesion.
  - They extend the survival rate, supporting a long-term benefit of initiating early treatment.
Three different IFNβ formulations are available in Lebanon:

- Subcutaneous IFNβ -1b, Betaferon/Betaseron, 250 µg QOD
- Intramuscular IFNβ -1a, Avonex, 30 µg weekly
- Subcutaneous IFNβ -1a, Rebif, 22 or 44 µg TIW

IFNβ therapy is generally safe and well-tolerated. It often causes side effects, such as flu-like symptoms, and laboratory abnormalities, such as elevation in liver function tests or lymphopenia. However, these side effects are generally mild, tend to disappear within the first months of treatment, and thus do not necessitate discontinuation of therapy. Subcutaneous IFNβ might also cause injection site reactions, and higher doses of IFNβ are more likely to cause side effects. CBC, AST and ALT should be checked every month for the first 3 months, then every 3 months for the next 6 months, then every 6 months.

The biological effect of neutralizing antibodies to IFNβ is not fully clear.

There are few comparative studies between the different IFNβ, usually of short duration and with methodological biases; thus there is no evidence for superiority of one drug over the other.

A patient education program regarding the injections should be established.

It is appropriate to consider treatment with IFN β in RRMS (Type A).

Glatiramer Acetate (GA)

- GA is a synthetic co-polymer structurally similar to myelin basic protein (MBP), a major component of myelin. It acts at the level of the three-molecular complex antigen-recognition, producing anti-inflammatory effects mainly via functional inhibition of MBP-reactive T-lymphocytes and induction of Th 2 (T helper) lymphocytes in the CNS.

- GA is not available in Lebanon.

- Based on the available evidence, GA reduces attack rate by approximately 30-40% (Class I) and improves MRI measures of disease activity in patients with RRMS.

- There is similar efficacy between the IFNβ and GA

- GA is given as a daily 20mg subcutaneous injection (Copaxone; Teva Neuroscience, Kansas City)
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- Side effects to GA: benign palpitations are generally mild and injection site reactions usually following the first year of therapy are usually minimal. Lipoatrophy can occur. A so called SPIR (subacute post injection reaction) may be observed with flush, respiratory difficulties and feeling of fainting. This reaction is non allergic and resolved spontaneously within a few minutes.

- There is no need for laboratory follow-up.

- GA is used as a first line option, or in patients with contra-indications to INFβs—major depression, hypersensitivity to INFβ, poorly controlled epilepsy.

- GA is considered as a treatment option for patients with RRMS (Type A).

Switches between IFNβ formulations and glatiramer acetate have not demonstrated consistent benefits for either approach.

There is no class I evidence from randomized controlled trials examining the efficacy of switching from one FDA-approved monotherapy to another monotherapy in patients with insufficient response.

The decision for cessation of treatment should be taken if:

- Loss of efficacy
  - Frequency of relapses
  - Progressive MS without relapses
- Occurrence of side effects
- Desire of pregnancy

2- Immunosuppressive agents

Natalizumab

- Natalizumab (Tysabri; Biogen Idec), a selective immunosuppressor, is a humanized monoclonal antibody to the α4 subunit of αβ1 integrin (VLA-4), a protein found on the surface of lymphocytes. αβ1 integrin allows adhesion and subsequent migration of inflammatory cells into the brain and spinal cord. Natalizumab selectively blocks this interaction, thus preventing the transmigration of inflammatory lymphocytes across the blood brain barrier into the CNS. This agent increases the blood lymphocyte count.
In one study, patients on Natalizumab demonstrated a 68% reduction in annual relapse rate and a 42-52% reduction in confirmed progression over 2 years compared with placebo. In the sub-group of highly active MS (patients ≥ 2 relapses and ≥ 1 Gd+), there was an 81% reduction of annual relapse rate and a 64% reduction of progression of confirmed disability after 24 weeks, vs placebo.

MRI findings from the same study showed an 83% decrease in new T2 lesions at 2 years and a 92% decrease in Gd+ lesions at 2 years.

Natalizumab is given as an intravenous infusion at the dosage of 300mg monthly.

Monitoring of treatment:

- Allergic reactions:
  - 4% of patients.
  - Usually after the 2nd or the 3rd infusion.
  - May occur during the infusion or in the hour following it.
  - Cutaneous, rarely systemic reactions (respiratory difficulties, palpitations)
  - Treatment should be stopped if these occur.

- If after 8 or 9 months of treatment, a relapse occurs, check for Natalizumab antibodies at 3 months intervals; if positive (6% of patients), shift to another treatment.

- Brain MRI should be performed at least once per year.

- The prevalence of progressive multifocal leukoencephalopathy (PML), an opportunistic infection of the CNS associated with the JC virus, is currently estimated at one in 1000 patients treated with natalizumab (0.1%) [0.3% in those receiving < 25 infusions, 1.5% in those receiving 25-36 infusions, and 0.9% in those receiving 37-48 infusions]. This diagnosis is suspected if the patient has epileptic seizures or behavioral changes. A brain MRI should be performed in less than 24 hours. CSF analysis with an ultrasensitive polymerase chain reaction assay for JC
viral DNA confirms the diagnosis. Five to seven plasma exchanges are performed every other day. The proportion of survivors is near 70%.

- After plasma exchange, nearly all of the patients (91%) develop immune reconstitution inflammatory syndrome (IRIS). IRIS presents as new or worsening neurologic symptoms, tends to be severe, and usually occurs within days or weeks after rapid removal of natalizumab. By 6 months post diagnosis, most of these patients either recover from IRIS or start to recover. IRIS is suspected if brain MRI shows gadolinium+ lesions. IRIS is treated by cortisone.

- Role of anti-JC antibody will be determined in the future. It is recommended to determine anti-JVC antibodies before starting treatment to stratify the risk of developing PML. In case of positivity the benefits and risks should be assessed to guide the practice. Another treatment may be considered for high risk patients.

- Future plans are to request economical support from the industry to assist with costs.

- There is no guideline on the optimal duration of therapy with natalizumab, and patients may continue to receive the drug if perceived to be efficacious to their disease.

- Patients who are candidates for natalizumab treatment should be given detailed information about treatment and safety issues and should sign an informed consent before starting treatment.

- Natalizumab is contra-indicated in pregnancy.

- Thereafter, information should be reviewed with the patient and informed consent should be signed by him annually.

- Extensive education should be provided to prescribers, patients, and relatives as part of global risk-management programs for natalizumab and a registry should be established.

- There is little data concerning safety and efficacy in switching from natalizumab to fingolimod.
Natalizumab is recommended for patients with more active, rapidly evolving relapsing disease and in those who have failed to respond to first-line DMTs (IFNβ or glatiramer acetate).

Fingolimod  Fingolimod (Gylenia; Novartis, Basel, Switzerland) is a sphingosine-1-phosphate receptor (S1P1) agonist, which binds to S1P1 receptors on T-cells, affecting the receptor's signaling pathways. The result is inhibition of T-cell migration from lymphoid tissue into the peripheral circulation and target organs, including the CNS, thus attenuating inflammation without affecting their function.

- Lymphopenia is dose dependent and can be observed as early as 2 hours after a single dose, reaching nadir at 6–8 hours. With chronic treatment, nadir is reached at 2–4 weeks.
- One study investigated the effects of daily doses of fingolimod 0.5 and 1.25 mg compared with intramuscular IFNβ-1a 30 µg once weekly over a 12 months period. Compared to placebo and IFNβ-1a (Avonex), the 0.5 - and 1.25-mg doses of fingolimod showed a relative reduction of the annual relapse rate by 52 and 40%, respectively. In addition, there was a proved effect on short-term disease progression.
- Another study done over 2 years showed that compared with placebo, Fingolimod 0.5 mg/d reduced the annual relapse rates by 52% in patients with mild disability and by 66% in patients with moderate to severe disability. Fingolimod was also associated with a reduction in disability on short-term disease progression.
- Fingolimod is the first oral treatment approved for RR-MS in patients with high disease activity despite treatment with IFNβ and those with rapidly evolving RRMS.
- Dosage: 1 tablet 0.5 mg/d.
- Discontinuation rates due to side effects were low. Frequently reported minor side effects were nasopharyngitis, headache, diarrhea and nausea. Clinically asymptomatic lymphopenia was common.
- Serious Adverse Events were bradycardia (mostly asymptomatic, appearing 4-5 hours after therapy initiation, and transient) and rarely atrioventricular block. Oral fingolimod may also increase the risk of some infections. In addition, fingolimod may be associated with an increased risk of macular edema, hepatic effects and fetal toxicity.
• **Work-up before starting treatment:**
  o CBC, liver function tests, EKG, pregnancy test if indicated
  o Varicella-zoster IgG antibodies; if negative, Pox vaccination is given before starting treatment.
  o Ophthalmologic exam including optic coherence tomography in patients with diabetes or uveitis
  o Dermatologic exam and check for a history of melanoma (risk of melanoma)

• **First visit:** It is recommended to have close EKG and blood pressure monitoring for at least six hours after intake of the tablet. If the patient stops the treatment for more than 3 weeks, the same procedure of observation is repeated when the drug is reintroduced.

• **Follow-up:**
  o CBC, liver function tests monthly for 3 months
    If blood lymphocytes count falls below 200/mm³, treatment should be stopped.
  o Ophthalmologic exam including optic coherence tomography: 3-4 months after the first visit.

• Wash-out period of 3 months if fingolimod is replaced by another DMD.

• Since most MS patients are of childbearing age, it may be advisable to avoid pregnancy while taking fingolimod until more information is available and a registry is opened.

• A monitoring program for assessing the long-term safety of fingolimod and a registry of patients should be created.

• Fingolimod is recommended for RR-MS in patients with high disease activity despite treatment with IFNβ and those with rapid evolution.

**Mitoxantrone**

• Mitoxantrone is an anthrecenedione, a cytotoxic agent with immunosuppressive properties, used in various malignancies. It inhibits DNA repair and synthesis in dividing and nondividing cells through inhibition of DNA topoisomerase II. Mitoxantrone is thought to act via a wide range of mechanisms, which include inhibition of T-cell activation, suppression of T-cell, B-cell and macrophage
proliferation, impaired antigen presentation, prevention of macrophage-mediated demyelination and reduction of pro-inflammatory cytokines.

- Since 2000, it was approved in many countries for treatment of worsening relapsing-remitting MS, progressive relapsing MS and secondary progressive MS.
- There is no homogeneous protocol for mitoxantrone in MS patients. The cumulative lifetime dose permissible is 120 mg. The recommended protocol is 12 mg/m² of mitoxantrone every month for 3 months, then every 3 months.
- Although rare, the most serious adverse effects of mitoxantrone treatment are cardiotoxicity (0.2%) and acute leukaemia (0.4-0.7%). It is very important therefore to perform an echocardiography before starting treatment, followed by another echo after the first dose, then every 6 months for 3 years. If the left ventricular ejection fraction is < 50%, the treatment should be stopped. CBC should be checked once per month for 3 months, followed by once every 3 months for 3 years. Women of childbearing age should have β-hCG done before each course of treatment. They should be informed about the risk of amenorrhea, especially after the age of 38.
- Because of its potential accumulative side effects, mitoxantrone should be reserved for active, disabling RR-MS patients in whom disease progression cannot be controlled by established immunomodulatory therapeutics (frequent relapses, relapses with incomplete recovery giving an increase of a least 2 points in one year at the EDSS score, with gadolinium + lesions on the MRI). It may have an additional role as an induction therapy in treating early, aggressive MS, then relayed after at least 3 months by IFNβ or GA.

**Cladribine**

- Cladribine (2-chlorodeoxyadenosine) is a purine nucleoside analogue with lymphotoxic effects. It causes an accumulation of deoxyneucleotides in selected T-lymphocytes, which is detrimental to the cell's function and proliferation, resulting in their sustained depletion.
- Cladribine is an oral immunomodulatory agent that produces targeted, sustained reduction of T and B lymphocytes.
- In MS, this preferential lymphocyte-reducing agent results in immunological modulation that reduces relapses, neurological disease activity and disease progression.
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- Except in a few countries, cladribine is not approved for MS treatment because of safety concerns.

Azathioprine
  - Azathioprine is the first immunosuppressive drug used since 1970 for MS, now licensed for RR-MS by the EMEA based on different positive studies.
  - Because of its side effect profile, it is usually reserved for patients with moderately aggressive disease and should not be given more than ten years. There is a high risk for B cell lymphomas.

Glucocorticosteroids
  - Their efficacy has not been clearly demonstrated in RR-MS.
  - At present, they cannot be considered as a first-line treatment option. (Type C)

Intravenous Immunoglobulins
  - In MS, there is no clear supporting evidence for IVIG.

D - In Clinical Practice

Patients that may be treated are those having RR-MS, either clinically or with the McDonald criteria.

Patients presenting with a clinically isolated syndrome (CIS) may progress to clinically definite multiple sclerosis. Overall, approximately 50% of patients who develop a CIS will experience a second event within 2 years (CDMS). Initial and repeated MRIs help select those at high risk who should be considered for early treatment with IFN β (or glatiramer acetate), in order to prevent early disability.

McDonald criteria 2010 allow the diagnosis of MS at first event therefore treatment can be started.

Interferons β and Glatiramer Acetate
  - There are no head-to-head trials of interferons β in clinically first demyelinating event.
  - The observed benefit reported with these agents compared with placebo is generally comparable, with an adjusted 35–55% reduction in the risk of progression to MS
over 2–3 years. The studies have also demonstrated that these agents limit relapse rates and new MRI lesion activity.

- Consequently, there appears to be little to distinguish among IFNβ and GA therapies from an efficacy perspective. Important to note is that with both IFNβ and GA, a similar range of efficacy can be reached supporting the clinical relevance of both treatment principles.

- Although the logical conclusion from the studies is that DMT should be initiated at the onset of the first clinically demyelinating event, this may not be an advantage for all patients. Approximately 10% (ref.) may have a favorable or mild disease course, making lifelong treatment unnecessary. Moreover, the inconvenience of parenteral therapy and possible side effects may make it difficult for many patients to comply with long-term treatment. Ultimately, the decision as to when to commence disease-modifying therapy should be jointly made by the neurologist and patient after considering all the available evidence.

Other treatments

- No data is available for natalizumab or mitoxantrone. However, there is emerging evidence that use of these types of immunosuppressant treatments as a short-term ‘induction therapy' followed by maintenance therapy with an immunomodulatory treatment may be an effective strategy in patients who present with aggressive disease.

- Data are not currently available for fingolimod.

E-How to Treat Progressive MS

Irreversible progression is attributed to neurodegeneration, implying that standard anti-inflammatory disease-modifying agents may not have an impact on disease progression. The therapeutic approach to patients with SPMS is much more challenging, especially as the degree of disability and the inflammatory activity (as determined by the relapse rate) can differ significantly between patients. Thus, a treatment strategy must be designed on an individual basis while carefully weighing the expected clinical benefit and the potential adverse effects of the chosen therapy.
1-Interferon β

- It is appropriate to consider IFNβ as treatment for patients with SPMS still experiencing relapses or showing MRI activity (gad + lesions) (Type A)
- There is no utility of IFNβ in patients with SPMS that do not suffer superimposed relapses.
- IFNβ-1b and subcutaneous IFNβ-1a can be used for SPMS with superimposed relapses.
- Only one trial showed a slowing of disease progression with IFNβ-1b.

2-Mitoxantrone

- Mitoxantrone at a dose of 12 mg/m² given every 3 months reduces progression of disability and clinical exacerbations in patients with worsening RRMS or SPMS.
- To avoid cardiotoxicity, it is recommended that a lifetime cumulative dose of 120mg should not be exceeded.

3-Cyclophosphamide

- Cyclophosphamide is a cytotoxic alkylating agent exhibiting immunosuppressive effects.
- The role of cyclophosphamide as a disease-modifying therapy in SPMS is unclear and its application should be restricted to selected patients who have not responded to other, less toxic, alternatives or to those who have rapidly disabling SPMS.
- Dosage: 750 mg/m² IV infusion every month for 1 year followed by 750 mg/m² IV infusion every 2 months for 1 year.

4-Methotrexate

- Methotrexate is a competitive inhibitor interfering with the synthesis of DNA and RNA, and also demonstrates immunosuppressive activity.
- Dosage: 7.5 mg orally, one day per week.
- It is considered possible that methotrexate favorably alters the disease course in patients with progressive MS with upper limb motor disability (Type C).
5-Azathioprine

- This drug, titrated to a dose of 2mg/kg per day, has been studied in both RRMS and chronic progressing MS since 1971. A meta-analysis of the results of five double-blind and two single-blind, randomized, controls trials of azathioprine use in MS showed only a small difference after two years in favor of azathioprine. The study concluded that the side effect profile outweighs any small clinical gain.

**Cellcept** is used in SPMS although there is no evidence of its efficacy.

6-Cyclosporine

- Cyclosporine is a peptide with immunosuppressive and anti-inflammatory properties.
- It is possible that cyclosporine provides some therapeutic benefit in progressive MS (Type C), however the frequent occurrence of side effects, especially nephrotoxicity, makes it not recommended for this indication.

7-Methylprednisolone

MP-IV (500 mg/d for 3 days) every 2 months for 2 years can reduce disease activity (type C).

F. Treatment of PP-MS

Unfortunately, there are no effective therapies for PPMS and PRMS available at present. When considering one of the immunosuppressive drugs, the risk and cost associated with the use of unproven therapies should be carefully considered.

Monthly cyclophosphamide (700mg/m2) may be considered in rapidly disabling disease. Beta Interferons and Glatiramer acetate have so far shown no efficacy in PPMS.

The efficacy of fingolimod in primary progressive PPMS is currently being investigated. Mitoxantrone is sometimes used. The other treatments have not clearly demonstrated their efficacy or the risk/benefit ratio is not favorable.
G. Principles of Treatment Algorithm in RR-MS

- **Quiescent**: consider the necessity of treatment with first line treatments:
  - The three IFN β formulations
  - or
  - Glatiramer acetate
    depending on patient preference, given the safety and dosing profiles of the individual therapies.

- **Classical**: 0.7-0.9 relapse per year
  - Treat with first line treatments
    - The three IFN β formulations
      - or
    - Glatiramer acetate
      depending on patient preference, given the safety and dosing profiles of the individual therapies.
  - Possibility for fingolimod in needle-phobic patients, or patients who cannot tolerate/are unwilling to perform parenteral administration (still to be defined). Fingolimod is approved as first line therapy in RR-MS in some countries.

- **Active disease**: patients with high disease activity despite treatment with IFNβ and those with rapidly evolving RRMS (≥ 2 disabling relapses in previous year and an active MRI scan)
  - Natalizumab
    - or
  - Fingolimod
    - No comparative studies.
    - In needle-phobic patients, or patients who cannot tolerate/are unwilling to perform parenteral administration, fingolimod can be used.
  - Mitoxantrone can be used if fingolimod or natalizumab are unavailable.
Remarks:

1. Shifting between IFNβ formulations and glatiramer acetate have not demonstrated consistent benefits for either approach.

2. There is no Class I evidence from randomized controlled trials examining the efficacy of switching from one FDA-approved monotherapy to another monotherapy in patients with ‘insufficient response’.

3. Only the addition of monthly doses of oral methylprednisolone to IFNβ has demonstrated a beneficial effect on both relapse rate and MRI lesions.

4. A third approach to managing patients with breakthrough disease is to initiate treatment with a higher-efficacy monotherapy, such as fingolimod or natalizumab, although there is currently no Class I evidence to support the administration of any monotherapy in patients with breakthrough disease. In spite of this, the use of oral fingolimod among US patients with breakthrough disease is likely to increase in the coming months. Natalizumab will remain an important option in this setting, and the overall use of natalizumab may change if the JCV-assay proves an effective means to identify patients. Additional studies are warranted.

5. **Benign inactive MS**: no treatment is an option.

6. **Active MS**: discuss immunomodulation (first line). After one year, in case of inefficacy, discuss immunosuppression (escalation).

7. **Aggressive MS**: immunosuppressive treatment may be indicated as first line (induction). It may be followed with an immunomodulatory agent (add on). No combination therapy has been recommended so far.

8. **Malignant MS**: Rescue therapy can be offered.
IV. Follow-up

A. Natural History and Prognosis:

MS prognosis is variable and unpredictable at the individual level. Statistically some factors suggest a bad prognosis. The average patient with MS will develop one relapse per year. At a later stage, as secondary degenerative phase progresses, fewer relapses will be reported and neurological deficits will more likely progress over time. This is variable from patient to patient. Progression is defined by the slow evolution in EDSS in the absence of clear attacks suggesting early SPMS.

From Compston and Coles, The Lancet 2002:
- 25% of patients never lose the ability to perform activities of daily living.
- 15% become severely disabled within a short time.
- Mortality from MS as primary cause is low.

Weinshenker and coworkers (1989) in a longitudinal study suggest that most patients with relapsing-remitting onset would develop into the secondary progression stage but with variable delays:
- 12% at 5 years from onset
- 41% from 6-10 years after onset
- 58% from 11-15 years after onset
- 65.5% from 16-20 years after onset
- 89% at > 25 years from onset
- Median time to reach EDSS of 6 is 15-20 years; and to reach an EDSS of 8 is 46 years.

Clinical symptoms that would suggest poorer prognosis at first presentation:
- Multifocal presentation
- Motor deficit with cerebellar involvement
- Brainstem involvement
- Cognitive impairment
- Bladder /bowel symptoms
- High relapse rate at first 2-5 years
- Poor recovery after first attack
Better prognosis is suggested at clinical onset with symptoms such as:

- Monofocal presentation
- Isolated optic neuritis
- Sensory symptoms
- Low relapse rate at first 2-5 years

However, the T2 lesions load on the brain MRI at first presentation is a determinant prognostic factor: the risk of reaching EDSS 6 at 14 years from onset is 56% for patients with ≥ 10 T2 lesions at onset, 30% for those with 4-10 lesions, 17% for those with 3-4 T2 lesions. (Brex 2002, Miller 2005)

**Childhood onset:** The increased number of relapses in the first years of the disease, and the high frequency of patients with the relapsing remitting course suggests a more active inflammatory process in children with MS compared to adults. At a given age, patients with onset in childhood are more disabled than those with a later onset (Renoux et al. 2007; Boiko et al. 2002). Recent studies have demonstrated that approximately one third of children and adolescents with MS develop cognitive dysfunction early. (Amato et al. 2008; Banwell and Anderson, 2005; MacAllister et al. 2005)

**B- Methods of Evaluation**

1- **Clinical: Relapses, EDSS**

Clinical outcome measures include delay to second relapses, frequency of relapses, cognition. Evaluating the outcome from interventions at any stage of MS is extremely challenging but also of great importance if there is to be ongoing improvement in the process and impact of rehabilitation. Evaluating the effect on the patient requires the use of outcome measures that are scientifically sound (reliable, valid, and responsive) and clinically useful (short, simple, etc.). They also must be appropriate to the sample under study and the intervention being evaluated.

The standard outcome measure in therapeutic trials in MS, Kurtzke’s EDSS, is inappropriate for evaluating rehabilitation, not only because of its scientific limitations (particularly poor responsivenes) but also because it does not measure many of the relevant areas, such as fatigue and cognition, and does not incorporate the perspective of the patient.
Specific impairments such as the following list should be considered at each visit:

- Fatigue
- Bladder and urinary tract dysfunction
- Bowel problems
- Weakness
- Cardiorespiratory fitness
- Spasticity
- Spasms and contractures
- Ataxia
- Tremor
- Sensory loss
- Visual problems
- Pain and sensitivity
- Cognitive function
- Emotional: depression, anxiety
- Swallowing difficulties
- Speech difficulties
- Sexual dysfunction

2- MRI

a. Follow-up parameters: These include lesion load and active lesions. The first measure is restricted to research centers. In clinical practice the most useful parameter is T1Gd+ lesions. New T2 lesions are also useful. Active lesions are defined by T1Gd+ and new T2.

b. Is MRI follow-up needed?

MRI is used at the onset of the disease to establish diagnosis and determine disease activity. The need for routine MRI follow-up and its frequency depends on individual cases.

MRI may be helpful for:

- Decision to treat
- Type of treatment?
- Treatment efficacy?

Routine follow-up of all patients is not recommended.
**Efficacy of treatment may be delayed**

Efficacy of treatment frequently cannot be demonstrated on MRI and is variable according to studies and drugs, considering the limits of Gd+, the only evident parameter for follow-up. In addition it is not yet established if the treating neurologist should consider the natural history before treatment.

**3. Criteria for DMD Efficacy, Failure (Responders vs Non-responders)**

Ideally, the patient should be free from disease activity and progression, which means that there has been no relapses, no progression and no active lesions reported during follow-up. These three criteria depend on evaluation methods, and are rarely present during a long period of time. The following criteria have been proposed:

- **Responders:**
  a. Significant reduction in post treatment phase when compared before treatment initiation.
  b. Patients are to be considered disease free after 2 years of treatment in terms of relapse, progression of the disease (disability), and MRI activity (gadolinium enhancing lesions and new T2 lesions).
  c. Relative efficacy has been defined as following: after 2 years, < one relapse, one Gado + lesion and 2 new T2 lesions.

- **Non Responders:**
  1. A minimum of two clinical relapses, and progression towards disability, i.e., increase in EDSS of one point, within one year of treatment.
  2. More than two clinical relapses, more than 2 Gado + lesions and 3 new lesions on T2 on treatment.

- **Clinical Assessment without MRI (questionable)**
  1. One clinical relapse per year
  2. Variation of 0.5 on EDSS per year.
V. Managing MS

A. Informing the patient about the diagnosis

Diagnosis announcement is a difficult moment both for the patient and the physician. The suspected diagnosis is usually discussed with the patient after a first event that may suggest MS. Another consultation is necessary to explain the results of MRI and other investigations, as well as the therapeutic possibilities. At this occasion topic that may interfere with the socio-professional life are discussed.

Patients’ reactions are variable (copying). This may need a specific psychological care. The diagnosis of a long standing chronic disease should be accepted as well as the potential necessity to start a DMD.

For all these reasons, the diagnosis should be announced by a neurologist that is used to patients’ reactions, and may give answer to their questions. It is important to avoid diagnosis announcement in a radiological report or if the first episode is not suggestive of MS.

B. Topics to be addressed:

The neurologist should discuss with the patient the following:

- Pregnancy
- Travel
- Trauma
- Stress
- Vaccinations
- Genetic Counseling
- Surgery

Pregnancy is a period where the relapse rate decreases and then increases in the post-partum period. The DMD should be stopped during pregnancy and re-introduced after delivery. The following vaccines are contraindicated: yellow fever and the oral viral vaccines. Patient should continue his treatment during periods of travel and make sure he has an adequate amount of medication with him. Surgical procedures can be safely performed when needed. MS is not a hereditary disease. With a genetic background (susceptibility) that accounts for 25-30% of the risk for MS, environmental factors are also very important. Viral causes have not been confirmed. Tobacco smoking should be stopped, and vitamin D supplementation begun.
C. Psycho-social rehabilitation and maintenance: functional activities and social participation.

MS is a disease that causes emotional distress in many ways. It often starts at a young age when individuals are anticipating a happy prosperous future. It is unpredictable and causes much uncertainty. Emotional distress can be increased if the patient begins to feel loss of control, and also by alterations in the way families interact once the diagnosis is known. Emotional support is vital for patients with MS, especially in the early stages. Emotional support may take two forms: a formal therapeutic process (psychotherapy) that requires training and expertise; and an informal process that, although it may be improved by training, is part of many personal interactions which occur between the person with MS and both professionals and non-professionals with whom the patient comes in contact. Functional, psychosocial, and professional concerns should be included in the follow-up of the disease.

D. Economical aspects

From WHO 2009 and National MOH publication in 2009 (for year 2008)

- Health expenditure per capita is 1054 USD (8.1 % MOH 2008)
- Population estimated: 4,224,000 (WHO 2009)
- Almost all the approved medications for MS treatment are available on the Lebanese market (except for Copaxone®)
- Most of Lebanese MS patients would get their medications for MS free of charge, except those who are under the national Social Security regimen (around 300 patients, less than 30 %).
- Considering 1350 the total number of MS patients currently treated with DMDs from which, actually 1312 are filed from any governmental third party payer, either MOH, other NGO and military forces, the total cost for MS drugs (basically the cost of Interferons beta) is around 14 millions USD per year.

The MOH expenditure for MS drugs (basically interferonsβ) is around 13,776,000 USD. These patients would get their medication free of charge from the MOH and military forces, whereas, those covered with the National Social Security program will have to pay out from the pocket 15 % (estimated at 665,000 USD).
Total Costs / year (us $)  Cost / patient / month (us $)  MOH  ONG  MF
AVONEX 1,267 6,080,000 1,976,000 1,079,200
BETAFERON 1,667 4,000,000 1,000,000 260,000
REBIF 22 1,020 122,400
REBIF 44 1,400 3,696,000 1,226,400 285,600
TYZABRI 2,600 93,600 93,600
GYLENIA 3,900 9,360
TOTAL 13,776,000 4,427,760 1,718,400 \textbf{19,922,160}

MOH: Ministry of Public Health
ONG: National Social Security + Govermental Cooperative
MF: Military Forces: Army + Police and others

**Estimated cost of MS in Lebanon (2010)**

Considering that
-1500 patients (over 2000 in Lebanon) are treated with interferons, that the cost/month/patient is 1400 USD, the annual cost is estimated to 12600 USD/patient
-The patients suffer of one relapse/2years, the cost of hospitalization and IVMP is 1500 USD/patient/year
-40% of patients have a symptomatic treatment, with an annual cost of 2500USD, the total cost of symptomatic treatment is 1000 USD/year/patient

Thus the total direct expenses due to MS may be estimated to 15000 USD/year/patient.
VI. Clinical Research

A. Epidemiology Databases

This includes common data, incidence, prevalence, natural and treated history, specific to Lebanon. This collaboration may lead to genetic and environmental studies.

B. Pathophysiology

Immunology

MS is thought to be a dysimmune disease. Beside the classical immune dysregulation described in the disease, recent advances focus on the possible role of regulatory T cells functional deficit, and the role of B cells as antigen presenting cells.

Genetics

More than 30 years after the first description of associations between HLADR (B015) and MS, new genes are thought to have a role in the genetic susceptibility to MS (ILR2,17). Participation of the Lebanese MS group in the MS international consortium may be proposed.

NMR: non-conventional techniques

New MR techniques are highly specific and are able to show abnormalities in the normal appearing tissue (on conventional MRI) of patients with MS. Pathophysiological research projects will be discussed in the future using spectroscopy, magnetization transfer techniques, diffusion imaging, new contrast agents, etc.

C. Clinical trials

A group for clinical research will be proposed in a network allowing clinical studies to be performed by all neurologists with appropriate training in MS diagnosis and follow-up. The MS committee of the LSN would be responsible for such studies.
VII. Perspectives and Future Directions

During the past twenty years, substantial progress and achievements have been made in Lebanon. From the achievements:

1. Training of neurologists, organized primarily by the Lebanese Society of Neurology
2. Wide availability of MRI
3. Numerous laboratories available to ensure accurate laboratory evaluations needed in MS.
4. Financial coverage by the paying agencies for the cost of expensive treatments (100% by MOH, 80% by other public payers). However, the remaining 20% of public payers that has to be paid by the patient represents a substantial burden.

It is also worth noting that the patient perception of the disease has changed. The diagnosis is more easily accepted and no longer considered a taboo. Unfortunately, despite this more accepting atmosphere, a number of patients stop treatment and contact a healer. Finally, there was some limited epidemiology and research studies which took place.

Future perspectives that need to be developed:

1. Diagnosis:
   A. Training of general practitioners and ophthalmologists in MS awareness, so that earlier and better treatment can be provided.
   B. Imaging: the need for at least 1.5 tesla machines and the need to establish examination protocols in collaboration with the Lebanese Society of Radiology.
   C. Laboratory: standardize CSF exam techniques in collaboration with the Lebanese Society of Laboratory Medicine, in order to obtain reliable, reproducible results from all laboratories.
2. Therapy:
   A. The consensus statement of the Lebanese Society of Neurology is a major step in standardizing the management of MS. Its acceptance by the public and private health authorities should be the next step. Periodic review is scheduled.
   B. Financial aspect of treatment: covering the remaining 20% of the cost borne by patients
   C. All patients should have access to new therapies.

3. Research:
   A. Epidemiological Research: Create a registry for MS in Lebanon through a joint effort with the MOH, the Ministry of Social Affairs and the Lebanese Order of Physicians. Also to share information such as protocols with other countries.
   B. Clinical research and clinical trials: multicenter research to recruit as many patients as possible. The consensus developed allows for standardized treatment protocols to facilitate clinical trials.
   C. Basic research: it is desirable that all groups coordinate their work so as to define a common goal and area to be studied.
   D. The need to find appropriate funding for this research.

4. Socio-professional and Individual Issues:
   A. Support patients both emotionally and with educational material to keep them informed about the disease. Make the patient aware of the risks involved when treatment is interrupted. Explain that there is no scientific evidence for benefit of the treatments practiced by healers.
   B. Create a hotline for patients to answer questions, direct them to the proper caregiver, etc.
   C. Encourage the development of patient support groups.

5. Address ethical issues for all steps:
   Announcement of diagnosis
   Exam quality
   Public authorities attitude
   Research
VIII. Guidelines / Conclusion

Multiple sclerosis is a dysimmune and chronic inflammatory disease of the central nervous system, affecting young adults. It can lead to a burden some physical, cognitive and psycho-social handicap that interferes with daily activities. Thus, it has a negative impact on family life, economic and society. Although some prognostic indicators have been proposed from clinical and neuroimaging data, still the disease remains unpredictable at the individual level. Currently, there are no available specific markers allowing diagnostic certitude at the early stage. However, diagnosis can be made earlier with brain and spine MRI which may need to be repeated.

Disease modifying drugs are available. Their cost is a burden for the society and for the patient. Moreover, the benefit/risk ratio is well established. They are primarily active on the inflammatory component of the disease, and are more effective when initiated at the early stages. There is some variability in terms of patient response. Some patients are non-responders, either early when treatment is initiated or after a period of apparent drug efficacy, which is variable.

When patients are considered as non-responders to immunomodulators as first line therapy, second line therapies (immunosuppressors) may be used. These new more effective immunosuppressive DMDs raise the critical issues of risk/benefit ratios. However, their indication should be considered in line with their cost / efficacy ratio. In this perspective, recommendations and guidelines are needed.

More effective drugs are or will be available in a near future challenging the present therapeutic considerations and guidelines. Their cost may represent a higher burden and barrier for patients to obtain optimal care. Their safety needs to be verified in clinical use. There is no evidence-based agreement regarding clinical and para-clinical parameters allowing early diagnosis, treatment follow-up, definition of treatment failure and prognostic predictors. Hence, a consensus needs to be established.

The LSN created a committee to facilitate MS knowledge, standardize medical practices, propose future actions and promote clinical, pathophysiological and therapeutical research in Lebanon.

This MS committee, which originates from the LSN, aims at reaching a national consensus for MS management, optimization of care and should be composed of evidence based recommendations. The spread of comprehensive guidelines among neurologists will contribute to clinical research and better understanding of the pathophysiology of the disease.
in Lebanon.

The following points were submitted, and may be considered as guidelines:

1. **General considerations**: The management of MS should be arranged within a multidisciplinary team and under the neurologist supervision. Neurologists should be involved from the earliest stage of the disease in term of early diagnosis, treatment initiation, and regular follow up.

2. **Diagnostic considerations**:
   A. Diagnosis should be established and patient informed as early as possible, with particular care to the psychosocial impact on the patient.
   B. MRI is the most important para-clinical examination establishing diagnosis.
   C. CSF analysis is important to perform in most cases.
   D. Other electrophysiological and biological tests may be performed as a support for establishing positive and differential diagnosis.
   E. Diagnosis should rely on international criteria. Differential diagnosis is a key issue.
   F. According to international criteria the “disease” will be labeled “non MS”, “possible MS”, or “MS”.

3. **Treatment considerations**:
   A. Relapse treatment relies essentially on IVMP
   B. Symptomatic treatment and rehabilitation are important to consider.
   C. When the neurologist consider that a first line DMD should be initiated, the efficacy, tolerability and side effects should be considered irrespective of the drug’s cost.
   D. First line therapy relies on immunomodulators, with no clear evidence of differences between drugs, route of administration, frequency or dosage. Compliance, tolerability and long-lasting side effects may limit their use.
   E. In more aggressive cases, immunosuppressors may be needed as first line treatments. Other off-label therapies may also be considered. A risk management plan should be implemented and clear consent from patient should be obtained.
   F. Future therapies should be accessible to all.
   G. Team work should be encouraged.
4. **Follow-up:**
   A. Defining clinical and para-clinical markers are needed for follow-up.
   B. Clinical follow-up depends on activity (relapses) and progression (EDSS) of the disease. Other markers may be needed (e.g., PASAT, 9-HP, etc.).
   C. Neuroradiological follow-up may be needed to determine subclinical activity, to exclude another concomitant disease, and to propose second line therapies. In this case, MRI should be performed a minimum 4 weeks after the administration of IVMP.

5. **Future directions:**
   A. Psycho-social care will be an important issue to consider.
   B. There is a clear need to establish a national MS registry that includes all Lebanese MS patients. Such registry will help define the disease incidence and prevalence in Lebanon. This will require financial support from the MOH.
   C. Research protocols will be proposed and encouraged. They may start with epidemiological, economical and clinical trials with the support of the LSN.
   D. Informed consent should be considered for immunosuppressive drugs and research protocols.
   E. Updates and training sessions will be organized in the future to standardize the use of markers, especially modified or simplified EDSS. This will be important for clinical follow-up and epidemiological data-bases.
   F. A website will be created to share information. A patient website should also be considered.

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* CSF, cerebrospinal fluid; MS, multiple sclerosis; NPV, negative predictive value; PPV, positive predictive value.
* Data are given as percentages. PPV and NPV assumed a prevalence of 15%.

Table 1

Grading recommendation adopted

- A: requires at least one RCT as part of the body of evidence.
- B: requires availability of well-conducted clinical studies but no RCTs in the body of evidence.
- C: requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.
IX. Acknowledgements

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