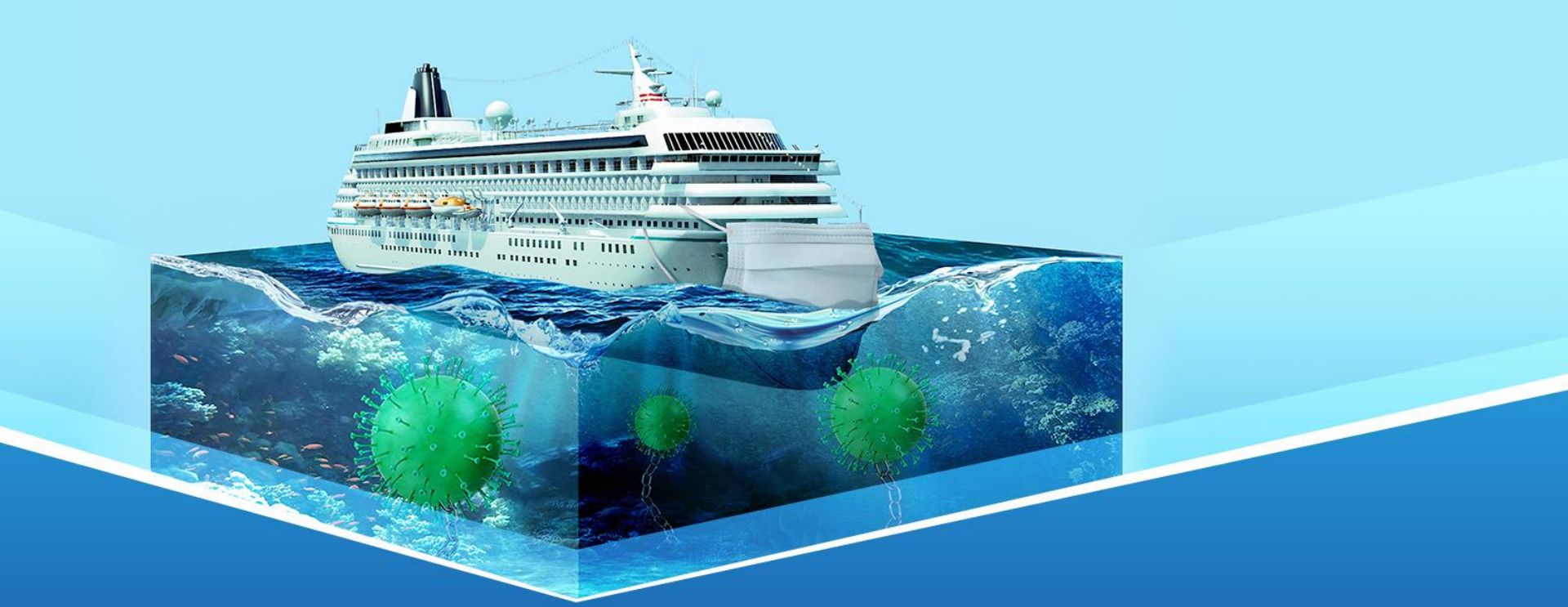
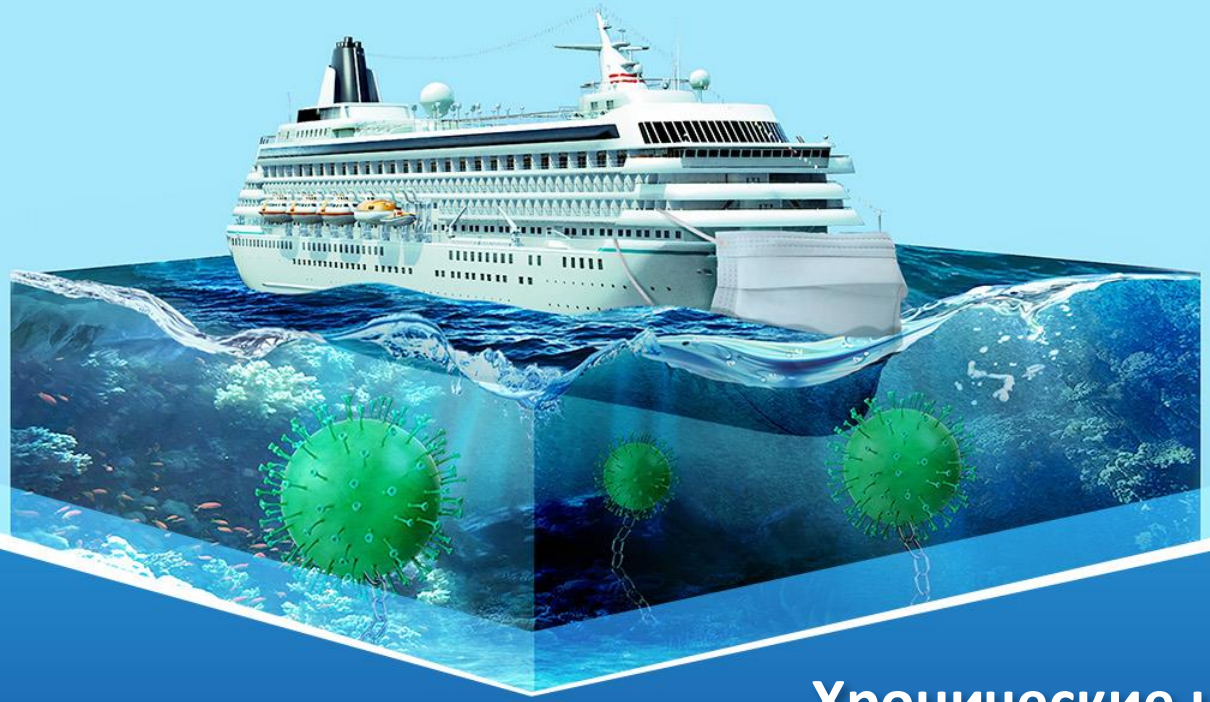


Chronic infections of nervous system. Demyelinating disorders of nervous system.

Prof. Leila Rinatovna Akhmadeeva

Ufa, Nov. 1, 2022



Хронические нейроинфекции и демиелинизирующие заболевания нервной системы

Prof. Leila Rinatovna Akhmadeeva

Ufa, Nov. 1, 2022

Plan

- What will we call CHRONIC infectious diseases
- The most common chronic infections of nervous system
- Demyelinating disorders of central and peripheral nervous system - examples:
  - Diagnosis
  - Management

Chronic meningitis

Chronic meningitis is arbitrarily defined as meningitis lasting for four weeks or more and is a complex entity with both infectious and noninfectious causes. Patients with chronic meningitis usually have a subacute onset of symptoms including fever, headache, and vomiting. The symptoms can remain static, fluctuate, and/or slowly worsen.

Clinically useful or important clues to the cause of chronic meningitis

Clue	Diagnosis
Positive tuberculin skin test or interferon-gamma release assay	Tuberculosis
Residence or travel to the southwestern United States, southern California, or Mexico	Coccidioidomycosis
Hypothalamic, optic, or pituitary lesions on cranial imaging	Sarcoidosis
Uveitis/iritis	Sarcoidosis, Behçet's disease, Vogt-Koyanagi-Harada syndrome
Radiculopathy and/or cranial nerve palsies	Lyme disease
Prior residence in Mexico, Central or South America, India, sub-Saharan Africa, or the Caribbean	Cysticercosis
Exposure to unpasteurized milk or contact with cows, goats, swine, or sheep (including butchering or working in a packing house)	Brucellosis
Peripheral 7th nerve paralysis	Sarcoidosis
Diabetes insipidus	Sarcoidosis
Poliosis (whitening of the eyebrows and eyelashes and vitiligo)	Vogt-Koyanagi-Harada syndrome
Recurrent genital or oral ulcerations	Behçet's disease
A preexisting immunosuppressive condition or therapy	Cryptococcosis, tuberculosis, toxoplasmosis, endemic mycoses
Predominately neutrophilic CSF pleocytosis	Nocardiosis, actinomycosis, aspergillosis, systemic lupus erythematosus, chemical or drug-induced meningitis
Eosinophilic CSF pleocytosis	Coccidioidomycosis, lymphoma, *Angiostrongylus*, cysticercosis, schistosomiasis
Hypogammaglobulinemia	Enterovirus

CSF: cerebrospinal fluid.

Chronic meningitis

- An array of infectious agents can present as chronic meningitis, but a nearly identical syndrome can result from a number of inflammatory, malignant, or other
- The clinical symptoms of patients with chronic meningitis rarely point to a specific etiologic diagnosis. However, occasionally, a historical or epidemiologic clue can lead to the discovery of an otherwise obscure diagnosis
- Patients with chronic meningitis typically undergo an array of complex diagnostic investigations including serologic assays, multiple imaging tests, and repeated lumbar punctures

The type of laboratory testing should be based upon the clinical features of an individual case and the subsequent probability that a specific disease is present. For example, routine evaluation of patients with chronic meningitis usually includes tuberculin skin tests, a chest radiograph, and serologic testing for syphilis as well as testing for the presence of HIV infection. However, tests for other infectious diseases, such as Lyme disease, cysticercosis, trypanosomiasis, and/or

Potential causes of chronic meningitis

Infections	Noninfectious conditions	Drugs
Mycobacterial ▪ *Mycobacterium tuberculosis* **Spirochetal** ▪ *Borrelia burgdorferi* ▪ *Treponema pallidum* ▪ *Leptospira* **Bacterial** ▪ *Brucella* ▪ *Francisella tularensis* ▪ *Actinomyces* ▪ *Listeria* ▪ *Ehrlichia chaffeensis* ▪ *Nocardia* ▪ *Tropheryma whipplei* (Whipple's disease) **Viral** ▪ Human immunodeficiency virus ▪ Cytomegalovirus ▪ Epstein-Barr virus ▪ Human T cell lymphotrophic virus I and II ▪ Enterovirus ▪ Herpes simplex virus ▪ Varicella-zoster virus ▪ Cache Valley virus **Fungal** ▪ *Cryptococcus* ▪ *Sporothrix* ▪ *Histoplasma* ▪ *Blastomyces* ▪ *Coccidioides* ▪ Other (eg, *Scedosporium apiospermum*, *Paracoccidioides*, dematiaceous molds) **Parasitic** ▪ *Taenia solium* (cysticercosis) ▪ *Angiostrongylus* ▪ *Schistosoma* ▪ *Toxoplasma* ▪ *Acanthamoeba*	▪ Neoplastic ▪ Sarcoidosis ▪ Systemic lupus erythematosus ▪ Granulomatosis with polyangiitis (Wegener's) ▪ Behçet's disease ▪ Fabry disease ▪ Central nervous system vasculitis ▪ Vogt-Koyanagi-Harada disease ▪ Chemical or drug-induced meningitis ▪ Idiopathic (up to one-third of cases) ▪ Rheumatoid arthritis	▪ Nonsteroidal anti-inflammatory drugs ▪ Intravenous immunoglobulin ▪ Intrathecal agents

Chronic meningitis

- Analysis of cerebrospinal fluid (CSF) reveals abnormalities in patients with chronic meningitis, but these abnormalities are rarely diagnostic with some notable exceptions. The presence of eosinophilia can provide an important clue to the presence of a parasitic etiology or coccidioidomycosis. Similarly, stained smears of a centrifuged sample of the CSF may occasionally reveal infectious agents, such as fungi or bacteria, and thus lead to a specific etiologic diagnosis. Antigen testing of the CSF for the presence of *Cryptococcus neoformans* and a Venereal Disease Research Laboratory test for syphilis should be performed on all patients with chronic meningitis. A sample of CSF should be submitted for cultures using media appropriate for growth of aerobic bacteria, mycobacteria, and fungi. Other studies that should be obtained are discussed above.
- Magnetic resonance imaging and computed tomography are useful in the evaluation of patients with chronic meningitis, but these imaging techniques lead to a specific diagnosis in a minority of patients. However, such imaging is important since it can exclude important abnormalities, such as a parameningeal focus of infection, abscess, or a tumor. Rarely, such imaging may disclose one of these processes or the cystic changes typical of cysticercosis.

Potentially useful diagnostic tests in patients with unexplained chronic meningitis*

Examination of CSF
Cell count with differential
Protein
Glucose
Special stains (for specific pathogens, eosinophils)
Cytology
Cryptococcal antigen testing
Cultures (CSF, blood, other fluids where relevant)
Aerobic and anaerobic bacterial
Mycobacterial (including acid-fast stains)
Fungal
Serologies (blood and/or CSF)
Fungal serologic tests for *Histoplasma*, *Coccidioides*, *Sporothrix*, *Cryptococcus* (CF or immunodiffusion)
Toxoplasma serologies (IFA)
Antibody tests for HIV-1, HTLV I/II (ELISA, Western blot)
Cysticercosis serology (EITB)
Lyme serologies (ELISA, Western blot)
Syphilis serology (treponemal and nontreponemal tests)
Brucella serology (standard tube agglutination, CF, ELISA)
Tularemia serology
Imaging studies
Computed tomography (head and chest)
Magnetic resonance imaging of the head with gadolinium
Other
Tuberculin skin test or interferon-gamma release assay
Serum and CSF 1,3-beta-D-glucan assay
Meningeal or cortical biopsy (histopathology and culture)
Bone marrow aspiration and biopsy (with cultures)
Extractable nuclear antigens, antineutrophil cytoplasmic autoantibodies, and antibodies to cyclic citrullinated peptide
Erythrocyte sedimentation rate
Skin or lymph node biopsy, when applicable
Nucleic acid amplification testing of CSF for *Mycobacterium tuberculosis*
CSF PCR for enterovirus
CSF PCR for *Tropheryma whipplei*
CSF metagenomic next-generation sequencing or 16S rRNA sequencing
Ophthalmologic examination

CSF: cerebrospinal fluid; CF: complement fixation; IFA: indirect fluorescent antibody; HTLV: human T-lymphotropic virus; ELISA: enzyme-linked immunosorbent assay; ETIB: enzyme-linked immunoelectrotransfer blot; PCR: polymerase chain reaction.

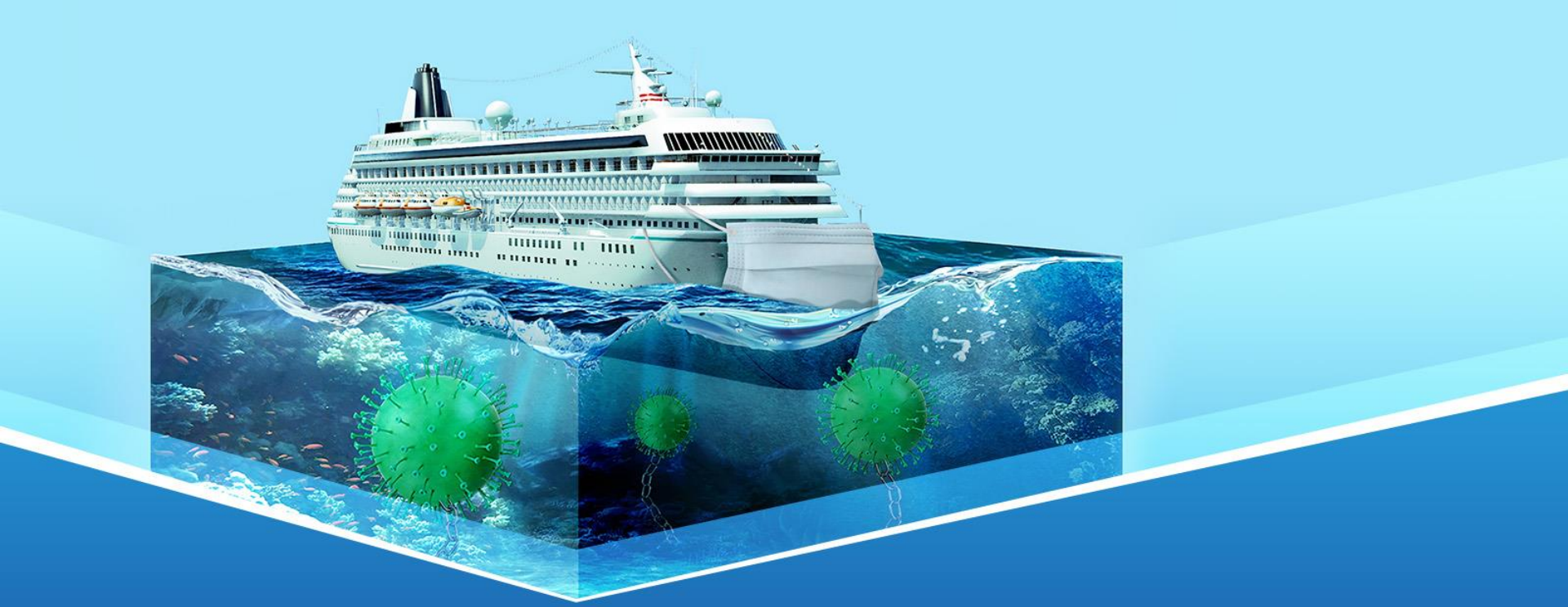
* The decision regarding which laboratory tests to perform should be based upon the clinical features of each individual patient and the probability that a specific disease is present. Refer to the topic reviews that discuss specific pathogens for a more detailed discussion of the different diagnostic tests.

Chronic meningitis

- Brain and meningeal biopsy may be useful in patients who have a progressive deteriorating course despite empiric therapy, particularly if focal findings are detected on brain imaging.
- If a diagnosis is not established despite a thorough search and if symptoms are severe or fail to improve after a period of observation, empiric therapy with antituberculous therapy may be useful. Empiric antituberculous therapy may also be warranted for patients with less severe symptoms if epidemiologic factors or clinical findings suggest a high risk for TB (eg, in patients with a past history of direct contact with others with TB or a prior positive tuberculin skin test).
- Empiric glucocorticoid therapy may be useful in selected patients who fail to improve during follow-up, despite the absence of carefully controlled studies demonstrating benefit in patients with chronic meningitis. Some patients with chronic meningitis in whom an infectious etiology was not detected have responded dramatically to empiric glucocorticoids

Chronic meningitis with neutrophilic pleocytosis in the cerebrospinal fluid

Fungal pathogens
Aspergillosis
Zygomycosis
Dematiaceous fungi
Candidiasis
Blastomycosis
Histoplasmosis
Coccidioidomycosis
Bacterial pathogens
Nocardiosis
Actinomycosis
Brucellosis
Tuberculosis
Noninfectious diseases
Systemic lupus erythematosus
Chemical or drug-induced meningitis



To know: Herpes, HIV, TB, sarcoidosis, syphilis, parasitic disorders, diphtheria, others

multiple sclerosis in adults

When to suspect MS – The most common presentation of multiple sclerosis (MS) consists of a single, monosymptomatic attack compatible with demyelination (eg, optic neuritis, a brainstem syndrome, or a spinal cord syndrome).

In some patients, the diagnosis of MS can be established at that point based on clinical, magnetic resonance imaging (MRI), and cerebrospinal fluid criteria.

Clinically isolated syndrome refers to a monosymptomatic attack that does not fulfill diagnostic criteria for MS but may predispose to clinically definite MS. Approximately 10 to 15 percent of patients with MS present with insidious neurologic worsening and accumulation of disability from spastic paraparesis or cerebellar ataxia, a pattern known as primary progressive MS.

Core MS phenotypes – The core multiple sclerosis (MS) phenotypes are those of relapsing and progressive disease. The pattern and course of MS is further categorized into several phenotypes or clinical subtypes as follows :

•A clinically isolated syndrome – This is the first potential attack of a disease compatible with MS that exhibits characteristics of inflammatory demyelination but has yet to fulfill MS diagnostic criteria. The typical patient presents as a young adult with a clinically distinct episode of central nervous system dysfunction (eg, optic neuritis, diplopia, brainstem or cerebellar syndrome, or partial transverse myelitis) with at least partial resolution.

•Relapsing-remitting MS – This phenotype is characterized by clearly defined relapses with full recovery or with sequelae and residual deficit upon recovery. There is no or minimal disease progression during the periods between disease relapses. This type of MS accounts for approximately 85 to 90 percent of MS cases at onset. However, most patients with relapsing-remitting MS will eventually enter a secondary progressive phase.

•Secondary progressive MS – This phenotype is characterized by an initial relapsing-remitting MS disease course followed by progression with or without occasional relapses, minor remissions, and plateaus. Some studies suggest that secondary progressive MS ultimately develops in most patients with relapsing-remitting MS and is the stage in which patients accumulate the greatest amount of neurologic disability.

•Primary progressive MS – This phenotype is characterized by disease progression from onset with occasional plateaus and temporary minor improvements allowed; acute attacks may also occur. This type represents approximately 10 percent of adult cases at disease onset.

MS

- **Disability progression** – Progression of disability due to MS is highly variable. The impact of MS varies according to a number of measures, including severity of signs and symptoms, frequency of relapses, rate of worsening, and residual disability. Accumulating evidence suggests that, in most patients, worsening is slow. At the extreme ends of the severity spectrum, there are benign and malignant forms of MS, but the determination of these is always retrospective and must be made cautiously.
- **Predicting outcome** – There are a variety of possible prognostic indicators in MS. However, none are established as reliable, and our ability to accurately predict outcomes for individual patients with MS is quite limited. The development of a progressive course of MS may be the single most adverse factor influencing prognosis.

Evaluation for MS – The evaluation of suspected MS begins with a **detailed clinical history and examination**. All patients should also have a brain MRI without and with contrast. For patients with a typical presentation who have insufficient clinical and MRI evidence to confirm the diagnosis of MS by the McDonald criteria, additional testing with lumbar puncture for cerebrospinal fluid-specific oligoclonal bands, visual evoked potentials, and/or optical coherence tomography can be used to support the diagnosis.

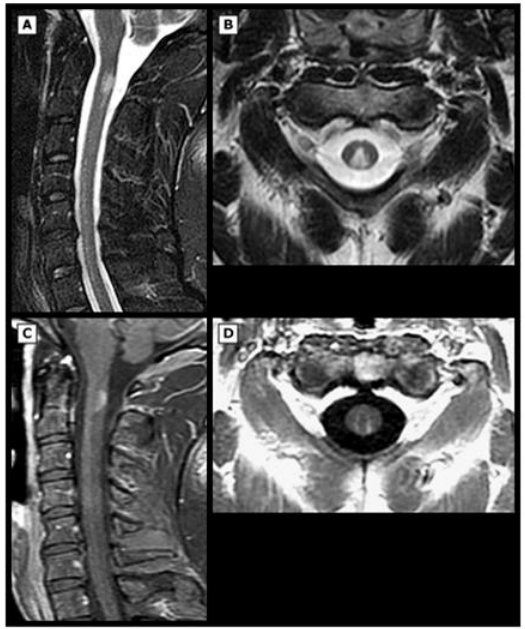
- For patients with a presentation other than a typical clinically isolated syndrome or patients with atypical findings in any aspect of the clinical history, examination, or brain imaging, additional testing with spine MRI, lumbar puncture, and/or autoantibody determination for aquaporin-4 (AQP4) and myelin-oligodendrocyte glycoprotein (MOG) antibodies is warranted to investigate alternatives in the differential diagnosis.

Typical MRI lesions

MRI lesions suggestive of MS are typically found in the periventricular region, corpus callosum, centrum semiovale, brainstem, cerebellum, spinal cord, and, to a lesser extent, deep white matter structures and basal ganglia.

MS lesions typically have an ovoid appearance. The lesions are characteristically arranged at right angles to the corpus callosum; when viewed on sagittal images, they are referred to as Dawson fingers. The MS brain lesions appear hyperintense on proton density and T2-weighted studies, and they are hypointense (if visible at all) on T1-weighted images. Spinal cord MRI lesions are nearly as common as brain lesions in patients with MS. Gadolinium-enhancing lesions on T1-weighted MRI are associated with new or newly active plaques.

Spinal cord MRI demonstrating transverse myelitis in a 37-year-old man with multiple sclerosis



T2-weighted sagittal (A) and axial (B) images show a focus of hyperintensity in the posterior columns of the cervical spinal cord at the C2 level. Post-gadolinium T1-weighted sagittal (C) and axial (D) images demonstrate enhancement consistent with an active plaque.

MRI: magnetic resonance imaging.

The 2017 McDonald criteria for the diagnosis of multiple sclerosis in patients with an attack at onset

	Number of lesions with objective clinical evidence	Additional data needed for a diagnosis of multiple sclerosis
≥2 clinical attacks	≥2	None*
	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location¶)	None*
	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRIΔ
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI◇ **OR** demonstration of CSF-specific oligoclonal bands§
	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRIΔ **AND** Dissemination in time demonstrated by an additional clinical attack or by MRI◇ **OR** demonstration of CSF-specific oligoclonal bands§

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined as a monophasic clinical episode with patient-reported symptoms and objective findings typical of multiple sclerosis, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection. Attack, relapse, exacerbation, and (when it is the first episode) clinically isolated syndrome are synonyms.

CNS: central nervous system; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid.

* No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or CSF examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (eg, CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered.

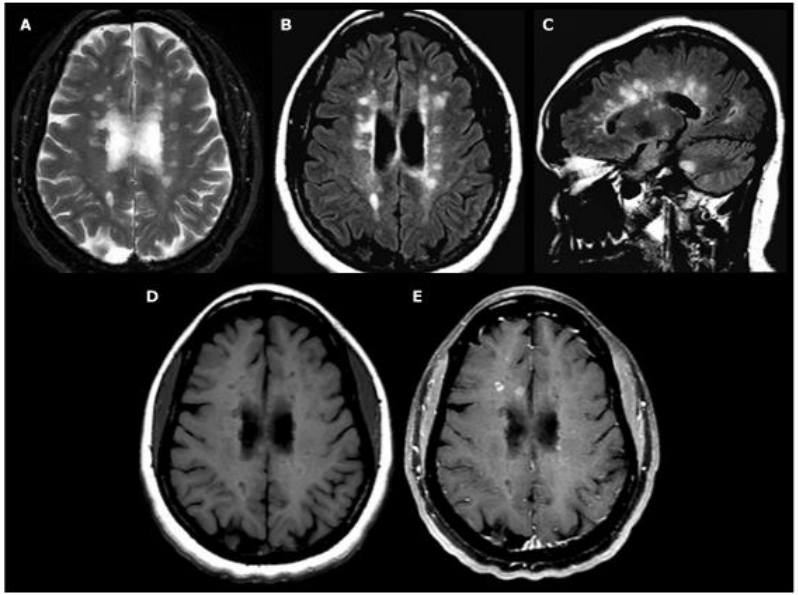
¶ Clinical diagnosis based on objective clinical findings for two attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack; at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed.

Δ The MRI criteria for dissemination in space are described in the text of the UpToDate topic on the diagnosis of multiple sclerosis in adults.

◇ The MRI criteria for dissemination in time are described in the text of the UpToDate topic on the diagnosis of multiple sclerosis in adults.

§ The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

Brain MRI of a 42-year-old woman with multiple sclerosis



Axial T2-weighted (A) and axial fluid attenuated inversion recovery (FLAIR) (B) images show multiple, ovoid shaped, hyperintense foci consistent with multiple sclerosis plaques. Sagittal FLAIR (C) image also shows these lesions to be radiating out from the corpus callosum. Axial precontrast T1-weighted (D) image shows that many of these lesions are hypointense, consistent with black holes. Axial postgadolinium fat saturated T1-weighted (E) image shows that some of these plaques enhance in a ring-like fashion consistent with active plaques.

McDonald criteria for dissemination in space

Dissemination in space is defined as the development of lesions in distinct anatomic locations within the central nervous system, indicating a multifocal process.

The McDonald criteria for dissemination in space are fulfilled if one of the following is present in a patient with a clinically isolated syndrome or typical MS attack:

- An MRI with one or more hyperintense T2 lesions that are characteristic of multiple sclerosis in at least two of four MS-typical regions of the central nervous system:
  - Periventricular
  - Cortical or juxtacortical
  - Infratentorial
  - Spinal cord
- Development of an additional clinical attack characteristic of multiple sclerosis, supported by objective clinical evidence, that implicates a different central nervous system site

Adapted from: Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018; 17:162.

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McDonald criteria for dissemination in time

Dissemination in time requires the development or appearance of new central nervous system lesions over time.

The McDonald criteria for dissemination in time are fulfilled if one of the following is present in a patient with a clinically isolated syndrome or a characteristic MS attack:

- The development of an additional clinical attack, supported by objective clinical evidence, that is characteristic of multiple sclerosis
- An MRI of the brain and/or spinal cord with the simultaneous presence of gadolinium-enhancing and nonenhancing lesions at any time, or by a new hyperintense T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan
- Finding of cerebrospinal fluid-specific oligoclonal bands (as a substitute for dissemination in time)

Adapted from: Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018; 17:162.

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Spinal fluid and oligoclonal bands – Oligoclonal bands are found in cerebrospinal fluid in up to 95 percent of patients with clinically definite MS. A positive cerebrospinal fluid is based upon the finding of either oligoclonal bands different from any such bands in serum (two to four or more), or by an increased immunoglobulin G (IgG) index.

Making the diagnosis – MS is primarily a clinical diagnosis (algorithm 1). The history and physical examination are most important for diagnostic purposes. The McDonald criteria for the diagnosis of MS (table 4) apply primarily to patients who have a typical clinically isolated syndrome at presentation suggestive of relapsing-remitting MS, and can also be applied to patients presenting with insidious neurologic progression suggestive of primary progressive MS. While useful when the diagnosis of MS is clinically suspected, the McDonald criteria are **not** intended for distinguishing MS from other neurologic conditions. The core requirement of the diagnosis of MS is the objective demonstration of dissemination of central nervous system lesions in both space (table 5) and time (table 6), based upon clinical findings alone, a combination of clinical and MRI findings, or in some instances an appropriate clinical syndrome and highly supportive MRI data.

Diagnosis of typical relapsing-remitting multiple sclerosis

Key concepts

Attack:
- A monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection
- Attack, relapse, exacerbation, and (when it is the first episode) CIS are synonyms

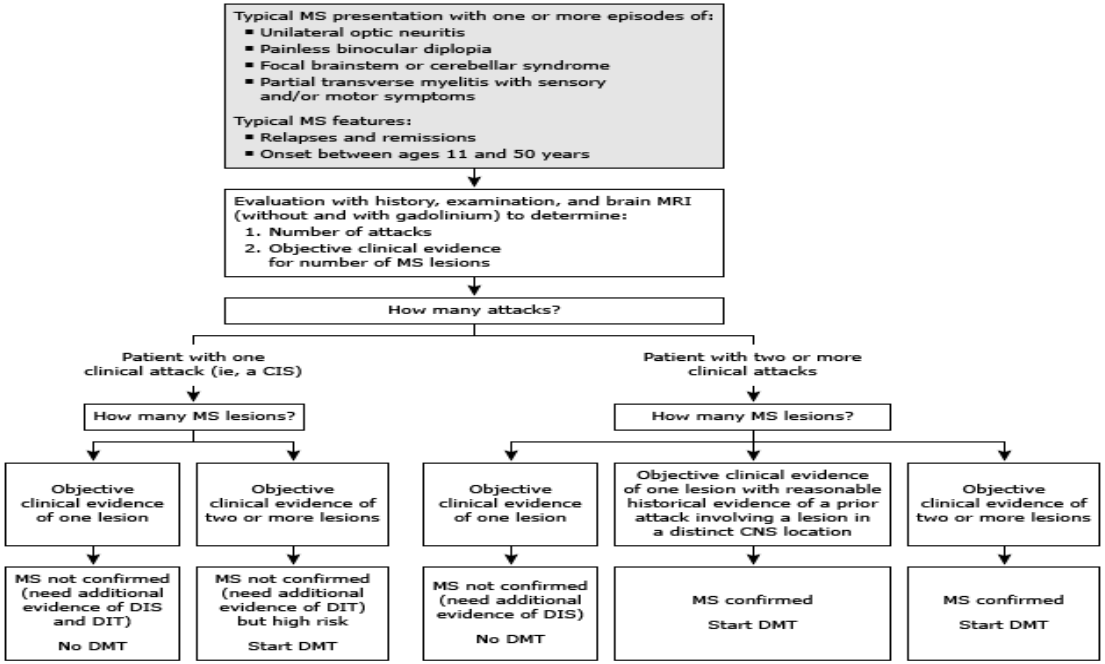
Objective clinical evidence:
- Related to a current or historical attack: An abnormality on neurologic examination, imaging (MRI or OCT), or neurophysiologic testing (VEPs) that corresponds to the anatomic location suggested by the symptoms

Reasonable historical evidence:
- Reasonable historical evidence for one past attack, in the absence of documented objective neurologic findings, can include historical events with symptoms and evolution characteristic of an inflammatory demyelinating attack

Key definitions

Dissemination in space (DIS):
- One or more hyperintense T2 esions on MRI that are characteristic of MS in at least two of four MS-typical regions (periventricular, cortical or juxtacortical, infratentorial, and spinal cord),
  or
- An additional clinical attack implicating a different CNS site

Dissemination in time (DIT):
- An additional clinical attack,
  or
- Simultaneous presence on MRI of gadolinium-enhancing and nonenhancing lesions at any time,
  or
- A new hyperintense T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan,
  or
- Demonstration of CSF-specific OCBs (as substitute for dissemination in time)



CIS: clinically isolated syndrome; CNS: central nervous system; CSF: cerebrospinal fluid; DIS: dissemination in space; DIT: dissemination in time; DMT: disease-modifying therapy; MRI: magnetic resonance imaging; MS: multiple sclerosis; OCBs: oligoclonal bands; OCT: optical coherence tomography; VEPs: visual evoked potentials.

Differential diagnosis

The differential diagnosis of MS includes a number of inflammatory, vascular, infectious, genetic, granulomatous, and other demyelinating disorders, but depends on the clinical setting.

Differential diagnosis of multiple sclerosis

Inflammatory disease
Acute disseminated encephalomyelitis
Behçet disease
Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
Clinically isolated syndromes suggestive of multiple sclerosis
Myelin oligodendrocyte glycoprotein IgG-associated encephalomyelitis
Neuromyelitis optica spectrum disorder
Paraneoplastic encephalomyelopathies
Polyarteritis nodosa
Primary angiitis of the central nervous system
Sjögren syndrome
Systemic lupus erythematosus
Infectious disease
Human immunodeficiency virus
Lyme neuroborreliosis
Neurosyphilis
Progressive multifocal leukoencephalopathy
HTLV-1-associated myelopathy/Tropical spastic paraparesis
Genetic disease
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
Granulomatous disease
Lymphomatoid granulomatosis
Sarcoidosis
Granulomatosis with polyangiitis (Wegener's)
Disease of myelin
Adrenoleukodystrophy
Adult metachromatic leukodystrophy
Other
Arnold-Chiari malformation
Compressive spinal cord lesions
Vascular malformations
Vitamin B12 deficiency
Spinocerebellar disorders

Human T-lymphotropic virus, type I; IgG: Immunoglobulin G.

Treatment of acute exacerbations of multiple sclerosis in adults

Definitions – An MS exacerbation or relapse is defined as a monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the central nervous system, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection. MS exacerbation, relapse, and attack are synonyms.

Definitions – An MS exacerbation or relapse is defined as a monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the central nervous system, developing acutely or subacutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection. MS exacerbation, relapse, and attack are synonyms.

Clinical features – Relapses in MS are highly variable and may include one or multiple neurologic deficits involving sensory disturbance, motor weakness, visual disturbance (eg, monocular visual loss or diplopia), imbalance, fatigue, or cognitive difficulty.

Glucocorticoid treatment – For patients with an acute MS exacerbation (relapse, attack) that results in neurologic symptoms and increased disability or impairments in vision, strength, or cerebellar function, we recommend a short course of high-dose glucocorticoid therapy (**Grade 1B**). The main goal of treatment is to speed recovery time from the MS attack. However, acute treatment has no apparent benefit for improving long-term disability or for reducing the risk of subsequent attacks. Our preferred regimen is intravenous methylprednisolone 1000 mg daily for five days without an oral taper. However, the data suggest that high-dose oral glucocorticoid regimens are just as effective. Repository corticotropin injection gel, where available, is an alternative for patients with MS exacerbations who cannot tolerate high-dose glucocorticoids or have poor venous access or prefer self-injection. Infection must first be ruled out.

Poor response to glucocorticoid treatment – For patients with acute, severe neurologic deficits caused by MS who have a poor response to treatment with high-dose glucocorticoids, we suggest treatment with plasma exchange (**Grade 2C**).

Role of disease-modifying therapy – Patients with relapsing-remitting MS who have current disease activity manifested by clinical symptoms or MRI lesions should be offered disease-modifying therapy.

Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults

Types of disease-modifying therapy (DMT)

A number of immunomodulatory agents have important beneficial effects for patients with relapsing-remitting multiple sclerosis (RRMS), mainly a decreased relapse rate and a slower accumulation of brain lesions on magnetic resonance imaging (MRI). These disease-modifying therapies (DMTs) for multiple sclerosis (MS) are available as monoclonal antibodies, oral therapies, and older (platform) injectable drugs.

Comparative efficacy of DMTs

The available evidence suggests that several monoclonal antibodies (natalizumab, ocrelizumab, alemtuzumab, and ofatumumab) and an oral DMT (cladribine) have the highest efficacy, while oral fingolimod and oral dimethyl fumarate have an intermediate efficacy, and oral teriflunomide and the older injection DMTs (interferons and glatiramer) have the lowest efficacy.

Assessing the risk of MS worsening

Clinicians should assess patients with RRMS at presentation and periodically thereafter for features associated with a poor prognosis and higher risk of future relapse and severe disability. The most important factors predicting a worse clinical course and poor long-term outcome are the presence of highly active disease (eg, frequent relapses and new MRI lesions), extensive radiologic involvement of MS lesions (eg, multifocal lesions, high lesion number; and high T2 burden of disease), and/or poor relapse recovery.

Patient- and drug-specific factors influencing DMT choice

A number of issues may narrow DMT options, including patient values and preferences and drug-specific factors. Women of childbearing potential may wish to avoid some or all DMTs with the potential for fetal harm.

Shared decision-making – Using shared decision making, the patient, clinician, and care team should jointly consider the decision to start a DMT and select the best option, evaluating the evidence of benefits, risks, and burdens of the available DMTs.

Treatment paradigms – There is no uniform method for selecting initial DMT for patients with RRMS. Two broad treatment paradigms are advocated by different experts: starting with highly effective therapy or starting with low-risk therapy. In addition, some experts and patients prefer to start with oral therapy, which is intermediate for efficacy and risk.

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Our approach – For patients with RRMS, we recommend DMT (**Grade 1A**). We typically start with one of the agents listed below

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•**Higher effectiveness DMTs for initial treatment**
-Intravenous natalizumab
-Intravenous ocrelizumab
-Subcutaneous ofatumumab
•**Intermediate effectiveness DMTs for initial treatment**
-Oral dimethyl fumarate, diroximel fumarate, or monomethyl fumarate
-Oral fingolimod

•**Lower effectiveness DMTs for initial treatment**
-Oral teriflunomide
-Intramuscular recombinant human interferon beta-1a
-Subcutaneous recombinant human interferon beta-1a
-Subcutaneous pegylated recombinant human interferon beta-1a
-Subcutaneous recombinant human interferon beta-1b
-Subcutaneous glatiramer acetate

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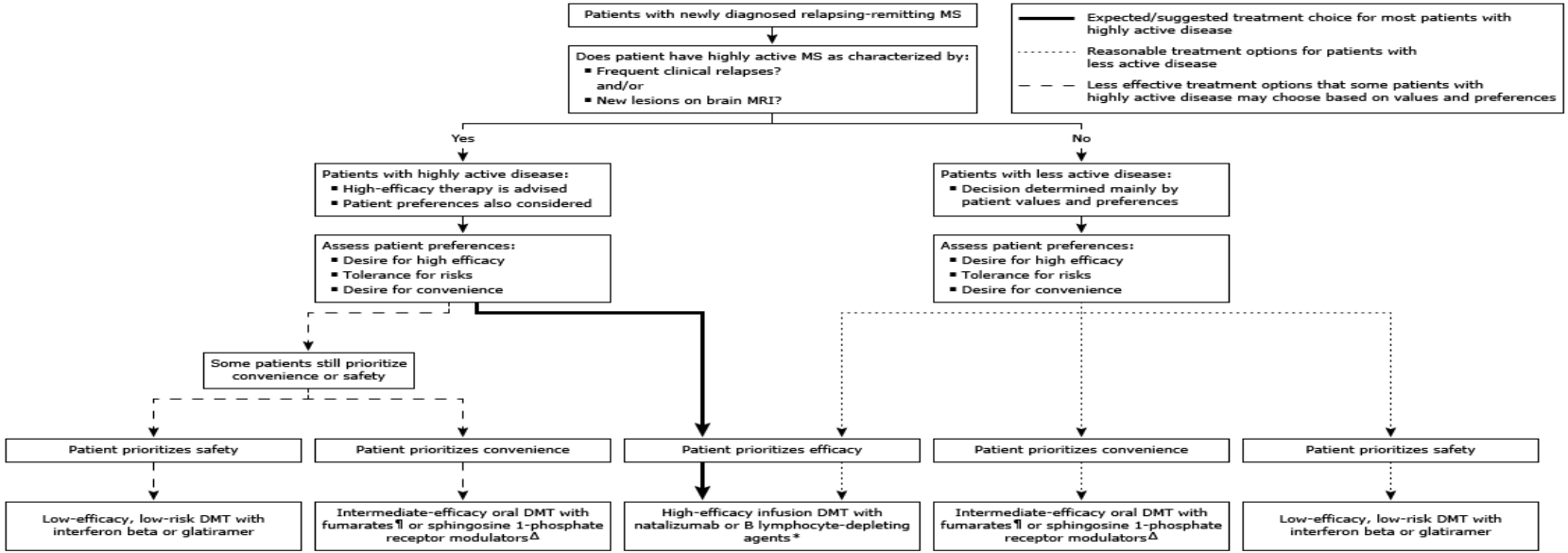
- **Choosing among the DMT effectiveness categories** – In choosing among these and other available DMTs, clinicians should incorporate individual patient prognostic factors, values and preferences, and drug-related factors (adverse effect profile, cost, availability, and burden of administration), using a shared decision making to optimize choices for individual patients (algorithm 1). The following options are reasonable guides to selecting therapy:

-For patients with highly active disease, and for patients who place a high value on efficacy and are relatively risk-tolerant, start with highly effective therapy using intravenous natalizumab or ocrelizumab.

-For patients with less active disease, and for patients who value convenience using a self-administered medication compared with medications requiring injections or infusions, start with oral dimethyl fumarate or oral fingolimod.

-For patients who place the highest value on safety and have less active disease, start with one of the beta interferons or glatiramer.

Initial disease-modifying therapy for relapsing-remitting multiple sclerosis



There is no uniform method for selecting initial DMT for patients with relapsing-remitting MS. The following are reasonable options for choosing initial DMT:

- For patients with highly active disease and for patients who place a high value on efficacy and are relatively risk-tolerant, start with highly effective therapy using intravenous natalizumab or a B lymphocyte-depleting agent.
- For patients with less active disease and for patients who value convenience using a self-administered oral medication compared with medications requiring injections or infusions, start with an oral fumarate or sphingosine 1-phosphate receptor modulator.
- For patients who place the highest value on safety and are willing to accept lower effectiveness, start with one of the beta interferons or glatiramer. The response to DMT can be monitored by careful monitoring for acute MS attacks (relapses) and new lesions on brain MRI to ensure effectiveness for the individual patient while minimizing risk.

DMT: disease-modifying therapy; MRI: magnetic resonance imaging; MS: multiple sclerosis.

* B lymphocyte-depleting agents include ocrelizumab, rituximab, ofatumumab, and alemtuzumab.

¶ Fumarates include dimethyl fumarate, diroximel fumarate, and monomethyl fumarate.

∆ Sphingosine 1-phosphate receptor modulators include fingolimod, siponimod, and ozanimod.

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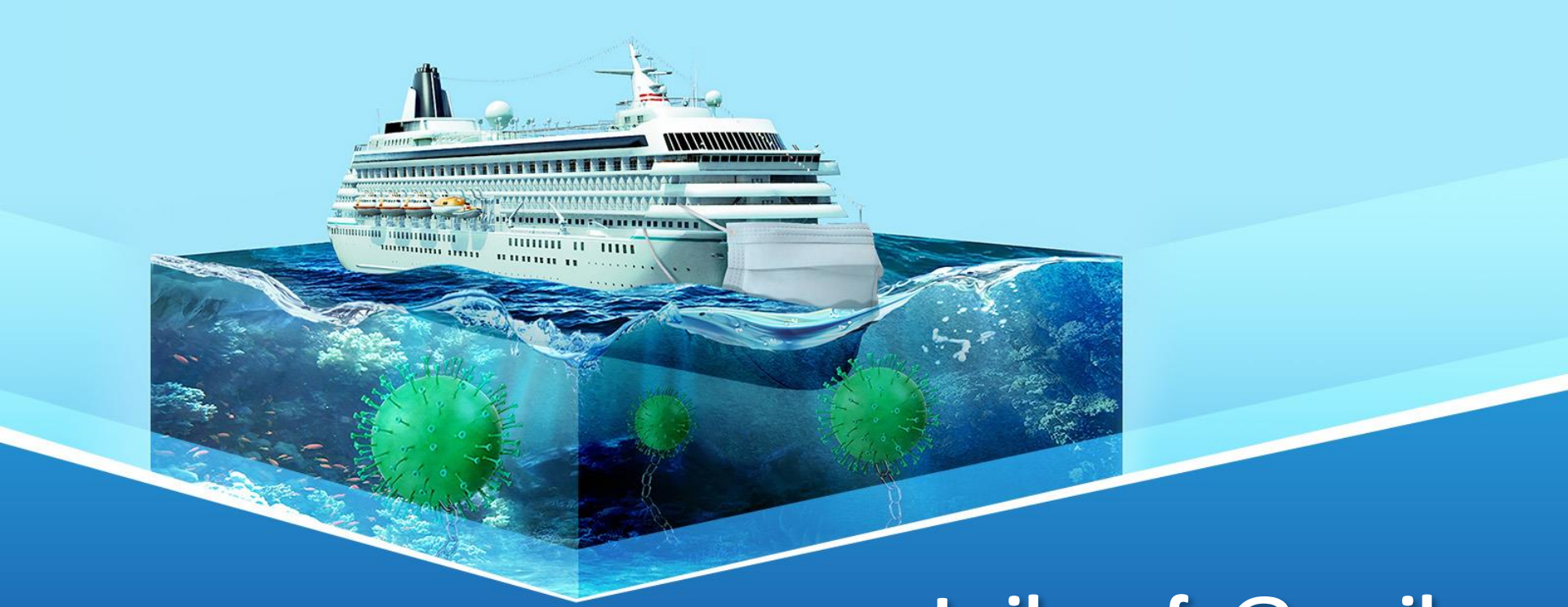
Monitoring response to therapy

– The response to DMT can be monitored by clinical follow-up with careful attention to possible manifestations of MS disease activity including acute attacks (relapses), new or contrast-enhancing lesions on MRI, and, possibly, the onset or progression of sustained disability.



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