Reducing infection risk in multiple sclerosis and neuromyelitis optica spectrum disorders: a Brazilian reference center's approach

Redução do risco de infeção em esclerose múltipla e doença do espectro neuromielite óptica: abordagem de um centro de referência brasileiro

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Abstract

Background Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD) are the most common autoimmune diseases of the central nervous system (CNS). They present chronic relapsing courses that demand treatment with disease-modifying drugs (DMDs) to prevent inflammatory activity. Disease-modifying drugs lead to immunomodulation or immunosuppression through diverse mechanisms (e.g., shifting lymphocyte and cytokine profile, suppressing specific lymphocyte subpopulations). Thus, patients are more prone to infectious complications and associated worsening of disease.

Objective To present feasible strategies for mitigating the infection risk of MS and NMOSD treated patients.

Methods Targeted literature review concerning the management of infection risk with an emphasis on vaccination, therapy-specific measures, and particularities of the Brazilian endemic infectious diseases' scenario.

Conclusion We propose a vaccination schedule, infectious screening routine, and prophylactic measures based on the current scientific evidence. Awareness of emergent tropical diseases is necessary due to evidence of demyelinating events and possible parainfectious cases of MS and NMOSD.

Keywords
- Multiple Sclerosis
- Neuromyelitis Optica
- Vaccines

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Resumo

Antecedentes A esclerose múltipla (EM) e a doença do espectro neuromielite optica (NMOSD) são as doenças autoimunes mais comuns do sistema nervoso central (SNC). Ambas apresentam curso crônico com recaídas (surtos) e exigem tratamento com drogas modificadoras de doenças (DMDs) para a prevenção de atividade inflamatória. As DMDs levam à imunomodulação ou imunossupressão através de diversos mecanismos (por exemplo deslocando e/ou suprimindo subpopulações linfocitárias ou alterando perfil de produção de citocinas). Desta forma, os pacientes com EM ou NMOSD são mais propensos a complicações infecciosas, as quais podem levar ao agravamento de suas doenças de base.

Objetivo Apresentar estratégias viáveis para mitigar o risco de infecção de pacientes com EM ou NMOSD sob tratamento.

Métodos Revisão bibliográfica focada em manejo de risco de infecção com ênfase em vacinação, medidas específicas de tratamento e particularidades de doenças infecciosas endêmicas do Brasil.

Conclusão Propomos um calendário de vacinação, rotina de triagem infecciosa e medidas profiláticas baseadas em evidências científicas atuais. A conscientização das doenças tropicais emergentes é necessária devido a evidências de eventos desmielinizantes e possíveis casos parainfecciosos de EM e NMOSD.

Palavras-chave

- Esclerose Múltipla
- Neuromielite Óptica
- Vacinas

INTRODUCTION

Multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSDs) are the most common demyelinating diseases of the central nervous system.[1] Relapses are the hallmark of clinical activity and add up to increasing disability, particularly in NMOSD, in which case they tend to be more severe and refractory to treatment. Available disease modifying drugs (DMDs) lead to immunomodulation or immunosuppression through diverse mechanisms, which halt disease activity but also impair the body's defense response against infections.

In patients with MS or NMOSD, infections may increase the risk of relapses and worsening of disease. While using DMDs, infections can be more frequent and severe; thus, adequate infection risk management is required. Feasible measures include adequate infectious screening prior to DMDs initiation, a well-suited approach to vaccination, and prophylactic measures during treatment.

In this article, we will present feasible strategies for mitigating the risk of infection of MS and NMOSD treated patients with an emphasis on vaccination, therapy-specific measures, and particularities of the Brazilian endemic infectious diseases' scenario.

METHODS

We performed a targeted literature review to address questions (**Supplementary Material**, available online only) determined by a panel of specialists in neuroimmunology and infectious diseases. Information from Pubmed, Web of Science, Cochrane, medication labels, and official reports from the Brazilian Society of Immunizations (SBIm) and the Brazilian Ministry of Health were searched, compiled, and reviewed by four junior neuroimmunologists from March to November 2020. All resulting evidence was assessed by a panel of three senior neuroimmunologists and two senior infectious disease specialists with a focus on the management of immunocompromised patients. Suggestions were elaborated through the consensus of all specialists.

Objective

The objective of this paper is to provide Brazilian neurologists with practical strategies for mitigating the risk of infection of MS and NMOSD treated patients.

Infection prevention

Infectious screening

Infection risk can be mitigated through vaccination and treatment of latent infections before the beginning of DMDs for the treatment of MS or NMOSD. At the first clinical visit, it is recommended to screen patients' serological status and vaccination records aiming to rule out differential diagnoses and identify lack of immunity against vaccine-preventable diseases (►**Table 1**)[2–6] In addition, prior to switching DMDs, it is advisable to re-check immunity and infections against specific DMD-relevant infectious agents (►**Table 2**).[4–6]

Vaccine Efficacy in MS and NMOSD Patients under Treatment

Influenza is the most studied vaccine in the MS and NMOSD treated populations. Vaccination response to other vaccines is often surmised based on the available knowledge of that vaccine. Studies have found that the influenza vaccine response is reduced in patients being treated with:

Table 1 First appointment suggested screening in multiple sclerosis/ neuromyelitis optica spectrum disorders patients to reduce infection risk.

First appointment screening in MS/NMOSD patients
• Serology for HIV • Serology for syphilis (FTABs and VDRL) • HBsAg, anti-HBs and Anti-HBc • Serology for hepatitis C • Serology for varicella, measles, and rubella • Serology for toxoplasmosis • IGRA or tuberculin test • Chest X-ray or CT • Review vaccination chart

Abbreviations: anti-HBc, antibody against hepatitis B core antigen; CT, computed tomography; FTABs, fluorescent treponemal antibody absorbed; HBsAg, hepatitis B surface antigen; anti-HBs: antibody against hepatitis B surface antigen; HIV, human immunodeficiency virus; IGRA, interferon gamma release assay; VDRL, venereal disease research laboratory.

fingolimod,[7] natalizumab,[7] rituximab,[8] ocrelizumab,[9] and mycophenolate-mofetil.[8] The influenza vaccine response has been found to be effective in patients under interferons[10] and teriflunomide, though decreased response is seen in the latter.[11] Data are conflicting regarding glatiramer-acetate.[12,13] Influenza vaccine response in patients using dimethyl-fumarate, cladribine, azathioprine, and methotrexate has not been studied in the MS and NMOSD populations. However, data from kidney transplant patients indicates that the vaccine's response is maintained in azathioprine users.[14] In addition, vaccine response during the use of dimethyl fumarate has been shown to be adequate for tetanus-diphtheria toxoid, pneumococcal, and meningococcal vaccine when compared with interferon.[15] Data on routine serological screening after immunizations in patients under DMDs is lacking and not widely recommended.

Timing of vaccines

Vaccines are more effective if administered before the beginning of immunosuppressive or immunomodulatory treatments. Therefore, as vaccines do not increase the risk of relapses in MS patients, vaccination prior to DMD initiation is recommended.[16,17] Contrarily, NMOSD patients who are not on immunotherapy have a higher likelihood of presenting relapses following immunization. Thus, immediate initiation of DMDs following diagnosis and subsequent vaccination are recommended when safe in patients with NMOSD.[18]

To maintain vaccination efficacy, ensure protection before immunosuppression, and reduce the risk of side effects, following Brazilian Society of Immunizations (SBIm) and Brazilian Ministry of Health guidelines, we recommend

Table 2 Disease modifying drugs specific screening suggestion

Disease modifying drug (DMD)	Screening tests
Interferon-β 1a/1b (Avonex®, Betaferon, Rebif)	–
Glatiramer-acetate (Copaxone)	–
Dimethyl-fumarate (Tecifidera)	Tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti- HCV
Teriflunomide (Aubagio)	Tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti- HCV
Fingolimod (Gilenya)	VZV IgG, cervical cytology (for sexually active women), tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti- HCV
Natalizumab (Tysabri)	JCV, HBsAg, anti-HBs, anti-HBc, Tuberculin test/IGRA
Anti-CD20 monoclonal antibodies (MabThera, Truxima®, Rixathon, Ocrevus)	Tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti- HCV, VZV IgG
Alemtuzumab (Lemtrada)	Tuberculin test/IGRA, cervical cytology (for sexually active women), HBsAg, anti-HBs, anti-HBc, anti- HCV
Cladribine (Mavenclad)	Tuberculin test/IGRA, cervical cytology (for sexually active women), HBsAg, anti-HBs, anti-HBc, anti- HCV, VZV IgM/IgG, HIV
Azathioprine (Imuran)	Tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti- HCV, VZV IgM/IgG
Methotrexate (Miantrex CS)	Tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti-HCV, VZV IgG
Mycophenolate-mofetil (Cellcept)	Tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti-HCV, VZV IgG
Eculizumab (Soliris)	Tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti-HCV, VZV IgG, gonorrhea NAAT or culture in patients with increased risk for STDs and their sexual partners
Satralizumab (Enspryng)	Tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti-HCV, VZV IgG
Inebilizumab (Uplizna)	Tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti-HCV, VZV IgG
Tocilizumab (Actemra)	Tuberculin test/IGRA, HBsAg, anti-HBs, anti-HBc, anti-HCV, VZV IgG

Abbreviations: HB, hepatitis B; anti-HBc, antibody against hepatitis B core antigen; HBsAg, hepatitis B surface antigen; anti-HCV, antibody against hepatitis C virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; igM, immunoglobulin M; IGRA, interferon gamma release assay; JCV, John Cunningham virus; NAAT, nucleic acid amplification Test; VZV, varicella zoster virus.

starting DMDs at least 2 weeks after inactivated vaccines and at least 4 weeks after live-attenuated vaccines have been administered.[19,20] If vaccination prior to drug initiation is impossible, inactivated vaccines may be administered during treatment; however, they will probably lead to compromised immune responses. In patients who are not severely immunocompromised, careful individual assessment should precede live-attenuated vaccines administration. Multiple sclerosis patients treated with cladribine may receive live vaccines after their leucocyte count resumes to normal.[21]

Vaccination schedule for MS and NMOSD patients

In 2019, the American Academy of Neurology (AAN) and the Société Francophone de la Sclérose en Plaques (SFSEP) issued recommendations regarding the immunization of MS patients. Both statements highlight the current evidence on vaccine safety and efficacy in this population. Vaccines are considered safe and efficient in MS patients without DMD use, similar to the general population, supporting the rationale to provide proper immunization prior to starting DMDs. The recommended vaccine schedule includes vaccines that are standard for the general population plus specific vaccines based on local epidemiology.[16,17]

For patients already using DMDs, each medication may require a specific approach. While immunomodulators such as betainterferons and glatiramer acetate seem to have less impact in vaccine safety and efficacy, most DMDs require well-timed vaccine administration for optimal efficacy. Special attention should be given to the administration of live-attenuated vaccines, which cannot be prescribed to patients under immunosuppressive drugs, including prednisone $\geq$ 20 mg/day.

In Brazil, the Brazilian Society of Immunizations (SBIm) has published schedules for special patients, including those with autoimmune diseases or immunosuppression.[19] There are no schedules specific to MS or NMOSD patients. Our vaccine schedule suggestion for MS and NMOSD patients over the age of 10 is displayed in ►**Table 3**.

Close contact vaccination

The Infectious Disease Society of America (IDSA), SBIm and Brazilian Ministry of Health guidelines recommend healthy immunocompetent persons who live with immunocompromised patients should receive a broader vaccination schedule than the general population.[19,20,22] Close contacts of immunosuppressed patients should receive yearly influenza vaccine and be questioned about history of varicella and immunization status. They should be vaccinated for measles, mumps, rubella, and varicella, if susceptible. Oral polio vaccine should not be administered to people living with immunocompromised patients, as the living virus can be excreted in the feces. The inactivated vaccine is preferred.[22]

Impact on the vaccination of newborns of mothers who received immunosuppressants

Experts recommend that live vaccine administration should be withheld in the first year of newborns that were exposed to rituximab in utero, particularly if exposed in the third trimester.[23] Though BCG, measles, and rubella vaccines can be postponed with minimal impact to infants, the rotavirus vaccine poses a challenge. The latter is a major cause of acute gastroenteritis associated with significant death and hospitalization rates in newborns and infants. Hence, the benefits of rotavirus vaccine may outweigh the risks in normal schedule. The SBIm considers that newborns of mothers who received rituximab should not receive BCG or rotavirus vaccines in the first 6 to 8 months of life as no consensus can be reached regarding optimal safety in this scenario. To the best of our knowledge, there is no literature addressing the impact of other DMDs on newborn vaccination. Nonetheless, we suggest caution when administering live vaccines to newborns of immunosuppressed mothers.

Vaccination in pediatric population diagnosed with MS and NMOSD

Pediatric onset MS and NMOSD are extremally rare, accounting for $\sim$ 3 to 10% of all cases.[24] There are several reports of CNS inflammatory events following infections and vaccination in children.[24] The link between exposure to infections and immune dysregulating triggering autoimmune disorders, including acquired demyelinating syndromes (ADS), is a special concern in the pediatric population.[25,26] No association between vaccination and acquired demyelinating syndromes (ADSs) has consistently been described, including pediatric-onset of MS.[27,28] Studies focusing on pediatric NMOSD are lacking. It is currently accepted that vaccines might act by accelerating the transition from subclinical to clinically relevant inflammatory events. However, the risk of developing vaccine-preventable infectious diseases is considered higher than the risk of developing vaccine-triggered demyelinating events.[29]

Thus, recommendations for the pediatric population with neuroimmunologic disorders are similar to those of adults: (1) children with incomplete vaccination charts should be vaccinated according to age and serology prior to beginning immunosuppressive drugs; (2) all pediatric patients should receive the influenza vaccine annually; (3) live-attenuated vaccines are contraindicated in patients on immunosuppressive drugs. Infectious screening should be performed as in the adult population (►**Tables 1** and **2**).

Other infection prevention measures

Immunoglobulin replacement

Rituximab has been associated with increased risk of infections.[30] Hypogammaglobulinemia is a possible causal mechanism, which is observed in almost half of the patients treated with the drug[31]. Intravenous immunoglobulin (IgIV) replacement in patients with recurrent infections and low IgG levels ($<$ 5 g/dl) should be performed, as it is associated with a reduction of the infection rate of patients receiving rituximab, at least in observational studies[31] Although IgIV replacement is not suggested for all MS/NMOSD anti-CD20/CD19 treated patients, we recommend immunoglobulin dosing (IgG, IgA, and IgM), or protein

Table 3 Vaccination schedule for multiple sclerosis and neuromyelitis optica spectrum disorders patients > 10 years of age

Vaccine	Safety in immunosuppressed patients/Commentaries	Schedule	Availability in the Brazilian public health system
Influenza	Safe	1 dose annually	3V: Yes; 4V: No.
Pneumococcal conjugate (PCV 10 or 13)	Safe *Commentary: 1. Always start by applying the PCV 10/13 and follow with the PPSV 23 after a minimal 2-month interval. 2. Individuals who have previously received the PPSV 23 and not received the PCV 10/13, should receive the PCV 10/13 12 months after the last PPSV 23. They can receive the PPSV 23 booster dose 5 years after the first dose.	Children > 2 months old	PCV 10: For all children up to 5 yo; PCV 13: From 5 yo, for HIV, cancer, and transplant patients
Pneumococcal polysaccharide (PPSV 23)		Individuals > 2 yo: two doses with a five-year interval. If the second dose is administered > 60 yo, a third dose is recommended after a 5-year interval.	A two-dose regimen, with a minimum five-year interval, is available to eligible patients.
Haemophilus influenzae type b (Hib)	Safe	Immunosuppressed patients: two doses with a two-month interval.	Yes
Meningococcal C/ ACWY	Safe *commentaries: 1. Immunosuppressed individuals should receive a booster dose every five years. 2. Whenever possible, use the ACWY conjugated meningococcal vaccine.	Unvaccinated immunosuppressed children > 1 year, adolescents, and adults: two doses with a two- month interval.	Men C: Yes Men ACWY: Available to adolescents and patients who will start eculizumab.
Meningococcal B	Safe	Adults: 2 doses with a 2-month interval.	No
Hepatitis A (HepA)	Safe	Previously unvaccinated adults: two doses with a 6-month interval.	Yes
Hepatitis B (HepB)	Safe *Commentary: Hepatitis B serology should be requested one to two months after the last dose of the regimen. Anti HBs ≥10 UI/mL means effective immunization. If the serology is negative, repeat the three- or four-dose vaccination schedule (according to recommendation) once.	Immunosuppressed individuals: four doses at 0, 1, 2,and 6 months, with twice the recommended volume for the age group.	Yes
HPV	Safe *commentary: Two vaccines are available in Brazil: HPV4, licensed for girls and women from 9–45 yo and boys and men from 9–26 yo; and HPV2, licensed for girls and women from 9 years of age. We suggest applying the HPV4 vaccine.	Three doses: at 0–1 and 2–6 months.	HPV2: No HPV4: Available to all children from 9 to 14 yo and up to 26 yo to other eligible patients (including immunosuppressed patients)
Herpes zoster	Unsafe *Commentary: Only the live-attenuated vaccine is currently available in Brazil	Non-immunosuppressed individuals > 50 years of age: One dose.	No
Diphtheria, tetanus, & acellular pertussis (Tdap), Diphtheria, tetanus (Td)	Safe	1. Adults with complete basic vaccination schedule: reinforcement with Tdap every ten years. 2. Adults with incomplete basic vaccination schedule: one dose of Tdap at any time + complete basic vaccination with Td (total three doses of vaccine containing the tetanus component). 3. Unvaccinated and/or unknown vaccination history: one dose of Tdap and two doses of Td in schedule 0, 2, and 4–8 months	Td: Yes Tdap: available to pregnant women, health workers and bone marrow transplant patients

(*Continued*)

Table 3 (*Continued*)

Vaccine	Safety in immunosuppressed patients/Commentaries	Schedule	Availability in the Brazilian public health system
Mumps, measles, and rubella (MMR)	Unsafe	Non- immunosuppressed individuals > 1 yo: two doses, with a minimum interval of one month between them.	Yes
Yellow fever (YFV)	Unsafe *Commentary: There is no consensus on the duration of the effect of the vaccine.	World Health Organization's recommendation: 1 dose for non-immunosuppressed individuals ≥ 9 months of age.	Yes
Varicella (VAR)	Unsafe	Two doses for susceptible non-immunocompromised patients.	Yes
Dengue fever (DF)	Unsafe * Commentary: Approved use for adults < 45 yo, who previously had dengue fever.	Individuals who have previously been infected: three doses with a 6-month interval (0–6-12 months).	No

Abbreviations: ACWY, meningococcal bacteria A, C, W, and Y; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine.

electrophoresis, and infection monitoring every 6 months with immunoglobulin replacement, in case of recurrent infections.[31]

Antibiotic and antiviral prophylaxis

Prophylactic antibiotics and antivirals are routinely used in MS patients treated with alemtuzumab. Herpes infections occurred in 6% of alemtuzumab-treated patients in clinical trials and were serious in 0.1 to 0.2% of patients.[32] Acyclovir 200 mg twice a day is recommended for at least 60 days after last alemtuzumab administration and until CD4 lymphocyte count is above 200 mg/uL. However, only ~ 50% of patients have return of CD4 count above 200 mg/uL in 9 months and 80% of patients in 12 months after alemtuzumab dose.[33] Hence, if CD4 levels are not monitored, we recommend prophylactic acyclovir for at least 2 years. Cotrimoxazole prophylaxis can also be prescribed to prevent both listeria infection and *Pneumocystis jiroveci* pneumonia until lymphocyte count is above 200 mg/uL.[6] Hygienic measures for patients using alemtuzumab include listeria-free diet and toxoplasmosis-free diet in toxoplasmosis IgG-negative patients.

Eculizumab, a terminal complement inhibitor, requires special attention to bacterial infections due to its mechanism of action tampering immune response to encapsulated bacteria. Particularly, patients may present severe meningococcal infections. Risk of meningococcal infection can increase up to 2.000 times during treatment. Vaccination decreases but does not eliminate this risk. Quadrivalent meningococcal vaccine plus vaccine against B serogroup should be administered at least 2 weeks before beginning of therapy. A booster dose of quadrivalent meningococcal vaccine after 5 years is recommended. Antibiotic prophylaxis should be given for at least 4 weeks after immunization, as to protect against infection during assembly of proper immune response to vaccination. Penicillin V potassium 250 mg 12/12h or ciprofloxacin 500 mg daily for at least 4 weeks after last vaccination are feasible regimens.[34]

Patients living with MS/NMOSD frequently have neurogenic bladder after spinal cord lesions and may need clean intermittent self-catheterization (CISC) to empty their bladder. In this population, 25% of patients experience recurrent urinary tract infection (UTI). Based in the AnTIC trial,[35] patients using CISC with two episodes of symptomatic UTI in the last year or with one episode of UTI that leads to hospitalization should be submitted to prophylactic antibiotics to reduce the risk of a new symptomatic UTI. Options for prophylactic antibiotics include: 50 mg/d nitrofurantoin, 100 mg/d trimethoprim, or 250 mg/d cefalexin. Nevertheless, this strategy is associated with increased bacterial resistance in new events of UTI and, hence, trials of discontinuation of prophylactic antibiotics after 12 months may be considered to reduce this complication. We also recommend urological consultation for patients experiencing bladder disfunction and recurrent urinary tract infections (UTIs).

Hepatitis B reactivation management

Vaccination remains the most effective intervention to prevent hepatitis B virus (HBV) infection. However, previously infected individuals may present HBV reactivation during immunosuppressive treatment and require adequate monitoring. Particularly, B-cell depleting therapies have been associated to reactivation;[36] nonetheless, screening for HBV is mandatory before beginning of any immunosuppressive treatment.

The American Gastroenterological Association and the European Association for the Study of the Liver have issued guidelines regarding the management of HBV reactivation during immunosuppressive treatment. Antiviral prophylaxis is strongly recommended to high-risk patients defined as having anticipated incidence of reactivation higher than 10%. In MS and NMOSD, this population is comprised of patients presenting positive antiHBc receiving B cell depleting DMDs, alemtuzumab, or cladribine for more than 4 weeks. Patients receiving azathioprine, methotrexate, and prednisone at low doses for any duration are considered low risk for

reactivation and are not required to receive prophylaxis. A less supported alternative is to screen HBV DNA every 3 months.[37,38]

Hepatitis B reactivation is less clear during treatment with other DMDs. Clinical trials of oral DMDs were not uniform in screening HBV, and severe liver disease has not been reported.[39] Nonetheless, screening is recommended, and monitoring may be considered individually.

HPV in MS and NMOSD treated patients

Human papillomavirus (HPV) viruses are responsible for the occurrence of cutaneous warts, 99% of cervical cancers, and most of anogenital cancers.[40] Multiple sclerosis and NMOSD treatments may compromise normal antiviral response to HPV. Fingolimod therapy, for instance, has been associated with treatment refractory warts.[41]

There are 2 vaccines currently available in Brazil for the prevention of HPV, the HPV 2 (HPV 16 and 18 serotypes) and HPV 4 (HPV 6, 11, 16, and 18 serotypes) vaccines. The national public health system (SUS) offers the HPV4 vaccine to boys and girls aged from 9 to 14 and to HIV, cancer, transplant, and immunosuppressed patients from 9 to 26 years of age free of charge. Nonetheless, the HPV4 vaccine has been approved for use in females between 9 and 45 and males between 9 and 26 years of age. As MS and NMOSD treated patients are more prone to developing HPV infection clinical manifestations, we recommend all male and female patients receive the HPV4 vaccine when possible.

Brazilian guidelines on cervical cancer screening suggest collecting cervical cytology yearly in all women over 25 years of age who are or have previously been sexually active. Periodic screening should be maintained until the age of 64.[40] Due to the potential increased risk of cervical cancer in MS and NMOSD treated patients, in agreement with other specialists, we suggest carrying yearly cervical cytology in conjunction with pelvic examination in all previously sexually active patients.[40] In addition, we recommend avoiding DMTs associated with impaired antiviral response, such as fingolimod, in case of cervical cancer diagnosis.

Tuberculosis screening

Latent tuberculosis should be screened annually in patients using MS DMDs, except for interferons and glatiramer.[39,42,43] Interferon gamma release tests (IGRAs), such as QuantiFERON, are more accurate than tuberculosis skin tests and BCG vaccination does not interfere with them. A meticulous medical history should be taken aiming to identify previous contact with confirmed cases of tuberculosis. In addition, chest radiography or tomography should be performed to differentiate active from latent tuberculosis infection. The latter is treated with isoniazid 300 mg/d for 6 to 9 months or rifampicin for 4 months. We recommend at least a month of antituberculosis therapy before starting DMDs for patients with latent tuberculosis.

Varicella virus zoster infection in patients on fingolimod or high-dose corticosteroids

Fingolimod augments the risk of varicella zoster virus (VZV) reactivation. Although overall low, the risk associated with fingolimod is higher than with placebo (11 versus 6 per 1,000 patients/year). Hence, we recommend that patients without evidence of VZV immunity (i.., IgG negative) should receive 2 doses of the vaccine with a 4-week interval. The first dose of fingolimod should be scheduled for at least 1 month after the second dose. Moreover, in case of recent high-dose corticosteroid use for the treatment of a relapse, the VZV vaccine must be administered at least 30 days following corticosteroid interruption.[44]

PML

Progressive multifocal leukoencephalopathy (PML) is a poliomavirus-associated disease caused by the John Cunningham virus (JCV) which often leads to permanent disability or death. Progressive multifocal leukoencephalopathy has been described in MS patients treated with natalizumab, fingolimod, dimethyl-fumarate, and ocrelizumab.[44] There are no reports of PML on MS or NMOSD patients treated with rituximab; however, cases of PML have been described in patients suffering from other diseases who were treated with the drug.[45–47]

Concern about the risk of developing PML is the main reason for discontinuing natalizumab.[48] Risk factors for natalizumab-associated PML include prior immunosuppressant (IS) therapy, the presence of serum anti–JC virus (JCV) antibodies, and longer natalizumab therapy duration—especially beyond 2 years.[49,50] Mindfulness of the risk factors is important in preventing the disease. We recommend monitoring at each medical appointment, according to the table below (►**Table 4**). Strategies for minimizing PML risk include extended interval dosing of natalizumab (i.e., infusions every 6–8 weeks) or switching treatment to other high efficacy options, such as anti-CD20 monoclonal antibodies, alemtuzumab, or cladribine.[51]

Multiple sclerosis patients with previous natalizumab use may experience PML due to "carry-over" risk, even after being switched to other drugs. In fact, most of the patients who developed PML on fingolimod, dimethyl-fumarate, or ocrelizumab fit into that category. Nonetheless, "*de novo*" PML cases have been described for each of the aforementioned medications. "Carry-over" PML risk can be mitigated through prevention and surveillance. We suggest magnetic resonance imaging (MRI) screening every 3 to 4 months up to 12 months following the switch from natalizumab to any of those medications.[52]

Few cases of PML have also been reported in patients under treatment with alemtuzumab, cladribine, teriflunomide, and interferons. Nonetheless, all are associated with low risk of developing PML, as most of the reported cases had coexisting risk factors for the development of the disease.[53]

Post exposure measures – measles and chickenpox

Immunocompromised patients can develop severe forms of measles and chickenpox. Therefore, postexposure measures for susceptible individuals are imperative and involve timely vaccination and immunoglobulin administration. A restricted group of patients will be eligible to receive postexposure vaccination, as live vaccines should be avoided in immunosuppressed patients.

To prevent severe forms of chickenpox, the VZV vaccine should be administered up to 5 days following significant

Table 4 Progressive multifocal leukoencephalopathy, risk stratification on natalizumab-treated patients*

	JCV status	PML risk	Suggested monitoring
Without previous IS	Negative	<1/10,000	Anti-JCV every 6 mo MRI at baseline and every 6–12 mo
	< 0.9	1–24 m: 1/10,000	Anti-JCV every 6 mo MRI at baseline and every 6–12 mo
		>24 m: 1/748	Review risks and benefits
	≥ 0.9	1–24 m: 1/1,062	New anti-JCV not required MRI at 6–12 mo
		>24 m: 1/101	New anti-JCV not required MRI at 3–6 mo Consider change DMD
Previous IS	Independent	1–12 m: ½.500	Anti-JCV every 6 mo (if negative) MRI at baseline and every 6–12 mo
		12–24 m: 1/1,250	Anti-JCV every 3 mo (if negative) MRI at baseline and every 3–6mo
		24: 1/250	Anti-JCV every 3 mo (if negative) MRI at baseline and every 3–6 mo Change DMD (strongly recommended)

Abbreviations: DMD, disease modifying drug; IS, immunosuppression; JCV, John Cunningham virus; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy.
*Adapted from Ho et al. (2017).[52]

exposure of non-immunosuppressed patients (e.g., patients under beta-interferons or glatiramer acetate). Varicella zoster virus immunoglobulin administration should ideally be performed up to 4 days following significant exposure of immunosuppressed patients; however, it is still feasible up to 10 days after exposure. It is available in the Brazilian public health system (SUS). Less supported alternatives include intravenous immunoglobulin (IVIg) (400 mg/kg one dose), oral acyclovir (20 mg/kg each dose, 4 times daily for 7 days, maximum daily dose of 3,200 mg), or valacyclovir (20 mg/kg each dose, 3 times daily for 7 days, maximum daily dose of 3,000 mg) administration. When chosen, acyclovir and valacyclovir should be used after 7 to 10 days of exposure.[54]

Severe measles prevention can be achieved through post-exposure vaccine within 72 hours of exposure of non-immunosuppressed patients. Specific immunoglobulin is unavailable. Alternatively, IMIg (0.5 ml/kg up to 15 ml divided among multiple muscle groups) or IVIg (400 mg/kg one dose) should be administered up to 6 days following exposure of immunosuppressed patients.[55]

Prevention of yellow fever

Yellow fever is an endemic disease in Brazil without specific treatment. In 2017 and 2018, Brazil experienced one of the most severe yellow fever epidemics of all times with almost 3,000 infected patients and a 39.3% lethality rate.[56] Since then, the number of seasonally infected patients has decreased, but the single dose vaccine is still recommended for patients living in or travelling to endemic areas.

The yellow fever vaccine (YFV) is highly effective, inducing neutralizing antibodies in 99% of recipients.[57] It is a live attenuated virus vaccine and should not be administered to young (< 6 months of age), immunosuppressed, pregnant, or breastfeeding patients. The vaccine seems to be safe for MS patients being treated with injectable medications but should not be administered to patients on other DMTs, despite its reported safety on natalizumab-treated patients.[58] There is some controversy on whether the vaccine increases the chance of relapses in MS. Farez et al. reported a statistically significant increase in relapse rate following the YFV (rate ratio = 12.778; $p < 0.001$) in a 2011 study involving 7 MS patients living in endemic areas of Argentina.[59] However, in a recent study carried by Huttner et al., there was no reported increase in relapse rate after the vaccination of 23 patients travelling to endemic areas.[58] We recommend an individualized approach when indicating the YFV to patients living or travelling to endemic areas. Travelling should be discouraged, when possible. Patients on non-injectable DMTs may benefit from barrier methods, such as using insect repellent, placing nets on doors and windows, and wearing long-sleeved shirts and pants. If the infection risk is remarkably high, DMT interruption followed by vaccination may be indicated, if there are no records of recent MS inflammatory activity or previously aggressive disease. If it is decided to do so, the ideal conduct is to wait 3 to 6 months after cessation of immunosuppression prior to vaccination (patients who received B cell depleting DMDs should wait 6 months).[20] In case of recent MS inflammatory activity of previously aggressive disease, we recommend avoiding the vaccine, considering the current available evidence.

In conclusion, the long-term management of MS and NMOSD has become feasible due to the increasing number of DMDs being developed and approved. However, disease activity and adequate control are inevitably tied to increased risk of developing infections. Infections may worsen the course of MS and NMOSD through heightened risk and the severity of

relapses. Conversely, DMDs may tamper adequate immune response to infections, leading to possibly worse outcomes. Mitigating strategies of infectious risk must be assessed from time of diagnosis to DMDs initiation and follow-up.

Adequate infection screening and vaccination are primordial to reduce the risk of infection in MS/NMOSD patients. Neurologists should be mindful to screen for preventable and treatable infections such as tuberculosis, syphilis, hepatitis B and C, HIV, varicella, measles, rubella, and toxoplasmosis before starting DMDs.[2,6] When possible (i.e. patients with non-aggressive MS), immunizations should be offered prior to the initiation of DMDs. Disease-modifying drugs should be started at least 2 weeks after inactivated vaccines and at least 4 weeks after live-attenuated vaccines have been administered.[19,20] NMOSD patients should not have immunosuppressive treatment delayed due to vaccination, as there is an increased risk of relapses following vaccines in non-immunosuppressed NMOSD patients.[18]

Infection risk monitoring is also necessary during patients' follow-up. Neurologists should reassess infection risk when switching DMDs and take each specific DMD recommendation into consideration. Infection prophylaxis is indicated for patients who present recurrent UTIs, or who are receiving alemtuzumab or eculizumab. When in doubt, infectious disease specialists or urologists should be consulted. Lymphocyte counts, HBV/HCV/HPV infection, and PML risk should also be checked routinely. Neurologists should be reminded that PML has been associated to DMDs other than natalizumab. In addition, PML carry-over risk should be monitored after suspension of natalizumab, as PML is a preventable fatal disease, and a high level of suspicion is necessary.

There are currently no national guidelines on the infectious risk management of patients with CNS demyelinating disorders. Through this review, we have aimed to provide information and practical recommendations to assist Brazilian neurologists with infectious diseases scenarios which may be experienced in clinical practice.

Authors' Contributions

BAGRG: conceived and wrote the review; LBF, GDS, CCDD, RBP: wrote the review; ANL, ACT: critically appraised the review; MFM, SLAP, DC: conceived and critically appraised the review.

Conflict of Interest

Samira Luisa Pereira Apóstolos, Maria Fernanda Mendes, and Dagoberto Callegaro have participated in lectures and developed written educational materials for Biogen, Roche, Merck, and Novartis.

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