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Preventing infectious complications when treating non-malignant immune-mediated hematologic disorders

Luis Malpica[1] | David van Duin[2] | Stephan Moll[1]

[1]Department of Medicine, Division of Hematology and Oncology, University of North Carolina School of Medicine, Chapel Hill, North Carolina

[2]Department of Medicine, Division of Infectious Diseases, University of North Carolina School of Medicine, Chapel Hill, North Carolina

Correspondence
Luis Malpica, University of North Carolina, Department of Medicine, Division of Hematology and Oncology, 170 Manning Drive, CB# 7035, Chapel Hill, NC, 27599.
Email: luis.malpicacastillo@unchealth.unc.edu

Abstract

Immunosuppressants, targeted antibody therapies, and surgical splenectomy are amongst the treatment choices for immune-mediated non-malignant hematologic disorders, with infection being the most common non-hematological adverse event from these therapies. Corticosteroids are associated with a length-of-treatment and dose-dependent risk for infection, including opportunistic infections. Screening and antimicrobial prophylaxis against tuberculosis, *Strongyloides stercoralis*, and *Pneumocystis jirovecii* pneumonia, are indicated in selected patients on steroids and with certain risk factors for infection. Rituximab is associated with hepatitis B virus reactivation. All patients planned to be started on rituximab should be screened for hepatitis B surface antigen and total core antibody, with antiviral prophylaxis given depending on test results. In eculizumab treated patients, immunization against meningococcal serogroups ACWY and B is recommended. In addition, some guidelines suggest antibiotic prophylaxis for the duration of eculizumab treatment. In splenectomized patients, counseling and immunization are cornerstones of infection prevention. Several federal and society guidelines about immunizations and prophylactic antimicrobial therapies for patients treated with various immunosuppressive agents exist and are summarized in this manuscript in a clinical-focused table. In addition, management suggestions are made where no formal guidelines exist.

1 | INTRODUCTION

Immunosuppressive therapies in the treatment of non-malignant immune-mediated hematologic disorders, such as immune thrombocytopenic purpura, thrombotic thrombocytopenic purpura, autoimmune hemolytic anemia, antiphospholipid syndrome, and acquired coagulation factor deficiencies, lead to an increased risk for infections. This includes bacterial infections, reactivation of tuberculosis or toxoplasmosis, viral infections, and viral reactivation including varicella zoster virus and viral hepatitis. As infectious complications can severely affect a patient's outcome, preventive strategies - immunization, prophylactic antiviral and antibiotic therapy, and patient education about risk - are essential tools in minimizing risk. This article reviews the published data on the infectious complications with the various immunosuppressive therapies used to treat non-malignant immune-mediated hematologic disorders and existing recommendations about prevention strategies from medical societies, the Centers for Disease Control (CDC), regulatory agencies and expert panels. It also highlights areas where limited evidence exists and discusses our clinical approach given the existent knowledge base. Finally, the available data and suggested management strategies for the prevention of infection in patients treated with these agents are summarized in Table 1.[1-11]

2 | PATIENT COUNSELING

An important part of infectious disease prevention in immunocompromised patients entails the education of the patient, family, and friends. Household and other close contacts of persons with altered immunocompetence should be educated in hand hygiene and avoid contact with the patient when they are experiencing an infectious process.[12] Proper food and water hygiene measures are important to prevent

TABLE 1 Guidance for vaccination, and infectious disease screening in adults (>18 years) receiving rituximab, eculizumab, or undergoing splenectomy for non-malignant immune-mediated hematologic disorders[1-11]

Therapy	Risk for Infections	Prevention Strategy	Vaccine Series / Screening / Antimicrobial prophylaxis	Additional Recommendations
Rituximab (RTX)	*Recognized association*: • Hepatitis B reactivation (HBVr) • Impaired response to vaccines *Reported cases*: • Viruses: Hepatitis C reactivation, CMV, VZV, Echo virus, PML • Bacteria: tuberculosis • Fungi: *Aspergillus*, *Candida*, *Cryptococcus* • Others.	1. ***Hepatitis Screening*** • *Hepatitis B screening (HBsAg and anti-HBc)* • *Hepatitis C screening (anti-HCV)* ***2. Vaccination***:[a] • *Streptococcus pneumoniae* PCV13 (Prevnar) PPSV23 (Pneumovax) • *Haemophilus influenzae* • *Neisseria meningitides* MenACWY (Menactra) MenB-4C (Bexsero)	***Pneumococcal vaccine***[b] • Primary Series 1 dose of PCV13 or 1 dose of PPSV23 if uncertain time to splenectomy. 1 dose of PCV13 followed by PPSV23 ≥ 8 weeks later if known plan for splenectomy. • Booster PPSV23 every 5 years[c] ***Haemophilus influenza type b vaccine*** • Primary Series 1 dose • Booster Not applicable ***Meningococcal vaccine*** • Primary Series 2 doses of MenACWY at least 8 weeks apart or 2 doses of MenB-4C at least 1 month apart if uncertain time to splenectomy. 2 doses of MenACWY at least 8 weeks apart and 2 doses of MenB-4C at least 1 month apart if known plan for splenectomy. • Booster MenACWY every 5 years Not applicable for MenB-4C	***1. Hepatitis B reactivation***: • If HBsAg-positive/ anti-HBc-positive initiate antiviral prophylaxis (entecavir or tenofovir). • If HBsAg-negative/ anti-HBc-positive, the AGA recommends antiviral PPX; alternatively preemptive therapy could be considered[d]. • Rituximab can be started 1 week after antiviral treatment is instituted. • Continue therapy for at least 12 months after last RTX dose. • Monitoring for HBVr should continue for at least 12 months after the end of antiviral prophylaxis. • Misleading anti-HBc can occur in pts treated with IVIG. Anti-HBc should be obtained before or 3 months after IVIG administration. ***2. Vaccination***: • We recommend vaccination in anticipation to need for splenectomy. • Administer vaccines at least 2 weeks before starting therapy. • Counsel pts on potential risk of vaccine unresponsiveness after RTX. • HZ vaccine if ≥50 years-old[e].

(Continues)

TABLE 1 (Continued)

Therapy	Risk for Infections	Prevention Strategy	Vaccine Series / Screening / Antimicrobial prophylaxis	Additional Recommendations
				• Annual viral influenza vaccine. • Live attenuated vaccines should not be provided until at least 6 months of therapy completion.
Corticosteroids	*Recognized association*: • Bacteria: skin and soft-tissue infection, tuberculosis (TB) • Viral: HZ reactivation • Fungi: *Candida*, PJP • Parasite: *Strongyloides* *Reported cases*: • Bacteria: non-TB mycobacteria Fungi: *Aspergillus*, *Cryptococcus*	***1. Infectious screening***: • Tuberculosis • Strongyloidiasis[f] ***2. Vaccination***: • Influenza virus • VZ virus.	***Vaccination*** • Administer at least 2 weeks before starting therapy. • HZ vaccine if ≥50 years-old[e]. • Annual viral influenza vaccine. ***Preventing opportunistic infection*** • Latent TB screening if long-term steroid (>10 mg PEQ for ≥4 weeks)[h]. • *Strongyloides* screening if long-term steroid, and current or previous history of living in endemic areas[e]. • PJP ppx[h]: Pts on PEQ ≥10 mg QD, and 1. age ≥ 65 years with co-existence lung disease, or 2. if used in combination with CP or RTX.	• HCV screening as per USPSTF guidelines[g]. • HIV screening as per CDC guidelines[g]. • Live or live attenuated vaccines are contraindicated in pts on 10 mg QD of PEQ, or if cumulative ≥700 mg of PEQ in 3 months. • Live or live attenuated vaccination should be deferred at least 1 month after discontinuation. • Patients with chronic diseases (ie, diabetes, renal disease) have increased risk for infections.
Eculizumab (Soliris ®)	*Recognized association*: • Serogroupable, and non-serogroupable *Neisseria meningitidis*. *Reported cases*: • Bacteria: *Staphylococcus*, *Klebsiella oxytoca*, *Escherichia hermannii* • Fungi: *Aspergillus*, *Scedosporium*.	***1. Vaccination***: • *Neisseria meningitides* MenACWY (Menactra) MenB-4C (Bexsero) ***2. Antibiotic prophylaxis***	***Vaccination***: • Primary Series 2 doses of MenACWY at least 8 weeks apart and 2 doses of MenB-4C at least 1 month apart if known plan for splenectomy. • Booster MenACWY every 5 years Not applicable for MenB-4C ***Antibiotic prophylaxis***: • If Eculizumab is given before vaccination, start antibiotic ppx against *N. meningitides* and continue it until at least 2 weeks after vaccination. • Antibiotic choice[i]: Penicillin, ciprofloxacin, azithromycin.	• Administer vaccines at least 2 weeks before starting therapy. • Both vaccines can be administered the same day but in different anatomic site. • HZ vaccine if ≥50 years-old[e]. • Annual viral influenza vaccine. • Enrollment in the Risk Evaluation and Mitigation Strategy (REMS) is highly recommended by the FDA. • Educate pts about early signs of infection (fever,

(Continues)

TABLE 1 (Continued)

Therapy	Risk for Infections	Prevention Strategy	Vaccine Series / Screening / Antimicrobial prophylaxis	Additional Recommendations
				rash, mental status changes). • Hospitalize if signs are presented and treat immediately. First-line antibiotic choice will depend on local sensitivity.
Splenectomy	*Recognized association*: • Encapsulated organism: *S. pneumoniae, H. influenza, N. meningitidis* • Bacteria: *Salmonella sp*., *Enterococcus*, *Bacteroides*, *Capnocytophaga* (animal bite) • Parasite: **Babesia**, **Ehrlichia**, plasmodia	***1. Vaccination***: • *Streptococcus pneumoniae* PCV13 (Prevnar) PPSV23 (Pneumovax) • *Haemophilus influenzae* • *Neisseria meningitides* MenACWY (Menactra) MenB-4C (Bexsero)	***Pneumococcal vaccine***[b] • Primary Series 1 dose of PCV13 followed by PPSV23 ≥ 8 weeks later. • Booster PPSV23 every 5 years[c] ***Haemophilus influenza*** type b vaccine • Primary Series 1 dose • Booster Not applicable ***Meningococcal vaccine*** • Primary Series 2 doses of MenACWY at least 8 weeks apart or 2 doses of MenB-4C at least 1 month apart if uncertain time to splenectomy. 2 doses of MenACWY at least 8 weeks apart and 2 doses of MenB-4C at least 1 month apart if known plan for splenectomy. • Booster MenACWY every 5 years Not applicable for MenB-4C	***1. Vaccination***: • Vaccination is preferred 4 to 6 weeks prior to elective surgery. • In pts who have received PCV13, 5 years or more ago, repeat 1 dose of PCV13 followed by PPSV23 ≥ 8 weeks later. • HZ vaccine if ≥50 years-old[e]. • Annual viral influenza vaccine. • Malaria ppx for travelers. • Educate pts for signs of infection. ***2. Antimicrobial Prophylaxis***: • In our practice, since epidemiological data show an increased risk of overwhelming post-splenectomy infection within the first 2 years after splenectomy, we give penicillin V 500 mg oral twice daily for the first 2 years after spleen removal.
Antimetabolites (AZA, MMF) Cyclosporine (CYA)	*Recognized association*: • Virus: JC virus (AZA, and MMF), CMV, VZV • Fungi: PJP (CP)	***1. Vaccination***: • Influenza virus • VZ virus.	***Vaccination***: • HZ vaccine if ≥50 years-old[e]. • Annual viral influenza vaccine.	• Cyclosporine has a safe infectious profile. No specific preventive strategy has been issued.

(Continues)

TABLE 1 (Continued)

Therapy	Risk for Infections	Prevention Strategy	Vaccine Series / Screening / Antimicrobial prophylaxis	Additional Recommendations
Cyclophosphamide (CP)	*Reported cases in AZA and MMF* • Bacteria: *Listeria*, *Mycobacterium* sp. • Viral: BK virus • Fungi: *Cryptococcus*, *Aspergillus*, PJP • Parasite: Toxoplasma		***Progressive multifocal leukoencephalopathy*** Patients on AZA or MMF presenting with new-onset neurological manifestations (hemiparesis, apathy, confusion, cognitive deficiencies, ataxia, blurry vision or loss of vision, severe otalgia or hearing loss), should be evaluated for a neurotropic infection (eg, PML, HZ infection/reactivation).	• Selected pts on CP may need PJP ppx if pts are treated in combination with corticosteroids until dose is ≤5 mg of PEQ[j]. • If neutropenic fever, GCSF should be used in pts considered at risk for neutropenia complications (ie, older than 65 years-old, on active cancer therapy). • All immunosuppressive drugs must be discontinued during an episode of infection.

Abbreviations: AGA, American Gastroenterological Association; Anti-HBc, antibody against hepatitis B core antigen; AZA, azathioprine; CMV, cytomegalovirus; HBVr, hepatitis B virus reactivation; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; HZ, Herpes Zoster; IVIG, intravenous immunoglobulin; MenACWY, quadrivalent meningococcal conjugate vaccine; MenB-4C, meningococcal vaccine serogroup B; PCV13, pneumococcal 13-valent conjugate vaccine; PEQ: prednisone equivalent dose; PML, progressive multifocal leukoencephalopathy; PPSV23, pneumococcal polysaccharide vaccine; PPX, prophylaxis/prophylactic; Pts, patients; TMP/SMX, trimethoprim/sulfamethoxazole; VZV, varicella zoster virus.

[a]This is not an established national recommendation. The Center of Disease Control, the American Society of Hematology, and some European guidelines recommend that patients with ITP should receive vaccines against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitides* at least 2 weeks before therapy in anticipation that some patients will go on to require splenectomy. In our practice we also include patients with other immune-mediated hematologic disorders such as autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura, and acquired coagulation factor deficiencies treated with rituximab.

[b]If primary series already received (eg, patients with known concomitant immunosuppression like HIV or age > 65 years), revaccinate with PPSV23 every five years.

[c]The Advisory Committee on Immunization Practices recommends a single revaccination dose of PPSV23 five years after the first PPSV23 dose. Some experts recommend vaccination every 5 years regardless in patients with functional or anatomical asplenia.

[d]Preemptive antiviral therapy consists on withholding antiviral therapy while obtaining monthly HBV DNA levels for one year and preemptively starting antiviral therapy during the initial stages of HBV reactivation.

[e]Zoster vaccine recombinant (Shingrix®) is preferred over zoster vaccine live (Zostavax®). Clinicians may choose to administer HZ vaccine off-label in people younger than 50, if in their clinical judgment, they think the vaccine is indicated (eg, history of recurrent HZ). The patients should be informed that the use is off-label, and that efficacy and safety of the vaccine have not been tested in people younger than 50.

[f]Risk population for *Strongyloides stercoralis* (SS) are uniformed-service veterans, or long-term travelers who returned from tropical regions (Southeast Asia and South Pacific: Peru, Brazil, Colombia, Ecuador), or U.S. natives (Appalachia and southeastern regions). Both, stool sample for ova and parasites, and serum IgG against SS should be taken. In our practice, given the poor sensitivity, and high cost of *Strongyloides stercoralis* screening, empiric therapy with ivermectin represents a safe and cost-effective approach in patients at high-risk for strongyloidiasis.

[g]Screening for HCV infection in persons at high risk (ie, intravenous drug users), and a one-time screening in adults born between 1945 and 1965. HIV screening recommended to all people 13 years and older.

[h]We recommend IGRA in patients already taking corticosteroids given increased risk for false negative TST. If positive test, refer to an Infectious Disease specialist.

[i]First-line antimicrobial ppx: penicillin at 500 mg orally twice daily. Because eculizumab recipients remain at risk for meningococcal disease even after vaccination, some health care providers in the U.S. and in other countries recommend antimicrobial ppx for the duration of eculizumab treatment since a lifelong course of therapy is expected for many pts.

[j]TMP/SMX as either daily intake of one single strength tablet (80 mg TMP and 400 mg SMX), or one double strength tablet 3 times weekly. If TMP/SMX intolerance or contraindicated, alternative therapy with atovaquone, dapsone, or once monthly nebulized pentamidine can be pursued.

disease.[13] Patients should always be advised to seek prompt diagnosis and treatment of any febrile illness. Early management of animal bites is critical in immunocompromised patients.[14] For travelers, the use of tick and mosquito repellents, netting while sleeping, anti-malarial prophylaxis when traveling to endemic areas, and the advice from an infectious disease physician are all recommended.[13] All patients should receive annual influenza virus vaccine. Patients 50 years and older should be treated with the herpes zoster vaccine (the CDC recommends the recombinant herpes zoster vaccine [Shingrix] over the live attenuated vaccine [Zostavax]).[15] Human immunodeficiency virus status should be known in any patient with a non-malignant immune-mediated hematologic disorder.

3 | CORTICOSTEROIDS

Corticosteroids are widely used in the management of non-malignant immune-mediated hematologic disorders.

There are three major effects from corticosteroids that leads to a disruption on the immune responses against pathogens. First, diminished opsonization, and macrophage phagocytic and microbicidal function that increases the risk for bacterial infections; second, impaired T cell migration and proliferation that increases the risk for mycobacterial, viral, and fungal infection; and third, promotion of eosinophil apoptosis either directly or by attenuating synthesis of IL-5 (a cytokine that promotes eosinophil survival) increasing the risk for parasitic infection.[16]

3.1 | Infection risk

The current evidence base detailing the risk of infections with corticosteroids is largely derived from rheumatologic studies, and although randomized controlled trials evaluating short-term lower dose steroids in this population have reported little to no increased risk for infections, observational studies have shown dose-dependent increases in risk for serious infections, including opportunistic infections.[17,18] Infection risk also increases with age and is higher among those with diabetes, prescribed higher glucocorticoid doses (more than 10-20 mg of prednisone daily), and with low albumin.[19] No significant difference in risk for infection has been found in clinical trials between pulse doses of steroids and steroid taper regimens.[18]

Opportunistic infections associated with corticosteroids use include *Pneumocystis jirovecii* pneumonia, herpes zoster reactivation, tuberculosis, nontuberculous mycobacterial disease, aspergillosis, candidiasis, strongyloidiasis, and cryptococcosis.[20-23] The current evidence regarding the association between *Pneumocystis jirovecii* pneumonia and corticosteroids is largely derived from case series and single center studies, many of which concluded that there is an association of *Pneumocystis jirovecii* pneumonia and a prednisone dose above 30 mg daily.[24] Several large population-based studies have found an association between corticosteroid use and herpes zoster infection/reactivation. Use of systemic corticosteroids of more than 7.5-10 mg daily compared to no steroids in patients with rheumatoid arthritis has been shown to increase the risk of herpes zoster (HR 1.78-2.52).[17] A few observational studies have evaluated the risk of tuberculosis with corticosteroid use. A retrospective case control study of 497 new cases of tuberculosis and 1966 age and sex-matched controls found that the adjusted odds ratio for tuberculosis was 2.8 (95% CI 1.0, 7.9) for prednisone-equivalent doses less than 15 mg/day and 7.7 (95% CI 2.8, 21.4) for doses greater than 15 mg/day.[25] Another study found that patients with tuberculosis were more likely to have received intravenous pulse dose methylprednisolone.[26]

Strongyloides stercoralis (threadworm) is an intestinal nematode unique in its ability to replicate in the human host allowing ongoing cycles of autoinfection, persisting for decades within the same host. Hyperinfection syndrome, a widespread dissemination of the larva, has been associated with corticosteroid use, and is often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.[27] A large systemic review of case reports of threadworm infection found that 67% (163/244) of the cases occurred in patients on corticosteroid treatment, with a mortality rate of 62.7%.[28]

Hepatitis B reactivation with increased risk of reverse seroconversion (reappearance of HBsAg in serum in HBsAg-negative/antiHBcAb-positive individuals) has been reported on medium to high-dose corticosteroids (eg, prednisone 10-20 mg daily), therefore, screening and careful monitoring of these individuals is recommended.[29]

3.2 | Infection prevention strategies

3.2.1 | Laboratory screening

The American Gastroenterological Association recommends HBV screening in patients on chronic or high-dose corticosteroids (see antimicrobial prophylaxis section below).[2] The CDC guidelines recommend screening for tuberculosis in those who may need long-term immunosuppression, including long term prednisone use. The dose of prednisone-equivalent that might increase the risk for tuberculosis is 15 mg per day for 2 to 4 weeks as this dose has been shown to suppress tuberculin reactivity.[30] The U.S. FDA advises that corticosteroids should be used with great care in patients with known or suspected strongyloides infestation, and that the use of corticosteroids may exacerbate systemic fungal infections.[27]

In our practice, patients planned to be treated with 10-20 mg or more of prednisone per day for 4 or more weeks, are screened for HBV, HCV, latent tuberculosis and strongyloidiasis. As with rituximab, HBV screening should include both HBsAg and anti-HBcAb. HCV screening consists of hepatitis C antibody testing and, if positive, hepatitis C viral load. Latent tuberculosis screening should be performed with either tuberculin skin test (TST) or serum interferon gamma release assays (IGRAs). We would recommend using IGRAs for screening if patients are already taking corticosteroids given an increased risk for false negative results with TST.[31] If a test is positive, the patient should be referred to an infectious disease specialist for appropriate management. Patients who currently reside or previously lived in endemic areas for *Strongyloides stercoralis* (ie, uniformed-

service veterans, or long-term travelers who returned from tropical regions such as Southeast Asia and South America, or U.S. natives from the Appalachia and the southeastern regions) should be screened with a stool sample for ova and parasites, and serum IgG against *Strongyloides stercoralis*.[28] In our practice, given the poor sensitivity, and high cost of *Strongyloides stercoralis* screening, empiric therapy with ivermectin represents a safe and cost-effective approach in patients at high-risk for strongyloidiasis, that is, those who have lived in areas of high incidence or endorse a history of walking outside barefoot. Infectious disease input in such patients is warranted.

3.2.2 | Antimicrobial prophylaxis

The American Gastroenterological Association recommends HBV prophylaxis over no prophylaxis in "high risk" patients (defined as anticipated incidence of HBV reactivation of >10%), such as patients who are HBsAg-positive/anti-HBcAb-positive and on moderate-dose corticosteroids (10-20 mg prednisone-equivalent) chronically, or high-dose (>20 mg prednisone-equivalent) corticosteroids daily for ≥4 weeks.[2] Treatment with antivirals should be continued for at least 6 months after discontinuation of steroids. The American Gastroenterological Association suggests use of antiviral drugs with a high barrier to resistance (ie, entecavir or tenofovir) over lamivudine (weak recommendation).[2]

No recommendations regarding antimicrobial prophylaxis for opportunistic infections in the steroid-treated patient are available in national clinical guidelines. In our practice, patients treated with prednisone-equivalent ≥10 mg daily and additional risk factors (ie, age ≥ 65 years and co-existence of pulmonary disease,[32] or treated in combination with cyclophosphamide or rituximab) should be considered for *Pneumocystis jirovecii* pneumonia prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX).[33-35] Note, TMP-SMX should be prescribed as prophylaxis for either daily intake of one single strength tablet (80 mg trimethoprim and 400 mg sulfamethoxazole) or one double strength tablet three times weekly. For patients who exhibit either intolerance or contraindication (eg, glomerular filtration rate below 15 mL/min) to TMP/SMX, alternative therapy with atovaquone 1500 mg daily, dapsone 100 mg daily, or once monthly 300 mg nebulized pentamidine can be pursued.[17,33,35]

3.2.3 | Vaccination

All patients should receive herpes zoster vaccine if 50 years or older and the annual influenza virus vaccine. The recombinant herpes zoster vaccine is recommended over live zoster vaccine.[15] The U.S. FDA advises that the administration of live or live attenuated vaccines are contraindicated in patients receiving immunosuppressive doses of corticosteroids (more or equal to 10 mg of prednisone daily or a cumulative dose of more than 700 mg of prednisone in 3 months). Vaccination should be deferred for at least 1 month after discontinuation of such therapy. Killed or inactivated vaccines and toxoids may be administered; however, the response to such vaccines cannot be predicted.[27]

4 | RITUXIMAB

Rituximab is a chimeric monoclonal antibody targeting the B-cell antigen CD20, approved for various malignant hematologic and rheumatologic disorders. It has shown efficacy in autoimmune hemolytic anemia,[36] acquired coagulation factor deficiencies,[37] thrombotic thrombocytopenic purpura,[38,39] immune thrombocytopenic purpura (ITP),[40] and has been used in other disorders such as antiphospholipid syndrome,[41] and aplastic anemia,[42,43] but its use in these non-malignant immune-mediated hematologic disorders is off-label.

4.1 | Infection risk

4.1.1 | Hepatitis reactivation

Hepatitis B virus (HBV) and hepatitis C virus (HCV) reactivation can occur after the use of rituximab. Although no prevailing definition of HBV reactivation exists, experts often define reactivation as *de novo* detection of HBV DNA in individuals without previously detectable HBV DNA or a 1 to 2 log IU/mL rise in serum HBV DNA levels.[44] HBV reactivation has been reported in 20-50% of HBV carriers undergoing immunosuppressive therapy or chemotherapy.[45,46] In the setting of only rituximab therapy, a HBV reactivation rate of 16.9% has been reported.[2] Note, HBV reactivation is seen more often, and perhaps leads to more severe clinical presentations, in patients with ongoing hepatitis B infection (ie, patients who are hepatitis B surface antigen - HbsAg - positive and hepatitis B core antibody - anti-HBcAb - positive), compared to patients with resolved HBV infection (ie, patients who are HBsAg-negative/anti-HBcAb-positive).[44] Clinically, HBV reactivation can present with nonspecific symptoms such as fatigue, general malaise, and jaundice, to more severe presentations such as hepatic decompensation and fulminant hepatic failure.[47]

Hepatitis C virus reactivation can be defined as an increase of HCV RNA viral load greater than 1 log IU/mL and/or at least a 3fold increase in serum alanine aminotransferase in HCV infected patients.[47] In contrast to HBV reactivation, it is controversial whether HCV reactivation occurs with rituximab, with only anecdotic cases reported and no definitive association to rituximab therapy demonstrated.[48-51] HCV reactivation usually presents with an isolated elevation of aminotransferases, and/or increasing viral load, and although the morbidity and mortality rates of untreated HCV reactivation are similar to the ones reported in HBV reactivation, nowadays treatment of HCV is highly effective with cure rates approaching 100% in adherent patients.[47,52]

4.1.2 | Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a devastating, opportunistic demyelinating disease caused by the John Cunningham (JC) virus, an ubiquitous polyomavirus that is estimated to latently infect the kidneys in more than 50% of healthy adults.[53] In the context of

immunodeficiency, JC virus can undergo genetic rearrangements in non-coding regions and can transform to a neurotropic virus that is able to infect glial cells and cause PML.[53] The incidence of PML varies depending on the degree of immunosuppression and the underlying disease. Among rituximab users with immune-mediated diseases, reported estimated rates are 2.56 per 100 000 patients with rheumatoid arthritis and <1 per 10 000 patients with granulomatosis with polyangiitis, and microscopic polyangiitis.[54] Among patients with hematologic diseases, bone marrow transplantation increases the risk for PML and it is frequently seen in pediatric patients.[55] Although, rituximab currently carries an U.S. Food and Drug Administration (FDA)-mandated "black-box" warning for PML, the disease typically occurs in heavily treated immunocompromised patients, and data on the incidence of PML in non-malignant immune-mediated hematologic disorders is lacking.

4.1.3 | Late-onset neutropenia

Though no unique consensus exists, most experts define late-onset neutropenia as an absolute neutrophil count of ≤1500 cells/μl occurring 3-4 weeks after the last treatment with rituximab, in the absence of an alternative explanation for the neutropenia.[56] Late-onset neutropenia occurs in 3%-27% of patients receiving rituximab, with a median duration of neutropenia between 6 to 77 days.[56] Data as to which patients are at risk have not been consistent, but the following patients are generally considered to be at risk: patients above age 65; treated for hematologic malignancies rather than for autoimmune disorders; having received stem cell transplantation; treated for acquired immunodeficiency syndrome (AIDS)-related lymphoma; treated in combination with purine analogues; and having received cytotoxic chemotherapy with or without radiation therapy.[56-59] In addition, patients who have received multiple doses of rituximab are at risk.[58] The mechanism of late-onset neutropenia is poorly understood.[56] Infectious complications secondary to late-onset neutropenia are not common and not severe when rituximab is used as a single agent.[56,58,60] Pooling data from the major retrospective studies reveals an infection rate of around 16%; however, most infections were mild, and resolved promptly even in patients with febrile neutropenia.[56] Re-challenge with rituximab after late-onset neutropenia may result in recurrent episodes, but the implications and risks are uncertain at the present time. Whether granulocyte colony-stimulating factors is beneficial once late-onset neutropenia appears is unclear, but it is probably not needed.[56,57]

4.1.4 | Hypogammaglobulinemia

Long-term hypogammaglobulinemia has been observed after rituximab treatment for autoimmune cytopenias, with subsequent intravenous immunoglobulin (IVIG) dependency.[61] This complication may be more likely in patients with preexisting hypogammaglobulinemia[62] or after repeated rituximab courses.[63] Lower immunoglobulin levels have been more frequently observed in patients with malignant hematologic disorders receiving rituximab in combination with chemotherapy, rather than single-agent rituximab for autoimmune disorders.[64] In ITP, it was reported in two of 135 (1.5%) of patients treated with rituximab.[65] In a study using rituximab maintenance infusions for 2 years (one single infusion every 4 months over 2 years) in patients with relapsing ITP and autoimmune hemolytic anemia, three out of 16 patients (19%) developed hypogammaglobulinemia and needed IVIG treatment to treat recurrent infections.[66,67] Monitoring of immunoglobulin levels both before and after rituximab therapy, and association between immunoglobulin levels and risk for infections remains controversial.[64,68]

4.1.5 | Other infections

Reactivation of tuberculosis and viral and fungal infections have also been reported in patients treated with rituximab containing regimens.[54,67] Among viral diseases, cytomegalovirus, Epstein-Barr virus, parvovirus B19, echo virus, and varicella-zoster virus have been reported; fungal infections such as pulmonary aspergillosis, cryptococcal meningitis, mucormycosis, and invasive candidiasis have also been seen.[54,67] Although, patients who developed these infections had been treated with rituximab containing regimens, rituximab had been used in the setting of hematologic malignancies and after solid organ transplant where a greater immunosuppressive state would be expected.[67] It is not clear whether single agent rituximab in the treatment of non-malignant immune-mediated hematologic disorders increases the risk for viral and fungal infections other than HBV and HCV reactivation. Furthermore, it is reassuring that a systematic review of publications evaluating the use of rituximab for autoimmune diseases, the majority of with were ITP studies, found no difference in the rates of infections in the rituximab- vs the non-rituximab-treated patient control group, and also no difference in serious infections.[69]

4.2 | Infection prevention strategies

4.2.1 | Laboratory screening

The CDC, FDA, and American Gastroenterological Association recommend that all patients planned to be treated with rituximab should be tested for HBsAg and anti-HBc antibody (strong recommendation).[2,70,71] Patients who have been treated with IVIG may have positive HBV testing due to passive transmission of anti-HBc antibodies.[72] To avoid such misleading test results, anti-HBc antibody should be measured before or 3 months after IVIG administration.[72] Alternatively, an IVIG product known to be free of anti-HBc antibodies could be used (ie, IGIVnex).

Unlike HBV, HCV screening (anti-HCV) has not been a recommendation. However, there are currently several reports associating HCV reactivation and rituximab treatment.[47,51,73] If a patient is positive for HCV antibody, HCV RNA quantitative testing should be obtained.

4.2.2 | Antimicrobial prophylaxis

To date, prevention of HBV reactivation in patients with hematologic diseases receiving rituximab-based therapy has focused primarily on prophylactic antiviral therapy. The American Gastroenterological Association recommends that patients who are HBsAg-positive/anti-HBcAb positive or HBsAg-negative/anti-HBcAb-positive (regardless of their baseline serum HBV DNA status) should receive antiviral therapy which decreases the risk of HBV reactivation by 87%.[2,74] An alternative strategy is preemptive antiviral therapy, consisting on withholding antiviral therapy while obtaining monthly HBV DNA levels for one year and preemptively starting antiviral therapy during the initial stages of HBV reactivation. While limited data on patients with resolved HBV infection (HBsAg-negative/anti-HBcAb-positive patients) suggests that preemptive antiviral therapy may be effective in preventing HBV-related hepatitis,[75] sufficient data are unavailable to recommend this as standard of care. In addition, extension of this preemptive therapy to clinical practice would necessitate the use of a sensitive HBV DNA assay at monthly intervals and its availability across the different healthcare institutions, as well as, a new standardized definition of HBV reactivation (ie, HBV DNA levels ≥29 IU/mL) compared to historic definitions of HBV reactivation (ie, HBV DNA cutoff ≥100 IU/mL with increasing serum aminotransferase levels or at least a 10-fold rise in HBV DNA). In our practice, we follow the American Gastroenterological Association recommendations providing antiviral therapy to all patients receiving rituximab-based therapy who are anti-HBcAb-positive.

Although, there is no consensus as to the optimal therapy or duration of treatment to prevent HBV reactivation, the American Gastroenterological Association suggests using an antiviral drug with a high barrier to resistance (eg, entecavir or tenofovir) over lamivudine (weak recommendation).[2] Treatment with rituximab can be started 1 week after antiviral treatment is instituted and should be continued for at least 12 months after the last dose of rituximab. Recommendations related to laboratory liver enzyme and viral monitoring are rather unspecific, with most details proposed by the European Association for the Study of the Liver: ALT, and HBV DNA at an interval of 1-3 months; for at least 12 months after withdrawal of immunosuppression.[74]

With regards to HCV infection, if a patient is positive for HCV antibody along with a detectable HCV RNA, gastroenterology consultation for evaluation and possible treatment appears appropriate. No drugs are approved for HCV reactivation prophylaxis.

4.2.3 | Vaccination

Polysaccharide vaccines (pure or conjugate polysaccharide vaccines) are a unique type of inactivated subunit vaccine composed of long chains of sugar molecules that make up the surface capsule of certain bacteria.[76] Pure polysaccharide vaccines typically trigger a T-cell independent response, which means these vaccines are able to stimulate B cells without the assistance of T-helper cells. However, antibodies induced with pure polysaccharide vaccines has less functional activity than those induced by protein antigens, because the predominant antibody produced in response to most polysaccharide vaccines is IgM, and only little IgG.[76] This limitation has been overcome through a process called conjugation, a chemical combination of a polysaccharide with a protein molecule. Conjugation changes the immune response from T-cell-independent to T-cell-dependent, leading to increased immunogenicity and antibody booster response to multiple doses of vaccine.[76] Pure polysaccharide vaccines are available for pneumococcal and meningococcal disease, and conjugate polysaccharide vaccines for *Haemophilus influenzae type b* (Hib), pneumococcus, and meningococcus.

As a patient with certain non-malignant immune-mediated hematologic disorder may eventually undergo splenectomy and given the impaired response to vaccination demonstrated in patients after treatment with rituximab,[77] it may be worthwhile to vaccinate the patient, who is to be treated with rituximab, against encapsulated microorganisms. As an example, in ITP patients, the American Society of Hematology (ASH) and the CDC recommend: (a) immunization against *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*, administered at least 2 weeks before immunosuppressive therapy in anticipation that some patients will eventually go on to require splenectomy; and (b) patients should be counseled on the potential risk of vaccine unresponsiveness after rituximab.[1,3,77] European guidelines recommend vaccination of all patients receiving rituximab.[9]

In our practice, we aim at vaccinating patients planned to be treated with rituximab with pneumococcal polysaccharide vaccine (Pneumovax 23), *Haemophilus influenzae b* conjugate vaccine (HibTITER), and meningococcal (groups A, C, Y, W-135) polysaccharide diphtheria toxoid conjugate vaccine (Menactra), all given at least 2-4 weeks before instituting therapy. Revaccination every 5 years is recommended with pneumococcal polysaccharide and MenACYW vaccines. No booster is necessary with *Haemophilus influenzae b* conjugate vaccine.

4.3 | Other supportive considerations

4.3.1 | Progressive multifocal leukoencephalopathy (PML)

The FDA recommends considering the diagnosis of PML in any patient treated with rituximab presenting with new-onset neurological manifestations (hemiparesis, apathy, confusion, cognitive deficiencies, ataxia, blurry vision or loss of vision, severe otalgia or hearing loss), and to consider consultation with a neurologist as clinically indicated.[78-80]

4.3.2 | Late onset neutropenia

No specific recommendations from professional entities exist. In our practice, we do not give granulocyte-colony stimulating factor (eg, filgrastim) or prophylactic antibiotics in uncomplicated rituximab-related

late-onset neutropenia. Re-challenge with rituximab in patients with previous late-onset neutropenia should be decided on a case-by-case basis. No current guidelines exist on when and how long to monitor patients with late onset neutropenia.

4.3.3 | Hypogammaglonulinemia

In the absence of formal guidelines, thresholds for initiation of IVIG in populations with autoimmune diseases and rituximab-associated hypogammaglobulinemia vary. One study suggested initiating IVIG therapy in patients with autoimmune diseases if serum immunoglobulin G (IgG) is <2 g/L.[81] However, given the risk of infection even with moderate hypogammaglobulinemia, others have adopted higher IgG value thresholds for considering IVIG therapy.[82] In our practice, we do not routinely check immunoglobulin levels in rituximab-treated patients, unless a patient has a history of recurrent or persistent infections despite antimicrobial prophylaxis. Based on expert opinion and some clinical reports, if a patient has either moderate (IgG <5 g/L) or severe (IgG <3 g/L) hypogammaglobulinemia and recurrent or persistent infections, we consider IVIG infusion at doses comparable to the ones recommended in humoral immunodeficiency disorders (300 to 800 mg/kg every 3 to 4 weeks and depending on clinical symptoms and subsequent IgG levels).[81,82] No guidelines currently exist on when to monitor immunoglobulin levels (either before and/or after rituximab therapy) and for how long.

5 | ECULIZUMAB

Eculizumab is a humanized monoclonal antibody that blocks the activation of terminal complement at C5 and, thus, prevents the formation of C5a and the terminal complement complex, C5b-9.[83] It is approved by the U.S. FDA for the treatment of patients with paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and myasthenia gravis.[84]

5.1 | Infection risk

5.1.1 | Meningococcal infection

Since eculizumab blocks the terminal complement pathway, which is required for serum bactericidal activity, patients treated with eculizumab are at more than a 1000-fold increased risk of meningococcal disease.[85] While no deaths were reported in the paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome studies, fatal infections have subsequently been reported.[5,86] In the U.S., 52% of meningococcal disease are caused by serogroups A, C, Y or W-135 and 48% by serogroup B. In July 2017, the CDC reported a high risk for invasive meningococcal disease among patients receiving eculizumab despite receipt of meningococcal conjugate vaccine against serotypes ACWY (MenACWY) and serogroup B (MenB).[5] They identified 16 cases of meningococcal disease in the U.S. during 2008-2016; among these, 11 were caused by nongroupable *Neisseria meningitidis*.

5.1.2 | Other infections

Less is known about the association of eculizumab with other infections. The AEGIS study of Eculizumab reported a total of 159 treatment-associated infections, of which the majority were mild in severity (87.4%),[87] but only seven (4%) were considered probably related to eculizumab, three of these (one case each of pneumonia, cellulitis, and sepsis) were severe. Organisms identified in case reports of infections include bacteria such as staphylococcus, *Klebsiella oxytoca*, and *Escheria hermannii*,[88] and fungi such as *Aspergillus niger*[89] and *Scedosporium prolificans*.[90]

5.2 | Infection prevention strategies

5.2.1 | Meningococcal disease prevention

Vaccination

The Advisory Committee on Immunization Practices (ACIP) recommends that eculizumab treated patients receive both, quadrivalent meningococcal conjugate (MenACWY) and serogroup B (MenB) meningococcal vaccines. Immunization with a meningococcal vaccine should be at least 2 weeks prior to administering the first dose of eculizumab, unless the risks of delaying therapy outweigh the risks of developing a meningococcal infection.[4]

In our practice, we administer both, MenACWY and MenB vaccines, at least 2 weeks before eculizumab therapy. We administer MenACWY vaccine as single dose with boosters repeated every 5 years thereafter.[6] Depending on institutional policy, we administer MenB vaccine as either a two-dose series of MenB-4C (at least 1 month apart, or up to 6 months apart) or a three-dose series of MenB-FHbp (second and third doses administered 2 and 6 months after the first dose). The same vaccine product should be used for all doses and no booster is needed.[6] Based on available data and expert opinion, MenACWY vaccines may be administered concomitantly with MenB-4C or MenB-FHbp, in a different anatomic site.[5]

Antimicrobial prophylaxis

Eculizumab recipients remain at some risk for meningococcal disease even after receipt of meningococcal vaccines. However, benefits and risks of antibiotic prophylaxis for prevention of meningococcal infections in patients receiving eculizumab have not been established. Nevertheless, the Infectious Disease Society of America, as well as agencies in the United Kingdom and France, recommend to consider antimicrobial prophylaxis with penicillin for the duration of eculizumab therapy to potentially reduce the risk of meningococcal disease.[91,103] Based on strategies used during clinical trials, the FDA recommends the use of antibiotic prophylaxis in

the following settings when prescribing eculizumab: (a) if eculizumab is given before meningococcal vaccination, antibiotic prophylaxis should be given for at least 2 weeks after meningococcal vaccination, and (b) if the risks of delaying eculizumab therapy outweigh the risks of developing a meningococcal infection, start antibiotic therapy right away while planning for meningococcal vaccination.[84] Macrolides are typically recommended for penicillin-allergic patients.[5,91] Long-term penicillin prophylaxis is generally considered to be safe. In the U.S., first-line prophylaxis for prevention of meningococcal infection consists of penicillin V 500 mg orally twice daily.[92] This can vary depending on local sensitivity reports. Ciprofloxacin, rifampin, and azithromycin are alternative agents used in meningococcal prophylaxis.[87]

Other supportive considerations

The U.S. FDA recommends that health care professionals prescribing eculizumab enroll in the Risk Evaluation and Mitigation Strategy (REMS), and contact the U.S. FDA if any suspected adverse reaction occur.[84] The U.S. FDA and CDC recommend to monitor patients for early signs of meningococcal infections (even if previously vaccinated), and evaluate immediately if infection is suspected.[5,84]

In our practice, after completing above recommended immunization, patients are advised to seek immediate medical attention if signs of infection occur (fever, mental status changes, and rash). All patients receive antibiotic prophylaxis with oral penicillin for the duration of eculizumab therapy. If meningococcal infection is suspected in a physician's office or outpatient clinic, the patient should be transported promptly to an appropriate hospital facility. All attempts should be made to initiate parenteral antibiotics within one hour from outpatient presentation. Appropriate parenteral therapy can clear the cerebrospinal fluid of meningococci in less than six hours. Blood cultures should be drawn prior to initiation of antibiotic therapy, and antibiotic therapy should not be delayed while waiting for lumbar puncture to be performed. Third-generation cephalosporins are recommended. If the organism is proven to be penicillin-susceptible, the treatment can then be switched to penicillin, although it is also reasonable to continue therapy with a third-generation cephalosporin given the excellent efficacy, convenient dosing, and affordability of these agents.

6 | SURGICAL SPLENECTOMY

6.1 | Infection risk

Asplenia - either due to surgery or auto-infarction such in sickle cell disease - is an important risk factor for invasive infections, particularly with encapsulated bacteria such as *Streptococcus pneumoniae* (responsible for more than 50% of infections), *Haemophilus influenzae type b*, and *Neisseria meningitidis*.[12,93] Overwhelming post-splenectomy infection, a rapidly developing and often fatal syndrome,[94] can progress from a mild flu-like illness to fulminant sepsis in a matter of hours, with a mortality rate up to 50% regardless of maximal treatment.[93-95] Death can occur within 24 to 72 hours of onset of infections symptoms.[94] The estimated incidence of overwhelming post-splenectomy infection in asplenic patients is around 0.23-0.42% per year, with a lifetime risk of 5%. The highest frequency of life-threatening infectious episodes is observed during the first 2 years (30% of episodes occur within the first year, 50% within the first 2 years after splenectomy).[93] Sickle cell anemia and thalassemia major carry the highest risk for infections, likely from poorly controlled iron overload.[96] It is important to highlight that the above reported data on infection rates in asplenic patients come from studies performed prior to the modern advances on immunization practice and may, therefore, not be an accurate capture of what happens nowadays. However, comparable rates can still be seen in some low-income countries.[97]

Other infectious organisms reported in asplenic patients include intra-erythrocytic parasites such as *Babesia*, *Ehrlichia* and *Plasmodia*, and bacteria such as *Enterococcus*, *Bacteroides*, *Salmonella* and *Bartonella* species.[98] Infections with the gram-negative bacterium *Capnocytophaga canimorsus*, transmitted through animal bites (ie, dog, cat), have also been reported.[98]

6.2 | Infection prevention strategies

6.2.1 | Vaccination

The CDC and the ACIP recommend vaccination against encapsulated organisms and some viruses in patients undergoing elective splenectomy or in already asplenic patients.[12,99] Vaccinations against *S. pneumoniae*, *N. meningitidis*, *H. influenzae type b*, influenza virus, tetanus, diphtheria, pertussis (Tdap), and measles, mumps, rubella, varicella (MMR and V) are preferred to be administered 4 to 6 weeks before elective splenectomy surgery; however, if this is not possible, vaccines should be administered at least 2 weeks before surgery in elective cases, or at least 2 weeks after the surgical intervention in emergency cases.[12,99]

Pneumococcal vaccine strategy should include pneumococcal 13-valent conjugate vaccine (PCV13) and pneumococcal polysaccharide vaccine (PPSV23).[93] In patients without previous history of pneumococcal vaccination, one dose of PCV13, followed by one dose of PPSV23, at least 8 weeks later, is recommended, with a booster of PPSV23, 5 years after first PPSV23, and then no more booster until age 65 when one more dose of PPSV23 is recommended. In patients who have received PCV13 five years or more ago, one dose of PCV13 is to be repeated, followed by PPSV23 ≥ 8 weeks later, and a PPSV23 booster 5 years after the first PPSV23 dose, then no more boosters until age 65 as above. In patients who have previously received PPSV23, PCV13 is to be administered ≥1 year later, PPSV23 booster 5 years after first PPSV23 dose, then no more boosters until age 65 as above.

Meningococcal vaccine strategy should include MenACWY and MenB vaccines (see eculizumab, vaccination section for details).[93] Tdap booster should be given every 10 years. Measles, mumps, rubella, varicella vaccines should be used cautiously in patients on

active immunosuppressive drugs; serum antibody titers should be obtained in dubious cases (ie, vaccinated during childhood without vaccination certificate, history of previous infection).[93]

6.2.2 | Antimicrobial prophylaxis

No specific recommendations regarding antibiotic prophylaxis in asplenic patients are available in U.S. national guidelines. Even though there is no evidence from randomized control trials evaluating the efficacy of antibiotic prophylaxis in asplenic patients,[12] randomized studies conducted in pediatric patients with sickle cell disease may support the use of antimicrobial prophylaxis in asplenic patients.[100]

In our practice, since epidemiological data show an increased risk of overwhelming post-splenectomy infection within the first 2 years after splenectomy, we give penicillin V 500 mg oral twice daily for the first 2 years after spleen removal. Clarithromycin 250 mg oral once daily can be used for patients allergic to penicillin. This recommendation is supported by British and French guidelines.[7,93] Malaria chemoprophylaxis is recommended for patients traveling to endemic areas to avoid severe complications of the disease.[8] Precautions also include mosquito repellents, netting while sleeping, and the guidance from an infectious disease physician and an expert travel advisor before departure. Asplenic travelers should not only be advised to seek prompt diagnosis and treatment of any febrile illness, but should also consider carrying a stand-by dose of an appropriate antibiotic to take, should any fever occur, particularly if medical care is not readily accessible. The need for urgent evacuation must also be anticipated.

6.2.3 | Other supportive considerations

Asplenic individuals should wear a medical alert bracelet or necklace if possible. In addition, education of patients and their families about the risk of infections in patients with asplenia should take place, to include the strong recommendation to seek immediate medical attention if there is concern for infection.[8,93] Patients need to be aware that they are more vulnerable to infection after tick and animal bites, and, therefore, need to seek medical attention if bitten. In the case of suspicion for infection after an animal bite, antimicrobial therapy against *Pasteurella* and *Capnocytophaga* spp. is recommended. Amoxicillin-clavulanic acid 875 mg by mouth twice daily for 5 to 7 days is a reasonable consideration in these cases. *Babesia*, a tick-borne intraerythrocytic parasite transmitted to wild and domesticated animals, can produce severe infection with renal and hepatic failure in asplenic patients. Prevention of babesiosis consists of personal protective measures that minimize the exposure to ticks. No antimicrobial prophylaxis are known to reduce the incidence of babesiosis after a tick bite.

Asplenic patients that are admitted to the hospital presenting with a non-specific infective illness, it is essential to treat immediately with an appropriate antibiotic after blood and urine cultures are obtained. We suggest using a third-generation cephalosporin if feasible.

7 | OTHER IMMUNOSUPPRESSIVE DRUGS

A variety of additional immunosuppressive drugs (eg, azathioprine, mycophenolate mofetil, cyclosporine and cyclophosphamide), drug combinations, and dosing regimens are used to treat non-malignant immune-mediated hematologic disorders in the setting of first-line therapy failure,[36,101,102] all of which are off-label for these disorders.

7.1 | Infection risk

7.1.1 | Antimetabolites: azathioprine and mycophenolate mofetil

The risk of antimetabolites for opportunist infections has been reported in different frequencies, some reports favoring a better risk profile for azathioprine when compared to mycophenolate mofetil, especially in the elderly; however, this remain controversial.[103,104] Very limited experience exists on the risk of infection using these drugs in the treatment of non-malignant immune-mediated hematologic disorders.

A variety of cases of infectious complication in patients treated with azathioprine and mycophenolate mofetil have been published. Bacterial infections (common and atypical bacterial infections including *Listeria monocytogenes*, and mycobacterium species),[105,106] fungal infections (*Cryptococcus neoformans*, *Aspergillus*, *Mucor*, *Pneumocystis jirovecii*),[79,80,107] parasitic infection/reactivation (*Toxoplasma gondii*),[108] and viral infection/reactivation (disseminated herpes zoster, varicella reactivation, JC virus, and polyomavirus associated nephropathy associated with BK virus infection) have been reported in azathioprine and mycophenolate mofetil users.[79,80] The FDA places a special emphasis on the risk of JC virus-associated progressive multifocal leukoencephalopathy in azathioprine and mycophenolate mofetil users.[79,80] Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. Disseminated varicella zoster virus infection is a rare complication, reported in several case reports with mycophenolate mofetil use.[109,110] Presentations of disseminated varicella zoster virus range from diffuse cutaneous/dermatome involvement, to multi-visceral disease (hepatitis, pneumonitis, myocarditis, retinitis, Ramsay Hunt syndrome).[109,110]

7.1.2 | Cyclosporine

Cyclosporine selectively impairs T cell function[111] and increases a patient's risk for localized and generalized infections (viral, bacterial, fungal, or parasitic).[113,114] In clinical trials the risk for infection is reported as being less than 1%. Reactivated viral infections in patients treated with cyclosporine as monotherapy or in combination are uncommon.[113] However, severe and fatal infections have been observed in transplanted patients as opposed to patients treated for autoimmune diseases.[112]

7.1.3 | Cyclophosphamide

In the treatment of non-malignant immune-mediated hematologic disorders, cyclophosphamide is typically administered intravenously in pulses (500-1000 mg/m^2 every 3-4 weeks × 2-3 courses) or orally as a continuous treatment (1-2 mg/kg daily).[101] Myelosuppression with leukopenia and neutropenia, bone marrow failure, and severe immunosuppression may lead to serious and sometimes fatal infections, including bacterial, fungal, viral, protozoal and, parasitic infections, as well as reactivation of latent infections (viral hepatitis, tuberculosis), *Pneumocystis jirovecii*, herpes zoster, *Strongyloides stercoralis*, sepsis and septic shock,[78] with incidence of infection ranging from 15% to 34%.[80,116] Bacterial pneumonia is a common infection (up to 30% of infections); however, fatal cases are uncommon. Neutropenia occurs less frequently when the drug is used in non-malignant disease, and in some studies was not a risk factor for infection.[115] Serious infections have been reported with cyclophosphamide in patients receiving plasma exchange or concomitant corticosteroids.[78,114,116] No difference in risk for infection has been found when using intravenous vs oral cyclophosphamide.[115]

7.2 | Infection prevention strategies

7.2.1 | Progressive multifocal leukoencephalopathy (PML)

The FDA recommends to consider the diagnosis of PML in any patient treated with azathioprine or mycophenolate mofetil presenting with new-onset neurological manifestations (hemiparesis, apathy, confusion, cognitive deficiencies, ataxia, blurry vision or loss of vision, severe otalgia or hearing loss), and to consider consultation with a neurologist as clinically indicated.[78-80]

7.2.2 | Antimicrobial prophylaxis

No specific recommendations regarding the use of antibiotic prophylaxis in patients on azathioprine or mycophenolate mofetil are available. All immunosuppressive drugs should be discontinued during an episode of infection. In our practice, we use antibiotic prophylaxis for *Pneumocystis jirovecii* pneumonia in patients treated concomitantly with cyclophosphamide and corticosteroids until prednisone-equivalent dose of ≤5 mg daily.[116]

7.2.3 | Vaccination

The FDA recommends that during treatment with mycophenolate mofetil or cyclosporine, the use of live attenuated vaccines should be avoided. Patients should be advised that vaccinations may be less effective while on treatment. All patients should receive herpes zoster vaccine if 50 years or older (recombinant herpes zoster recommended over live zoster vaccine).[15] The CDC and ACIP do not have a recommendation to administer either zoster vaccine in adults younger than 50 years old. However, clinicians may choose to administer a vaccine off-label if, in their clinical judgment, they think the vaccine is indicated (ie, history of recurrent shingles). The patient should be informed that the use is off-label, and that efficacy and safety of the vaccine have not been tested in people younger than 50.

8 | CONCLUSIONS

Infectious complications are not unexpected events occurring during the treatment of patients with non-malignant immune-mediated hematologic disorders. Immunization, patient counseling, and antimicrobial prophylaxis are needed strategies to prevent and minimize infectious complications. Being aware of existing immunization and prophylaxis recommendations from federal agencies and national professional medical societies is key in applying up-to-date immunization and prevention strategies. Antimicrobial prophylaxis and immunization outside of the routine age-based recommendation may be indicated in patients on specific immunosuppressive therapies.

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

AUTHOR CONTRIBUTION

L.M., and S.M. designed the research; and L.M., D.v.D., and S.M. searched data, and wrote the paper.

ORCID

Luis Malpica https://orcid.org/0000-0002-7082-1846

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