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REVIEW

Infectious Disease Prophylaxis During and After Immunosuppressive Therapy

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Immune-mediated renal diseases are a diverse group of disorders caused by antibody, complement, or cell-mediated autosensitization. Although these diseases predispose to infection on their own, a growing array of traditional and newer, more targeted immunosuppressant medications are used to treat these diseases. By understanding their mechanisms of action and the infections associated with suppression of each arm of the immune system, nephrologists can better anticipate these risks and effectively prevent and recognize opportunistic infections. Focusing specifically on nonkidney transplant recipients, this review discusses the infections that can be associated with each of the commonly used immunosuppressants by nephrologists and suggest interventions to prevent infectious complications in patients with immune-mediated renal disease.

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The kidney is a frequent target for immune-mediated diseases, with nephrologists often prescribing immunosuppressive therapy outside of the transplant setting. Renal damage is most often caused by direct effects of autoantibodies, antibody-antigen complex deposition, complement deposition, or T cell-mediated autoimmunity.[1] In this setting, nephrologists treating these conditions have several classes of immunosuppressing therapies at their disposal, including B cell-targeted agents, complement inhibitors, T cell-targeted agents and the classical broad targeted agents. Although there was hope that newer and more targeted agents would lead to fewer opportunistic infections, this has not necessarily been the case in clinical trials.[2] Furthermore, renal diseases themselves, particularly those associated with nephrotic syndrome, can predispose to infection.[3] Although the infectious risks associated with kidney transplantation are extensively described in the literature, similar discussions focusing on nontransplant immunosuppressed patients with renal disease are lacking. This in-depth review will discuss the major infections associated with the classes of immunosuppressive agents used to treat immune-related renal conditions in nonkidney transplant recipients and conclude by suggesting strategies to detect and prevent these infections.

B Cell-Targeted Agents

Patients with antibody-mediated autoimmune renal diseases are often treated with agents targeting B cells (Figure 1). The most well-known of these is rituximab, which targets CD20-expressing B cells for destruction via antibody-dependent cellular cytotoxicity.[4] This causes a profound B cell aplasia and a lack of adaptive B cell responses to vaccination or infection. Half of patients will develop hypogammaglobulinemia while on therapy, which is associated with an increased risk of infection for 6 months after the last dose.[5] However, some patients can experience prolonged hypogammaglobulinemia lasting up to 2 years after cessation of therapy, which is associated with an ongoing risk of infection.[6]

Belimumab is a more selective B cell-depleting agent that targets the B cell activating factor.[7,8] Patients in the BLISS-LN trial treated with belimumab plus classical immunosuppressive agents experienced the same number of infection-related adverse events as patients who received classical immunosuppressive agents alone, suggesting that the more targeted nature of

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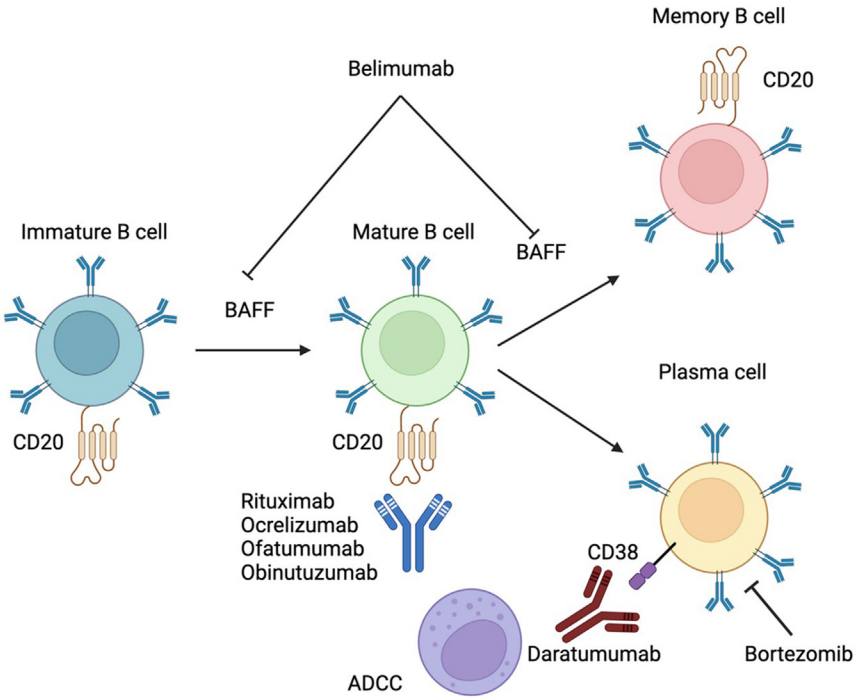

Figure 1. Mechanisms of action of B cell-targeted agents. Anti-CD20 antibodies rituximab, ocrelizumab, ofatumumab, and obinutuzumab broadly target B cells expressing CD20 for destruction by antibody-dependent cellular cytotoxicity (ADCC). Belimumab neutralizes B cell activating factor (BAFF), a necessary cofactor for B cell survival and maturation. Daratumumab targets CD38-expressing plasma cells for destruction by ADCC, whereas bortezomib targets plasma cells by inhibiting proteasomes. NFAT, nuclear factor of activated T cells; TCR, T-cell receptor. Created with Biorender.

belimumab likely does not add additional infectious risks,[9] although there have been reports of Pneumocystis jiroveci pneumonia (PJP) associated with belimumab monotherapy.[10] Newer anti-CD20 targeting antibodies, ofatumumab, ocrelizumab, and obinutuzumab may also be used as alternatives or to treat other B cell-related autoimmune diseases.[4] Daratumumab and bortezomib, agents that target more mature antibody-producing plasma cells, have also been used as salvage therapy in renal disease.[11-16] There is paucity of information on the infectious risk with these newer monoclonal antibodies; however, it is thought to be similar to that posed by rituximab.

Infections With Encapsulated Bacteria

Encapsulated bacteria are species that produce a protective polysaccharide capsule as a virulence factor allowing them to evade opsonization and phagocytosis.[17] Circulating Igs are essential to avoid invasive infection by these organisms. The most well-known examples are the vaccine-preventable Streptococcus pneumoniae (pneumococcus),[18] Haemophilus influenzae,[19] and Neisseria meningitidis (meningococcus),[20] although other pathogens may produce a capsule as well. Hypogammaglobulinemia most often manifests as recurrent sinopulmonary infections that can lead to bronchiectasis. Indeed, bacterial pneumonia was the most common infection associated with rituximab therapy for glomerulonephritis in a 10-year French cohort.[21] More invasive infections are also possible.[22]

The incidence of recurrent infections can be reduced with immunoglobulin replacement. I.V. Ig has been classically used but is associated with infusion-related side effects and inconvenience to patients who need to present for a monthly infusion. Subcutaneous Ig replacement can be self-administered at home, provides more stable immunoglobulin levels, and avoids infusion-related reactions. In fact, patients have reported better satisfaction and outcomes with subcutaneous Ig replacement over i.v. Ig in multiple studies.[23-25] Ig replacement therapy is often continued for as long as the patient is hypogammaglobulinemic in patients who have a history of recurrent sinopulmonary or invasive bacterial infections.

Nonbacterial Infections

Case reports have described chronic enteroviral meningoencephalitis[26,27] and persistent Giardia with protein-losing enteropathy and extraintestinal disease[28,29] in the setting of prolonged hypogammaglobulinemia caused by rituximab. Prolonged COVID-19 infection may also occur characterized by multiple relapses with persistent shedding of infectious virions over several months.[30,31] Importantly, this is associated with the acquisition of mutations possibly associated with immunological escape or antiviral resistance.[32,33]

Vaccination can overcome B cell aplasia by producing robust T cell responses in patients treated with rituximab.[34]

Rituximab, newer B cell-targeted agents, and daratumumab carry a US Food and Drug Administration black box warning for reactivation of hepatitis B virus (HBV). The risk of HBV reactivation depends on antibody status. Patients with chronic HBV infection (HBV surface antigen [HBsAg]- and/or HBV DNA-positive) are at highest risk of disease progression during immunosuppression. In addition, patients who have cleared natural infection (HBV core antibody [HBcAb]-positive, HBsAg-negative) can experience viral reactivation, because these patients remain with latent replication competent virus in their hepatocytes. The risk of reactivation without prophylaxis is greater than 10% and may result in fulminant liver failure and death, which is why it is essential to perform pretreatment screening with the full HBV serology panel and to continue monitoring for HBV reactivation while on therapy regardless of prophylaxis.[35,36] For HBcAb- or HBsAg-positive patients, daily tenofovir[36] or entecavir[35] treatment is recommended to prevent reactivation in consultation with an expert in viral hepatitis. This is typically continued for 6 to 18 months after the last dose of a B cell-targeted agent depending on the guideline that is being followed, although this has not been well-established.[36–39]

Herpes simplex virus (HSV) and varicella zoster virus (VZV) reactivation is also a frequent complication of B cell-depleting therapies, whereas cytomegalovirus reactivation in nonsolid organ transplant recipients is a much rarer complication.[21] Herpes zoster may be prevented by administering recombinant zoster vaccine 4 weeks before administering rituximab.[40] In patients with recurrent HSV or VZV infections, valacyclovir prophylaxis can be given until 6 months after the last dose of therapy. PJP may also be associated with rituximab, and potentially belimumab treatment particularly when combined with high-dose or prolonged corticosteroid treatment[41]; therefore patients on combination therapy should receive prophylaxis for as long as combination therapy with steroids is continued.

Complement Inhibitors

Eculizumab and ravulizumab inhibit the final common pathway of complement, in which the classical, alternative, and mannose-binding lectin pathways converge to form the membrane attack complex that lyses microbial cell membranes, or host cell membranes in the setting of complement-mediated autoimmune diseases.[42] The primary renal indication for these agents is atypical hemolytic uremic syndrome; however, they are also in clinical trials to treat a range of antibody deposition-mediated glomerulopathies.[43] These patients are susceptible to invasive infection with Neisseria meningitidis and Neisseria gonorrhoeae. A recent pharmacovigilance study identified a relative risk of 496.5 for meningococcal sepsis, 203.8 for meningococcal infection, 542.7 for meningococcemia, and 210.6 for meningococcal meningitis when compared to controls treated with rituximab.[44] The product monographs recommend vaccination of all patients with quadrivalent meningococcal vaccine (containing serotypes A, C, Y, and W135) as well as with 2 doses of meningitis B vaccine (at least 8 weeks apart). If therapy must be urgently started, the monographs recommend administering penicillin V prophylaxis for 14 days after receiving the vaccine, although some experts decolonize coverage with ciprofloxacin or ceftriaxone at the beginning of therapy and/or give prophylaxis for longer or even for the duration of therapy (personal communication). British and French groups recommend continuing prophylaxis for the duration of therapy and providing a "pill-in-pocket" strategy with ciprofloxacin in case of symptoms. All patients should be educated on the signs and symptoms of invasive meningococcal disease and to present promptly for care. The risk of disseminated gonorrhea is often overlooked and all patients should be counseled on safer sexual practices and regular screening for sexually transmitted infections.

Avacopan is a C5a receptor antagonist that is used as a glucocorticoid-sparing agent in antineutrophil cytoplasmic antibody-associated vasculitis. In the study that led to its approval, there were an equivalent number of infections and serious infections in patients treated with avacopan and those who received a glucocorticoid taper; however, there were half as many serious opportunistic infections (6 vs. 11) in patients treated with avacopan. Notably, avacopan does not predispose to meningococcal infections.[45]

T Cell-Targeted Agents

Agents that selectively target T cells can be used to treat diseases caused by cell-mediated immunity. The calcineurin inhibitors, cyclosporin and tacrolimus prevent T cell activation, effector functions, and proliferation (Figure 2).[46] Mycophenolate mofetil, which is frequently used to treat lupus nephritis, is a purine synthesis inhibitor which prevents clonal T cell proliferation after activation by limiting the availability of nucleotides to allow mitosis. Azathioprine, a prodrug of 6-mercaptopurine, is less frequently used but also acts as a purine synthesis inhibitor.[47] Antithymocyte globulin and the anti-CD52 agent, alemtuzumab act as polyclonal and monoclonal T cell depleting agents, respectively, with alemtuzumab causing particularly

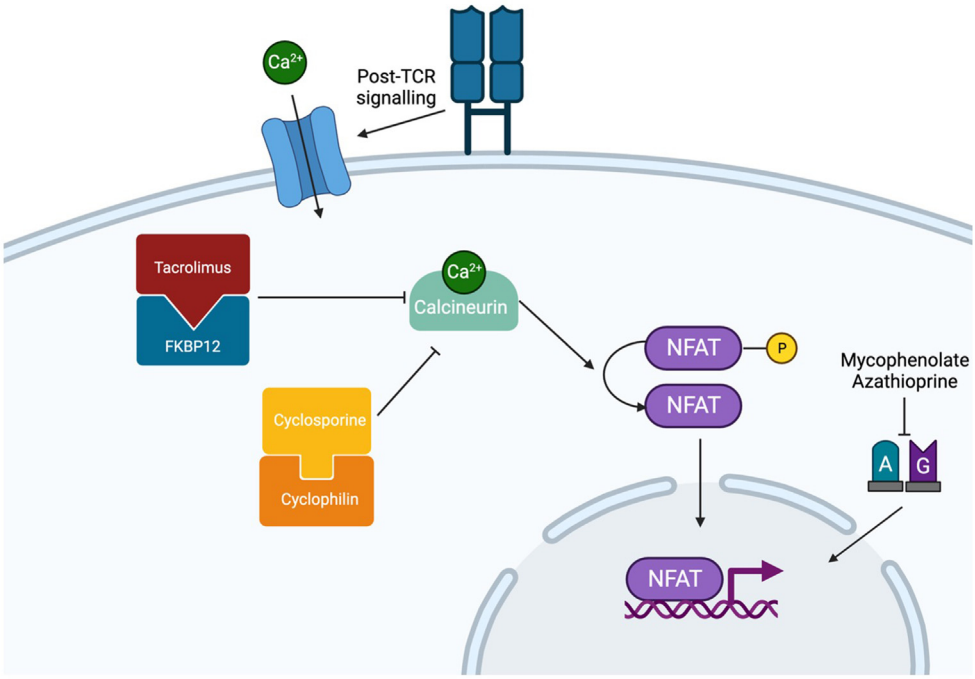

Figure 2. Mechanisms of action of T cell-targeted agents. Tacrolimus and cyclosporine both indirectly inhibit calcineurin by binding to their targets FKBP12 and cyclophilin, respectively, which prevents calcineurin from dephosphorylating nuclear factor of activated T cells (NFAT), trapping it in the cytosol and preventing transcription of genes required for T cell activation. Mycophenolate and azathioprine inhibit purine metabolism, thus limiting T cell activation and proliferation. TCR, T-cell receptor. Created with Biorender.

profound and prolonged immunosuppression because it also depletes B cells, NK cells, monocytes, and dendritic cells.[48]

Viral Infections

T cell immunosuppression is most associated with reactivation of latent herpesviruses. Patients receiving these agents are at risk of orolabial and genital HSV reactivation, disseminated HSV, HSV hepatitis, and HSV encephalitis.[49] VZV seropositive patients also are at risk for herpes zoster, including sight threatening ocular involvement, disseminated disease (defined as affecting 3 or more dermatomes), and central nervous system involvement.[50,51] Immunocompromised patients are also at higher risk of postherpetic neuralgia after limited herpes zoster.[52] Seronegative patients are susceptible to primary VZV infection, which can progress to severe, life-threatening disseminated infection with a 5% to 25% mortality rate.[53,54] Therefore, VZV serostatus should be determined in all patients undergoing T cell immunosuppression. Seronegative patients should be offered vaccination with live-attenuated vaccine if not already immunosuppressed, because live virus vaccines are absolutely contraindicated after starting immunosuppression due to the risk of vaccine-derived disease. Seropositive patients can be offered the nonlive recombinant zoster vaccine to reduce the risk of zoster.[55] Patients with frequent HSV or VZV reactivation may also receive valacyclovir prophylaxis for the duration of therapy. Cytomegalovirus reactivation is also a frequent complication of T cell immunosuppressive therapy, particularly when combined with glucocorticoids[56]; however, there is paucity of data in the non-transplantation setting. As a result, though patient serostatus should be determined, primary prophylaxis cannot be recommended outside of high-risk transplant recipients at this time.

Like patients receiving B cell targeted agents, T cell immunosuppressed patients are at risk for rapid progression of chronic HBV or reactivation of latent HBV virus infection with the possibility of fulminant hepatitis and must be screened and offered prophylaxis for the duration of therapy if HBcAb- or HBsAg-positive.[36] Patients chronically infected with hepatitis C virus, defined as positive hepatitis C virus antibody and polymerase chain reaction testing, are also at risk for accelerated liver damage.[57] Viremic patients should be referred for hepatitis C virus therapy because this infection can now be readily cured with 8 to 12 weeks of oral therapy with minimal side effects in up to 98% of patients.[58]

Norovirus causes self-limited gastroenteritis in immunocompetent patients but can cause prolonged diarrhea with malabsorption and wasting in the setting of T cell targeted therapies. This is often treated with nitazoxanide or with oral immunoglobulins or colostrum in refractory cases,[59] although the efficacy for either intervention has not been established.

Bacterial Infections

Legionella pneumophila is an intracellular bacterium that causes severe pneumonia and, in some cases, extrapulmonary disease. It inhabits contaminated water sources such as air conditioner cooling towers, humidifiers, plumbing systems (especially hot water tanks), hot tubs, and other aerosolizing devices.[60] In a 15 year review from the University of Washington, 32 cases of Legionella disease were identified of which all except 1 were immunocompromised, including 22 transplant recipients on T cell immunosuppression and 2 nontransplant immunocompromised patients.[61] Legionellosis can be avoided by not using or thoroughly cleaning devices that aerosolize water and keeping hot water tanks at least at 50 °C, although a higher temperature of 60 °C may provide better protection against Legionella but needs to be balanced against the risk of scalding.[62]

Listeria monocytogenes is carried in the gastrointestinal tract of ruminants and can grow at 4 °C and thus can continue to grow on refrigerated products. Soft cheeses and deli meats have been classically associated with outbreaks of listeriosis; however, raw vegetable products such as lettuce and coleslaw are now more commonly implicated due to contamination by agricultural runoff.[63] Invasive listeriosis causes bacteremia, meningitis, and rhombencephalitis.[64] Patients should generally avoid unpasteurized cheese and deli meats due to the risk of listeriosis and pay attention to publicized outbreaks. Similarly, Salmonella species are more likely to cause extraintestinal disease in patients with T cell dysfunction; thus, patients should observe good food hygiene and avoid consuming foods implicated in outbreaks.[65]

Tuberculosis (TB) latently infects an estimated 2 billion people worldwide, but only 5% to 10% will develop active TB disease during their lifetime.[66] However, T cell immunosuppression vastly increases that risk, with a relative risk of active disease of 74 in transplant recipients.[67] This can likely be extrapolated to nontransplant recipients receiving similar medications. Latent TB infection treatment reduces this risk to about 2% in transplant recipients[68] and a similar effect size could be expected in nontransplant recipients. Latent TB infection treatment with 4 months of rifampin is now preferred over isoniazid (INH) in the absence of significant drug interactions due to its shorter course, better tolerability, and improved completion rates.[69] However, rifampin is a potent cytochrome P450 3A4 inducer, which may cause significant drug interactions requiring dose adjustment or an alternative treatment such as INH.[70] Three months of daily combination INH and rifampin, 6 to 9 months of daily INH, or weekly INH and rifapentine are also accepted alternatives.[71] Notably, patients can be reinfected with TB after latent TB infection treatment due to residence in or travel to a high incidence country; thus, patients with ongoing risk should be counseled and monitored accordingly.

Fungal Infections

T cell immunocompromised patients are predisposed to mucocutaneous candidiasis, including oral thrush, esophagitis, and vulvovaginitis.[72] Topical nystatin prophylaxis may slightly reduce the incidence of oral thrush and candida esophagitis in the first 1 to 3 months after transplant; however, given the low magnitude of the effect, it is difficult to make a recommendation for universal prophylaxis in nontransplant recipients.[72,73]

Cryptococcus neoformans is a ubiquitous environmental yeast with worldwide distribution that acts as an intracellular pathogen.[74] Interestingly, patients receiving calcineurin inhibitor-containing regimens after organ transplantation have a lower rate of dissemination and mortality due to an apparent anticryptococcal effect of these agents.[75] Another species, Cryptococcus gattii, occurs in the Pacific Rim and affects more immunocompetent rather than immunocompromised individuals.[76] Although primary prophylaxis with fluconazole is recommended for people living with HIV with low CD4 counts and a positive serum cryptococcal antigen,[77] no such recommendation can be made for non-HIV patients at this time. Extended secondary prophylaxis for patients having experienced cryptococcal disease can be considered for the duration of therapy for particularly intense immunosuppressive regimens.[78]

The dimorphic fungi Histoplasma and Blastomyces have a worldwide distribution with a predilection for soil near freshwater sources, whereas Coccidioides is most prevalent in the southwestern United States and Central America, paracoccidioidomycosis occurs in South America, and talaromycosis (formerly penicillinosis) occurs in Southeast Asia. Emergomyces is an emergent dimorphic species that has been described in North America, Southern Africa, Europe, India, and East Asia. Exposure may be associated with bird droppings, activities that disturb and aerosolize soil such as construction and gardening, or decaying vegetation and should be avoided.[79] Primary prophylaxis for histoplasmosis or blastomycosis is generally not recommended for solid organ transplant (SOT) patients even in hyperendemic areas[79]; however, patients should be educated on activities to avoid and to monitor for signs or symptoms of infection. Itraconazole prophylaxis could be considered for patients diagnosed with histoplasmosis in the 2 years preceding

treatment; this should be discussed with an infectious disease specialist.[79] For patients living in Coccidioides endemic areas, primary fluconazole prophylaxis is recommended with 200 mg daily if seronegative pre-treatment or 400 mg daily if seropositive, typically for the first 6 to 12 months of treatment but possibly longer if seropositive.[79] It should be noted that endemic areas are likely to expand further north with climate change and clinicians should remain vigilant.[80] Although these recommendations are made for SOT recipients, they can likely be applied to nontransplant recipients with T cell immunocompromise, particularly those receiving intensive induction regimens. Patients traveling to areas with hyperendemicity for paracoccidioidomycosis or talaromyces should be counseled on the risk of acquiring infection during travel and to monitor for signs or symptoms; for very immunocompromised patients who cannot defer travel to talaromyces hyperendemic areas of Southeast Asia, itraconazole prophylaxis can be considered starting 3 days before arrival and continuing for 1 week after leaving the hyperendemic area as is done in advanced HIV.[74]

T cell immunocompromise itself is an independent risk factor for invasive mold infections, particularly those caused by Aspergillus or Mucorales species.[81,82] However, mold active primary prophylaxis is generally not recommended for most immunocompromised patients and thus is not suggested in the setting of medical renal disease.[83]

Pneumocystis jiroveci causes severe interstitial pneumonia with marked hypoxemia. Exposure to the causative agent cannot be avoided; however, PJP can be readily prevented with a variety of prophylactic regimens. A 2014 Cochrane review found that PJP prophylaxis leads to an 85% reduction in the incidence of infection and an 87% reduction in mortality in non-HIV patients.[84] The first line agent is sulfamethoxazole-trimethoprim, dosed either as 1 single strength tablet daily or 1 double strength tablet 3 times per week; however, patients can experience treatment limiting side effects (Table 1).[85] Dapsone is an alternative; however, patients must be tested for glucose-6-phosphate dehydrogenase activity before use because it can cause hemolytic anemia in deficient patients.[86] Oral atovaquone is another alternative but is associated with breakthrough infection and can be costly for patients.[87] Inhaled pentamidine is rarely used due to difficulty with administration, poor tolerability, and increased risk of breakthrough infection in the upper lobes.[88] Once monthly i.v. administration of pentamidine has been reported in case series with few breakthrough infections or adverse events.[89]

The intensity and duration of immunosuppression, and particularly combination of other agents with glucocorticoids, are important factors in deciding whether to start primary prophylaxis. The European League Against Rheumatism recommends starting prophylaxis in patients being treated with greater than 15 to 30 mg/d of prednisone equivalent for greater than 2 to 4 weeks, especially if combined with another immunosuppressant because the risk is additive.[90] A recent Japanese single-center study suggested a cut-off of 13.7 mg/d of prednisolone equivalent be used.[91] Specifically in patients with renal disease, the British Columbia Renal Glomerulonephritis Committee published guidelines in 2021 that recommend PJP prophylaxis in patients receiving at least 20 mg/d of prednisone equivalent for more than 4 weeks, alone or in combination with other immunosuppressants, triple immunosuppression, or combination of rituximab with another agent, for 6 months after the last dose of rituximab. The indication for prophylaxis in patients treated with a calcineurin inhibitor and antiproliferative is evaluated on a case-by-case basis.[92] For patients treated with a single agent, primary PJP prophylaxis is generally not recommended.

Parasitic Infections

Toxoplasma gondii is a protozoan with a complex lifecycle which can be acquired through ingestion of infectious oocytes from cat feces or bradyzoites from eating meat of infected animals or SOT from an infected donor. Blood transfusion or vertical transmission are other routes of infection.[93] Primary infection may cause a mononucleosis-like illness, whereas reactivation of bradyzoites after primary infection can cause toxoplasma encephalitis, with solitary or rim-enhancing brain lesions, or pneumonitis.[93] Primary infection can be avoided by not cleaning litterboxes from pet felines

Table 1. Pneumocystis jiroveci pneumonia prophylaxis regimens

Agent	Dosing	Side effects
Sulfamethoxazole-trimethoprim	1 single strength tablet/d or 1 double-strength tablet 3 times/wk	Elevated creatinine, hyperkalemia, myelosuppression, rash
Dapsone	100 mg/d	Hemolysis in G6PD-deficient patients
Atovaquone	1500 mg/d	Breakthrough infection
Nebulized pentamidine	300 mg/mo	Bronchospasm, difficult administration, breakthrough in upper lobes
I.V. pentamidine	4 mg/kg (maximum 300 mg)/mo	Requires infusion facility

G6PD, glucose-6-phosphate dehydrogenase.

(or changing the litterbox daily if unavoidable because oocytes take 24 hours to become infectious), thorough cleaning of vegetables before consumption, drinking treated water, and only consuming well-cooked meat.[94] Sulfamethoxazole-trimethoprim[94] or atovaquone used for PJP prophylaxis are also active against toxoplasmosis, although atovaquone may be associated with breakthrough infection,[95] and these agents are preferred for toxoplasma seropositive patients with an indication for PJP prophylaxis.

Trypanosoma cruzi is a bloodborne protozoan that causes Chagas disease, most often transmitted via the bite of the triatomine bug in endemic areas of Central and South America. Chronic infection results in megaesophagus, megacolon, and myocarditis. In T cell immunocompromised patients, parasitic reactivation is the main concern, occasionally resulting in severe disease including encephalitis. Therefore, patients from endemic areas who are planned to receive immunosuppressive therapies should be evaluated for chronic infection via serology testing and referred to an infectious disease specialist if positive.[94]

Gastrointestinal protozoa can also be problematic in patients with T cell dysfunction. Giardia can cause chronic diarrhea and wasting as in patients with B cell dysfunction. In addition, Cyclospora cayetanensis, Isospora belli, Cryptosporidium species, and Microsporidia cause prolonged diarrhea. All these pathogens are transmitted through consumption of untreated water, including well water, and this should be strongly discouraged in susceptible patients.[96] Cryptosporidium species are particularly problematic because chlorination is an ineffective treatment and large outbreaks associated with municipal water sources have occurred.[97] If a well is the only available water source, homeowners should install a commercial filtration system and have the well regularly tested for coliform contamination.[98] Boiling water for 1 minute is also effective at killing all pathogens, including Cryptosporidium. Consumption of commercially available bottled water is another alternative.[99] C. cayetanensis outbreaks have further been associated with contaminated fruits and vegetables, including frozen products, and patients should pay attention to publicized recalls.[100] Giardia[101] and Cryptosporidium[102] may also be associated with person-to-person transmission; thus, good hand hygiene practices should be observed.

Vector transmitted parasites can also cause severe disease. Malaria is present in humid tropical areas worldwide and is transmitted by the night biting Anopheles mosquito. Whereas falciparum malaria is the most severe form, Plasmodium vivax and P. ovale can form hypnozoites in the liver and recur decades later. Malaria can be prevented by wearing DEET-containing mosquito repellant, sleeping in air-conditioned quarters, using bed nets, and by taking chemoprophylaxis.[94] Travelers should be referred to a travel medicine expert to determine the best prophylaxis regimen to take for the intended destination.

Babesia is transmitted by Ixodes ticks which also transmit Lyme disease and parasitize red blood cells like Plasmodium. In T cell immunocompromised patients, it can cause death in up to 20% and a chronic, it is difficult to eradicate infection in survivors, thus prevention is paramount. Outdoor activities in Babesia endemic areas should be performed wearing DEET-containing insect repellant, permethrin-impregnated long-sleeved shirts and pants, and with at least daily tick checks.[94]

The intestinal nematode Strongyloides stercoralis can complete its entire lifecycle within its host and thus can maintain infection for decades. A recent modeling study estimated that 613.9 million people are infected worldwide.[103] In the setting of weakened T cell immunity, which is particularly associated with corticosteroid use,[104] larvae can enter an accelerated lifecycle causing patchy pneumonitis, or can disseminate to tissues not normally involved in their lifecycle, notably the brain, with high mortality due to sepsis.[105] This can be readily prevented by identifying and treating chronically infected individuals with ivermectin 200 mcg/kg (rounded to the nearest 3 mg) orally on 2 consecutive days, and repeating 14 days later, before initiating immunosuppression.[96] Screening is most often performed using serology due its high sensitivity and simplicity.[94] If reliable screening tests are not available in a timely fashion, empiric treatment of high-risk patients with ivermectin is an alternative strategy,[106] assuming that the patient is not at risk for filarial coinfection. Despite the ready availability of screening and treatment, a recent survey found that although 95% of nephrologists had heard of strongyloidiasis, 38% stated that they were otherwise unfamiliar with it, 22% were unaware that infection could last for decades, and 60% did not routinely screen at-risk patients for Strongyloides infection.[107]

Broadly Targeted Agents

Corticosteroids have broad and potent immunosuppressive effects against T cells and phagocytes alike, with doses above 20 mg/d of prednisone equivalent being considered high dose, and thus the most immunosuppressive.[90] These effects are additive with other immunosuppressants,[108] especially because corticosteroids are often used at high doses to rapidly induce immunosuppression while other immunosuppressants take effect, allowing steroids to be tapered off. High doses of steroids are particularly associated with the

risk of invasive mold infections,[109] PJP,[91] and severe strongyloidiasis.[105] Discussions of how to manage the infectious risks of high-dose corticosteroids combined with other immunosuppressants are included in the text above.

Cyclophosphamide is an alkylating chemotherapeutic agent that is also used as an immunosuppressant against primarily B cells in renal disease, but which has activity against T cells and phagocytes because it nonselectively prevents replication of actively dividing cells. The risk of infection appears to be dose-dependent.[110] The infectious risks are largely equivalent to the other B cell-targeted agents; however, due to the inhibition of other cell types, it has a higher risk of invasive fungal infection or PJP than rituximab in patients with renal disease, particularly at higher dose levels.[111]

Approach to the Patient Initiating Immunosuppression

With a thorough understanding of the iatrogenic immune deficits caused by the treatments described above, a personalized plan of screening, lifestyle recommendations, vaccinations, and antimicrobial prophylaxis can be developed for the patient initiating immunosuppression. Nephrologists should be familiar with the initial steps of this process and aware of when to refer to an Infectious Diseases specialist.

Screening

All patients should undergo a thorough history and physical exam. Careful attention should be paid to the patient's country of birth, foreign travel, potential occupational exposures, and previous infectious history. The patient's living situation, source of water, diet, pets, and hobbies should be explored to identify potentially risky activities. The vaccination history should also be reviewed, and the most complete vaccine records possible should be obtained. This will guide the subsequent investigations (Table 2), vaccines (Table 3), and counseling the patient receives.

All patients should be screened for hepatitis A immunity (IgG), HBV surface antibody, HBsAg, and HBcAb, and hepatitis C antibody followed by polymerase chain reaction if found to be antibody positive.[36,58] It is also prudent to screen for HIV as recommended in all adults by the US Preventative Services Task Force.[112] Patients who test positive for HBcAb, HBsAg or hepatitis C RNA, should be referred to a viral hepatitis expert for treatment or prophylaxis. Screening for latent herpes viruses with VZV IgG, cytomegalovirus IgG, and Epstein-Barr virus viral capsid antigen IgG should also be performed to allow for risk stratification, vaccination, and counseling. Serological screening for HSV is generally low yield and not recommended. All patients receiving T cell immunosuppression should also be screened with toxoplasma IgG. Patients born outside of North America and Western Europe should be screened for Strongyloides with at least a serology,[113] and patients born in or with extensive rural exposure to Central and South America should be screened for Chagas disease.[114] If a reliable vaccine history cannot be obtained, patients should be screened with serology for measles, mumps, and rubella immunity. Finally, patients should be screened for latent TB infection with chest x-ray and either an interferon gamma release assay or a tuberculin skin test, with the former often being more convenient because no special equipment or follow-up visit is required.[115] Patients with positive results should be referred to a physician experienced in treating TB.

Vaccinations

In a recent Swiss cohort study, 11.9% of SOT recipients experienced at least 1 vaccine-preventable infection, 43 times the rate in the general population.[116] The magnitude of this disparity is likely lower in non-SOT immunosuppressed patients; nonetheless, it highlights the importance of vaccination as a prophylactic strategy against infection in immunocompromised hosts. Although vaccination recommendations vary by jurisdiction, some general principles apply (Table 4). Childhood vaccinations should be brought up-to-date if required, including 1 dose of acellular pertussis vaccine as an adult and 2 doses of measles-mumps-rubella vaccine. If measles-mumps-rubella vaccination status cannot be reliably determined, serology should be performed, and seronegative patients revaccinated with at least 1 dose of measles-mumps-rubella. VZV seronegative patients should also receive 1 dose of live attenuated varicella vaccine, whereas seropositive patients aged >50 years should receive recombinant zoster vaccine and this can be considered in patients aged <50 years with shared clinical decision making. Note that measles-mumps-rubella vaccine must be administered 4 weeks before and VZV vaccine 6 weeks before initiating immunosuppression, because they are live vaccines that can cause disease in immunosuppressed patients.[117] Patients should also receive annual inactivated influenza vaccine (the live attenuated influenza vaccine is contraindicated)[117] and up-to-date COVID-19 vaccination, because at least some partial response may occur even in patients already on immunosuppression. Two new RSV vaccines, 1 adjuvanted and 1 nonadjuvanted have recently been approved to reduce the risk of hospitalization in adults aged >60 years and can be offered to eligible patients through shared clinical decision-making.[118] Patients who are seronegative for hepatitis A or HBV surface antibody should also receive

Table 2. Summary of agents and possible opportunistic infections

Target	Agents	Associated infections	Duration of risk
CD20	Rituximab	Encapsulated bacteria	6 mo from last dose
	Ofatumumab	Hepatitis B	
	Ocrelizumab	Hepatitis C	
	Obinutuzumab	Enteroviruses	
		Giardia	
		Herpes simplex	
		Herpes zoster	
		PML	
		PJP	
		TB	
BAFF	Belimumab	PJP	Not established
Terminal complement pathway	Eculizumab	Invasive meningococcal infection	Duration of treatment
	Ravulizumab	Disseminated gonorrhea	
Calcineurin pathway	Tacrolimus	Herpes simplex	Duration of treatment
	Cyclosporine	Herpes zoster	
Nucleotide synthesis pathways	Mycophenolate mofetil	CMV	Duration of treatment
	Azathioprine	EBV	
CD52	Alemtuzumab	Hepatitis B	12 mo from last dose
Polyclonal anti-T cell	Antithymocyte globulin	Hepatitis C	6–12 mo from last dose
		Norovirus	
		PML	
		Legionellosis	
		Listeriosis	
		TB	
		Mucocutaneous candidiasis	
		Cryptococcosis	
		Endemic Mycosis	
		Aspergillosis	
		Mucormycosis	
		PJP	
		Toxoplasmosis	
		Chagas disease	
		Intestinal protozoa	
		Malaria	
		Babesiosis	
		Strongyloidiasis	
Glucocorticoid receptor	Prednisone	Herpes simplex	Duration of treatment (dose-dependent and additive with other agents, see text)
		Herpes zoster	
		TB	
		PJP	
		Aspergillosis	
		Mucormycosis	
		Strongyloidiasis	
Alkylating agent	Cyclophosphamide	Encapsulated bacteria	Dose-dependent
		Hepatitis B	Higher risk of PJP and TB than rituximab (see text)
		Hepatitis C	
		Enteroviruses	
		Giardia	
		Herpes simplex	
		Herpes zoster	
		PML	
		PJP	
		TB	

BAFF, B cell activating factor; CMV, cytomegalovirus; EBV, Epstein-Barr virus; PJP, Pneumocystis jiroveci pneumonia; PML, progressive multifocal leukoencephalopathy; TB, tuberculosis.

a full vaccine series against these viruses, with the first 1 to 2 doses given preferably before starting immunosuppression.[117]

Patients should also be protected against invasive pneumococcal disease.[117] The 20-valent conjugated pneumococcal vaccine is a conjugated vaccine against

Table 3. Recommended screening investigations before initiating immunosuppression

Infection	Tests	Interventions
Hepatitis A	HAV IgG	Vaccinate patients without protective titers
Hepatitis B	HBsAb	Vaccine patients without protective titers (<10 mIU/ml)
	HBsAg	Refer HBsAg and HBcAb positive for evaluation and prophylaxis
	HBcAb	
Hepatitis C	HCV IgG	Perform PCR in seropositive patients or patients already on immunosuppression
	PCR	Refer PCR positive patients for treatment
HIV	Fourth generation antibody/antigen test	Refer positive patients for evaluation and treatment
Varicella zoster virus	VZV IgG	Vaccinate seronegative patients before starting immunosuppression
		Offer RZV to seropositive patients
Cytomegalovirus	CMV IgG	Counsel seronegative patients to avoid exposure
Epstein-Barr virus	EBV VCA IgG	Counsel seronegative patients to avoid exposure
Strongyloidiasis[a]	Strongyloides IgG	Refer positive patients for treatment
		HTLV-1 serology recommended for positive patients
Chagas disease[a]	T. cruzi IgG	Refer positive patients for treatment
Latent tuberculosis infection	IGRA or TST (PPD)	Refer positive patients or patients with suspicious chest x-ray findings to a TB expert
	Chest x-ray	Indeterminate patients are evaluated on a case-by-case basis

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBcAb, HBV core antibody; HBsAb, HBV surface antibody; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IGRA, interferon gamma release assay; PCR, polymerase chain reaction; RZV, recombinant zoster vaccine; TB, tuberculosis; TST, tuberculin skin test; VCA, viral capsid antigen; VZV, varicella zoster virus.
[a]Performed only on patients born or who have lived in high-prevalence countries.

20 different pneumococcal strains and can be given as a single dose, preferably before initiating immunosuppression.[119] In jurisdictions where 20-valent conjugated pneumococcal vaccine is not available, the conjugated 13-valent conjugated pneumococcal vaccine can be administered followed by the 23-valent polysaccharide pneumococcal vaccine 8 weeks later. A single dose of Haemophilus influenzae type B vaccine is also recommended for adults with an incomplete or unknown vaccination history.[117] One dose of quadrivalent meningococcal (covering serogroups A, C, Y, and W135) and 2 doses of meningitis B vaccine 8 weeks apart should be given to patients receiving a complement inhibitor. Patients aged <26 years should receive 5 doses of human papillomavirus vaccine, whereas those aged >26 years may receive human papillomavirus vaccine with shared clinical decision making.[117] Patients with Mpox risk factors should also receive 2 doses of the nonreplicating smallpox vaccine; this is not contraindicated in patients who have already started immunosuppression and no cases of vaccine-derived infection have been reported.[120] Yellow fever vaccination should be considered before vaccination in patients planning to travel to endemic countries; once therapy has begun vaccination is absolutely contraindicated and patients should be issued an

Table 4. Recommended vaccines for patients initiating immunosuppression

Infection	Vaccine formulation	Indication	Safe after starting immunosuppression
Diphtheria-acellular pertussis-tetanus	Inactivated	No adult dose	Yes
Measles-mumps-rubella	Live attenuated	Seronegative patients	No
Varicella	Live attenuated	Seronegative patients	No
Herpes Zoster	Adjuvanted recombinant	Age > 50 yr, VZV seropositive	Yes
Influenza	Inactivated	Annually	Yes
COVID-19	mRNA or recombinant	As recommended by local jurisdiction	Yes
RSV	Recombinant	Age > 60 yr through shared clinical decision making	Yes
Hepatitis A	Recombinant	All HAV seronegative	Yes
Hepatitis B	Recombinant	All HBsAb seronegative	Yes
Invasive pneumococcus	Conjugated or polysaccharide	All patients	Yes
Haemophilus influenzae B	Conjugated	All patients without an adult dose	Yes
Meningococcus A, C, Y, W135	Conjugated	Patients receiving complement inhibitors	Yes
Meningococcus B	Conjugated	Patients receiving complement inhibitors	Yes
Human papillomavirus	Recombinant	All patients aged < 27 yr Patients age < 47 through shared clinical decision making	Yes
Mpox	Live nonreplicative	All patients with Mpox risk factors	Yes
Yellow fever	Live attenuated	Planned travel to a yellow fever endemic country	No

HAV, hepatitis A virus; HBsAb, hepatisis B surface antibody; VZV, varicella zoster virus.

International Certificate of Vaccination or Prophylaxis card with the Medical Contraindication to Vaccination section completed.[117]

Healthy Living

Many of the diseases mentioned above can be prevented by avoiding exposure. Patients should be educated to practice good hand hygiene, avoid sick contacts, and possibly wear a procedure mask in public during periods of high respiratory virus activity. Patients should also practice safe food handling by disinfecting surfaces that have been in contact with raw ingredients and avoiding raw and undercooked meat and shellfish products. Unpasteurized dairy and deli meats should generally be avoided. Toxoplasma seronegative patients who have pet cats should not change the litter or should do so every 24 hours to avoid infection. Patients should be educated on safe drinking water and should increase the temperature of their hot water tank to avoid legionellosis. Humidifiers and air conditioners should be thoroughly cleaned, and hot tubs should generally be avoided. Patients who enjoy gardening should wear gloves and a mask. Long sleeves and pants should be worn for outdoor activities as well as DEET-containing insect repellant, with regular tick checks in areas where Ixodes are found. Immunocompromised patients who plan to travel should be referred to an expert in travel medicine for vaccination and prophylaxis recommendations.

Conclusion

Although immunosuppressed patients face many infectious risks, most of these are preventable with a combination of exposure avoidance, vaccination, and antimicrobial prophylaxis. Nephrologists who treat autoimmune disease can help their patients avoid serious infections by understanding the mechanism of immunosuppression and the associated infectious risks. Most screening and counseling can be easily accomplished before starting therapy, with referral to experts for patients who test positive for latent infections or more complicated exposures. Patients can continue to benefit from continuous risk assessments and education throughout therapy, particularly during periods of disease flares and consequently increased immunosuppression.

DISCLOSURE

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