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Review

Infection prevention in the immunocompromised traveler due to conditions other than transplantation: a review

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***Abstract*:** This narrative review explores the risks related to infection in immunocompromised travelers due to conditions other than transplantation, and evaluates the evidence behind current prophylactic strategies, including immunizations, antimicrobials, and non-pharmacological interventions, to prevent various infection and how the current evidence applies to this special patient population, from the perspective of a US-based traveler.

Keywords: immunization, immunocompromised traveler

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Introduction

The prevalence of immunosuppression among the general population has sharply increased over the last decade.[1] The development of novel immunomodulating therapeutics and new indications for their use have created new challenges in the field of travel medicine, related to both the prevention of travel-related infections and to stay abreast with the continuously evolving intricacies of this vulnerable population The itineraries of immunocompromised travelers are similar to those of the general population, frequently visiting countries with low human development indices.[2] In this two-part narrative review, we provide pertinent information about several immunosuppressive conditions and an update on the best practices for the protection of the immunocompromised traveler, from the perspective of a US-based traveler. This part is dedicated to immunocompromised travelers due to conditions other than transplantation.

In travel medicine, the appropriate categorization of the degree of immunosuppression is essential in determining the risk of adverse effects after administration of live-attenuated vaccines, the effectiveness of non-live vaccines, and susceptibility to complications related to an infection.[3] The degree of immunosuppression within and between certain medical conditions differs and can be difficult to objectively quantify. For instance, the risk of overwhelming post-splenectomy sepsis (OPSI) is not uniform; being greater in young children, within the first 2 years of splenectomy, and if the splenectomy was performed because of underlying hematologic condition as opposed to trauma.[4–6] The etiology, disease activity or stage, and treatment of other medical conditions such as chronic kidney disease, cirrhosis, multiple sclerosis, inflammatory bowel disease, and other autoimmune diseases also influence the degree of immunosuppression.

Recognized entities associated with severe immunosuppression include acquired immunodeficiency syndrome (AIDS), primary immunodeficiencies such as severe combined immunodeficiency, treatment with alkylating agents (e.g., cyclophosphamide) and antimetabolites such as methotrexate >0.4 mg/kg per week, azathioprine >3 mg/kg a day or 6-mercaptopurine >1.5 mg/kg a day. Disease-modifying immunosuppressants and other biologics or small targeted agents with immunosuppressive or immunomodulatory properties such as tumor necrosis factor-alpha (TNF-α) inhibitors, anti-CD20, and anti-CD52 monoclonal antibodies, interleukin-6 (IL-6) inhibitors, IL-1 inhibitors, T-cell activation blockage (e.g., abatacept), complement pathway inhibitors, and steroids (at a

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dose equivalent to 20 mg or >2 mg/kg daily of prednisone daily for 2 weeks) also cause severe immunosuppression.[3,7–9]

Principle of vaccination

As a rule, patients with chronic kidney disease, inflammatory bowel disease, multiple sclerosis, autoimmune disorders, and cirrhosis who are not taking immunosuppressants can receive live-attenuated and inactivated vaccines. In some of these populations, certain vaccines are indicated outside of the routine-age-based groups).[10] All adults with chronic liver disease should be, for example, vaccinated against pneumococcus regardless of age.[11]

Every effort should be made to administer live and non-live vaccines at least 2 weeks prior to initiation of immunosuppression. Certain immunosuppressive regimens might require an earlier vaccine administration. When immunosuppression is due to medications, discontinuation of the immunosuppressants can be considered in special circumstances and in conjunction with the input of the treating physician. Administration of live-attenuated vaccines and non-live vaccines can be done 4 and 2 weeks after stopping high-dose steroids, respectively. For lymphocyte-depleting agents and other biologics, the waiting period can range between 3 and 12 months depending on the agent.[8,12]

Severely immunocompromised travelers should not receive live-attenuated vaccines. Live viral attenuated vaccines (but not live bacterial attenuated vaccines) can be administered to patients with a defect restricted to the phagocytic function (e.g., chronic granulomatous disease). Non-live vaccines can be administered to immunocompromised patients, but short and long-term protection efficacy might be suboptimal, and it is therefore preferable to administer them before the initiation of immunosuppression. Inactivated influenza and severe acute respiratory virus coronavirus (SARS-CoV-19) vaccines are the only exceptions, which should be administered during the transmission season regardless of whether the patient is immunosuppressed.[10]

For household members of severely immunocompromised patients, the administration of live-attenuated vaccines such as oral typhoid, oral cholera, and polio vaccines should be avoided. Other live-attenuated vaccines such as the measles-mumps-rubella (MMR), yellow fever, rotavirus, varicella, and live-attenuated influenza (if the immunocompromised patient requires no protective environment is required) can be administered to susceptible household contacts.[8,10]

Basic preventive measures related to food and water exposures, and insect bite exposure include:

a. In areas with lower standards of environmental hygiene:
   i. Only use water that has been boiled, chemically treated or bottled and carbonated.
   ii. Only use ice prepared from boiled water.
   iii. Eat fruits and vegetables that can be cooked or peeled.
   iv. Avoid shellfish that has not been appropriately cooked due to the risk of invasive *Vibrio* infections.
b. Use insect repellents and protective clothing in areas with high mosquito burden.
c. Avoid swallowing water during water-based activities and avoid water that might be contaminated with animal waste or sewage.

Specific immunosuppressive conditions

Human immunodeficiency virus

The introduction of antiretroviral therapy (ART) has significantly improved the quality of life and physical fitness of patients living with HIV (PLWH), allowing for a diverse array of itineraries ranging from leisure to highly adventure travel.[13,14] Traditionally, a small proportion of PLWH seek pretravel advice[15,16] with contemporary cohort studies of travel clinics geared toward immunocompromised travelers reporting small numbers of PLWH.[14]

The traditional approach to pretravel counseling and immunization in PLWH has been based on their most recent CD4 count while on ART, rather than the nadir CD4 cell count. The immune status of PLWH can be classified into three groups: (1) asymptomatic HIV infection with CD4 cell count >500 cells/μL can be evaluated and managed as immunocompetent patients; (2) asymptomatic HIV infection with CD4 count 200–500 cells/μL. These patients are considered

with limited immune deficits and can receive vaccines such as the MMR vaccine, (3) PLWH with CD4 cell count <200 cells/μL, or AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV. These patients are severely immunosuppressed and live-attenuated vaccines are therefore contraindicated.[17,18] PLWH should not receive the live-attenuated influenza vaccine and the BCG regardless of the CD4 cell count.

A pretravel evaluation, ideally in a travel clinic, or at least with the clinician providing PLWH HIV care, should typically include the following:

1. Review the itinerary to determine the need for immunizations and prophylactic antimicrobials.[19]
2. Provide advice regarding food and water precautions, and insect bite prevention.[18,19]
3. Determine the traveler's immune status with a recent CD4 count.
   a. Newly diagnosed, ART-naïve PLWH with CD4 <200 cells/μL is recommended to delay travel until initiation of ART, CD4 recovery, and ideally until achieving virologic suppression. This approach would lower their risk for infections and avoid dealing with immune reconstitution inflammatory syndrome while abroad.[17–19]
4. Ensure enough supply of ART during the trip
   a. International travel has been associated with a drop in ART adherence among PLWH, particularly within the first 3 days.[20]
5. Review the current ART regimen for potential drug interactions with prophylactic antimicrobials, including malaria chemoprophylaxis, as well as alcohol or recreational drugs.[21]
6. Formulate a contingency plan in case medical care is needed abroad, identify potential clinics or hospitals in the traveler's destination or travel path, and secure travel insurance.[21]

Asplenia

Anatomic or functional asplenia predispose to life-threatening infections due to encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae* type B, and *Neisseria meningitidis*), *Capnocytophaga* spp., *Babesia* spp., and *Bordetella holmesii*.[5,6] The incidence of OPSI is 0.13 per 100 person-years with *S. pneumoniae* being responsible for 90% of cases. The mortality rate from fulminant sepsis is about 70% and usually occurs in the first 24–48 h.[6]

Chemoprophylaxis with penicillin is recommended in the first 2–3 years after splenectomy, in asplenic or hyposplenic individuals with other immunosuppressive conditions, and in those with a previous history of OPSI. These patients should also carry a supply of antibiotics in the event fever were to develop and be instructed to be evaluated expeditiously in the hospital. Asplenic travelers who suffer a dog or cat bite should start antibiotics (e.g., amoxicillin/clavulanic acid) without delay.[22]

Vector-borne diseases, such as malaria and babesiosis, in patients with asplenia can be life-threatening, stressing the importance of adherence to vector avoidance measures (i.e., mosquitoes and ticks) and chemoprophylaxis for malaria. Live-attenuated vaccines are not contraindicated in asplenia. Vaccination should target encapsulated bacteria typically associated with OPSI (Table 1).

Complement inhibition

Travelers with complement deficiency can receive live-attenuated and inactivated vaccines.[23] The most common cause of complement deficiency is due to the use of eculizumab and ravulizumab. These are monoclonal antibodies that block the formation of C5 convertase preventing the formation of the C5b-C9 complex.[24] They are indicated for the treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome–associated thrombotic microangiopathy, refractory acetylcholine receptor antibody-positive generalized myasthenia gravis, and aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder.[24]

Their use is associated with a 1000–2000-fold increased incidence of meningococcal disease due to decreased complement-facilitated bactericidal and opsonic function.[25] Furthermore, life-threatening and fatal infections with non-typeable strains of *Neisseria* species have been described despite receipt of meningococcal vaccines.[25]

Table 1. Vaccination of adults with asplenia or hyposplenia.

Vaccine	Initial series	Booster	Other considerations
Pneumococcus	Single dose of PCV-21, PCV-20 or PCV-15. Some administer PPSV-23 8 weeks later If PCV-15 is used, it should be followed by a dose of PPSV-23 at least 8 weeks later If PPSV-23, PCV-10, or PCV-13 was given before, wait one year to give PCV-20	PPSV-23 every 5 years	
Meningococcus Serotypes A, C, W, Y (Menacta, Menveo, Medquafi)	Two doses at least 8 weeks apart	Every 5 years	Menactra needs to be given 4 weeks after PCV-20
Meningococcus serotype B MenB-FHbp (Trumenba) or MenB-4C (Bexsero)	For MenB-4C two doses at least 1 month apart For MenB-FHbp three doses at 0, 1–2, and 6 months	One year after completion of the series and then every 2–3 years	
Haemophilus influenzae type B	One dose if not previously vaccinated or if vaccination status is unknown	None	
Influenza	Annually		

These medications need to be prescribed under a Risk Evaluation and Mitigation Strategy which mandates planned meningococcal vaccination long before treatment initiation. Meningococcal revaccination should follow the recommendations for asplenic individuals.[26] The protective effect of the vaccines can be predicted from the serum bactericidal antibody (SBA) titers.[27] SBA titers can be obtained 4–8 weeks after completion of vaccination, at 6 months, and annually thereafter to determine the need for vaccine boosters and to define the duration of antimicrobial prophylaxis.[24,27]

Antimicrobial prophylaxis is indicated for at least the first 4 weeks after completion of the meningococcal vaccine series with some recommending lifelong prophylaxis.[24,28] Travelers taking C5 inhibitors should be counseled about the need to maintain good dental hygiene and to adhere to safe sexual practices due to the increased risk of disseminated non-typeable *Neisseria* spp. and *Neisseria gonorrhea* infections, respectively.[24]

Multiple sclerosis

Management of multiple sclerosis requires the administration of disease-modifying therapies (DMTs). It is important to emphasize that there is no convincing evidence that vaccines, including the yellow fever, rabies, and tick-borne encephalitis vaccines, increase the incidence, frequency, or severity of multiple sclerosis flares.[29,30] In the event of a flare, administration of vaccines can be delayed for a period of 4–6 weeks. Every effort should be made to review and update the vaccination status before immunosuppression is started. It is particularly important to assess potential future travel to yellow fever endemic areas because live-attenuated vaccines need to be administered 4–6 weeks before starting DMTs.[31,32]

The degree and duration of immunosuppression elicited by the different DMTs is heterogeneous. Inactivated vaccines can be administered to patients with multiple sclerosis on DMTs although response rates might be diminished. Live-attenuated vaccines should generally be avoided in patients taking DMTs except for interferons or

glatiramer acetate.[31–33] Live-attenuated vaccines can be given after stopping the DMT and ensuring completion of a safety interval specific to each drug that allows for restoration of immunocompetence.[31,32]

Cancer

The number of options for cancer therapy has increased in recent years. There is a lack of data that estimates the relative risk of infection and response to vaccination among patients with malignancy. However, the CDC Yellow book considers all patients with active malignancy including active leukemia or lymphoma or generalized malignancy to be severely immunocompromised, including patients who have received checkpoint inhibitor therapy, recent radiation, chimeric antigen receptor T cell (CAR-T cell) therapy, or hematopoietic cell transplantation (HCT).[18] Other immunocompromising agents that are commonly used in cancer therapy include alkylating agents, tyrosine kinase inhibitors, and B-cell and T-cell depleting agents, such as rituximab and alemtuzumab, respectively.

For patients with cancer, general recommendations are to administer inactivated vaccines at least 2 weeks prior to immunosuppressive therapy initiation, while a gap of 4 weeks is recommended for live vaccines. In practice, delaying chemotherapy is rarely feasible, which limits adequate immunization in some situations. For patients who have already received chemotherapy, radiation therapy, or other medications considered highly immunosuppressive, live vaccinations should be delayed 3 months after completion of chemotherapy and until the disease is in remission for solid tumors. However, if lymphocyte-depleting agents have been administered, live vaccinations should be delayed at least 6 months, with some guidelines suggesting a delay of vaccination of up to 1 year.[7,18,34] Varicella, MMR, and yellow fever live vaccines should not be given to patients with cancer on immunosuppressive therapy.[34]

Prevention of specific infections

Rabies

All patients in whom rabies pre-exposure prophylaxis is indicated should contact with high-risk animals occur, should receive two intramuscular doses of human diploid cell culture vaccine or purified chick embryo cell culture vaccine on days 0 and 7 regardless of the immune status. Immunocompromised patients should have their rabies antibody titer checked 2–4 weeks after completion of the vaccination series. A booster dose should be administered if the titer is <0.5 IU/mL as measured by the rapid fluorescent focus inhibition test.[35]

Unimmunized immunocompromised travelers or travelers that have been previously immunized but have no documentation of a titer >0.5 IU/mL should receive, in addition to rabies immunoglobulin, five doses of the vaccine on days 0, 3, 7, 14, and 28 and have their antibody titers checked 7–14 days after the final dose to assess their response.[36]

Diseases transmitted by fecal-oral route

Several viruses, bacteria, and protozoa can be transmitted by fecal-oral route and cause severe disease in immunocompromised hosts. Patients with chronic liver disease, for example, are susceptible to life-threatening infections with hepatitis A and *Vibrio vulnificus* and should be advised to avoid raw or undercooked shellfish and contact with seawater.[37] Defects in the interferon-gamma (IFN-γ)/IL-12 pathway predisposes individuals to persistent and disseminated infections due to *Salmonella* spp. Patients with hypogammaglobulinemia are prone to chronic helicobacter and campylobacter infections.[38] Travelers living with HIV with decreased mucosal immunity and hypochlorhydria are significant risk factors for traveler's diarrhea.[39] In addition, PLWH remain at risk for chronic carriage and invasive disease due to non-typhoidal *Salmonella* and *Entamoeba histolytica*,[39] as well as for pathogens such as *Cryptosporidium*, *Cyclospora*, or *Cystoisospora*[40] seen in the setting of very low CD4 cell counts. Immunocompromised individuals are at higher risk of severe presentations and complications from hepatitis E infections.

Traveler's diarrhea can lead to the development of acute toxicities related to the increased levels of immunosuppressants in the event of impaired renal function related to dehydration. Guidelines support the use of rifaximin for a period no longer than 2 weeks as primary prevention of traveler's diarrhea in this patient population, recognizing that its use might be suboptimal in regions where *Campylobacter* spp. is common.[41] Non-antibiotic

options such as bismuth subsalicylate should be used with caution in patients taking aspirin and in those susceptible to dehydration. Probiotics should be avoided as a preventive measure for traveler's diarrhea in this population. Therapy for traveler's diarrhea should follow established guidelines.[41]

Vaccination for the protection of traveler's diarrhea is hindered by the diversity of the etiologic agents and by the lack of an effective vaccine against enterotoxigenic *Escherichia coli*, the most common cause of traveler's diarrhea. Few vaccines against pathogens transmitted via a fecal-oral route can be administered to immunocompromised travelers. For instance, the cholera vaccine and the live-attenuated typhoid vaccine—Ty21 (see section "Typhoid vaccine" below) are contraindicated in this population.

Polio

The inactivated polio vaccine (IPV) is safe to administer in immunocompromised hosts. Adults who are unvaccinated or incompletely vaccinated should complete a primary vaccination series. Travelers who have completed a primary vaccination series and are at increased risk of exposure to poliovirus should receive a booster dose.[42] Patients traveling for longer than 4 weeks to a country with circulating wild or vaccine-derived poliomyelitis should receive an IPV booster at least 12 months before departure from the endemic region.[43] The oral poliovirus vaccines are contraindicated in immunocompromised individuals.

Hepatitis A

Immunocompromised travelers have higher rates of fulminant hepatitis A and a suboptimal serologic response to immunization.[44] Ideally, two doses of the hepatitis A vaccine should be administered 6–12 months apart before travel in this patient population—a rare scenario in clinical practice. Preliminary data has shown that an extra priming dose of hepatitis A vaccine given either concurrently with or 4 weeks after the initial dose in patients taking a TNF blocker or methotrexate leads to similar seroconversion rates compared to healthy individuals.[45]

Hepatitis A vaccination is recommended to all PLWH regardless of the intent to travel.[46] Seroconversion rates and antibody titers are lower in PLWH compared to immunocompetent patients[47] albeit higher in PLWH with virologic suppression and higher CD4 cell counts (>300–500 cells/μL).[48,49] Post-vaccination serologic testing is thus recommended at least 1 month after completion of the immunization series.[18] An immunogenicity study comparing a three-dose series in PLWH to a two-dose series, demonstrated higher rates of seroconversion with higher antibody titers in the three-dose group[50]; however, a subsequent study only showed a marginally higher seroconversion rate with a third dose.[51] Additional studies are thus needed before a three-dose regimen can be routinely recommended.[46]

Travelers who decline hepatitis A vaccination or who will receive the first dose of hepatitis A less than 2 weeks before travel to endemic areas, should receive GamaSTAN S/D concurrently with the first dose of hepatitis A vaccine administered in different limbs. The dose is 0.1 mL/kg for trips of up to 1 month duration. A dose of 0.2 mL/kg provides protection for 2 months. Patients receiving routine intravenous immunoglobulin (IVIG) do not need to receive the GamaSTAN S/D.[52] The dosing provided here is relevant to the US market.

Immunocompromised travelers who have had potential exposure to hepatitis A and have not been previously immunized, should receive, on different anatomic sites, a dose of the hepatitis A vaccine and GamaSTAN S/D at a dose of 0.1 mL/kg as soon as possible and not later than 2 weeks after exposure.[52]

Typhoid vaccine

The Vi polysaccharide vaccine is an inactivated vaccine that is administered at least 2 weeks before travel as a single intramuscular dose needing boosters every 2–3 years. The efficacy in immunocompetent hosts after 1–3 years is estimated to be 69%, 59%, and 55%, respectively.[53,54] PLWH with CD4 <200 cells/μL might have a lower response rate compared to PLWH with CD4 >200 cells/μL and healthy controls.[54,55]

Two more effective typhoid conjugate vaccines have been prequalified by the World Health Organization (WHO) for use in children ages 6 months and 16 years of age residing in endemic countries but are not currently indicated for travelers.[56] The live-attenuated Ty21a vaccine is

contraindicated in the setting of immunosuppression, including HIV regardless of the CD4 cell count.[57]

Sexually transmitted diseases

Several global outbreaks of emerging pathogens have been efficiently transmitted and disseminated through high-risk sexual networks and international travel.[58] Immunocompromised travelers are at risk of severe and life-threatening sexually transmitted infections. Patients taking eculizumab, for example, may be at higher risk of disseminated gonorrhea infection.[59] Primary prevention of sexually transmitted infections through vaccination is thus of paramount importance. Human papillomavirus immunization with three doses in immunocompromised patients is recommended and safe.[60] The vaccine might also play in role in the treatment of benign epithelial proliferations induced by human papillomavirus.[61]

Immunocompromised men who have sex with men and transgender women who have had a sexually transmitted infection in the last 12 months or who plan to incur high-risk sexual behavior during travel can be prescribed post-exposure prophylaxis with doxycycline to be taken as a single 200 mg dose up to 72 h after condomless sex.[62]

Mpox can be fulminant in patients with AIDS with high rates of disseminated and necrotizing cutaneous lesions and systemic complications.[63,64] Immunocompromised travelers of at least 18 years of age at risk of Mpox exposure and infection should complete the Mpox vaccination with two doses at least 4 weeks apart and at least 2 weeks before departure with the modified vaccinia Ankara (MVA) vaccine (JYNNEOS in the United States, IMVANEX in the European Union and IMVAMUNE in Canada). The vaccine can be given as post-exposure prophylaxis, ideally within 4 days of exposure. Administration of the vaccine through 14 days after exposure might still offer some degree of protection. The ACAM2000 vaccine is contraindicated in immunosuppressed travelers including HIV regardless of the CD4 cell count.[65]

Hepatitis B

Patients with chronic kidney disease with a glomerular filtration rate of less than 30 mL/min or if on dialysis can receive a higher dose of the hepatitis B vaccines (two doses of adult 20 µg Engerix-B or Recombivax hepatitis B 40 µg dialysis formulation). Four doses (0, 1, 2, and 6 months) of Engerix-B and three doses of Recombivac HB dialysis formulation (0, 1, and 6 months) are recommended. Heplisav-B and PreHevbrio have not been evaluated for use in patients on dialysis.[66]

Hepatitis B vaccination is recommended for all PLWH due to the significant risks of HIV and hepatitis B coinfection.[46] Immunogenicity of the vaccine is reduced in PLWH, with varied reports regarding the loss of protective anti-HB antibodies years after immunization.[67,68] A vaccine schedule such as the one used for patients with chronic kidney disease can be considered for PLWH. ASCO guidelines recommend high antigen (40 µg) and three-dose series of Recombivax or a four-dose series of Engerix for patients with cancer.[34] Two doses of Heplisav-B can be used as an alternative. Preliminary studies of PreHevbrio in PLWH are encouraging.[69] A randomized controlled trial comparing an accelerated hepatitis B vaccine schedule (0–1–3 weeks, usually desired for the last-minute traveler) to the conventional schedule (0–4–24 weeks) in PLWH demonstrated significantly lower efficacy for the accelerated schedule, except in PLWH with CD4 >500 cells/µL where it was non-inferior.[70] Post-vaccination serologic testing is recommended regardless of the vaccination strategy.[18]

Post-exposure prophylaxis can be considered ideally within 24 h of exposure (up to 7 days after percutaneous exposure and up to 14 days after sexual exposure) in persons with no previous hepatitis B immunization or an incomplete vaccination series.[57]

Prevention of vector-borne infections

Mosquito and insect bite prevention methods should be a fundamental part of the pretravel consultation. Arboviruses can cause atypical, prolonged, and severe infections in immunocompromised patients. Patient taking rituximab and other B-cell depleting therapies, for example, usually have protracted and fatal neuroinvasive arboviral infections that can be difficult to diagnose because of their off-seasonality presentation and due to the lack of a serologic immune response typically used for diagnosis.[71]

A complete loss-of-function mutation in the CC chemokine receptor (CCR5) has been associated with severe neurotropic flavivirus infections such as West Nile virus.[72] There is, however, no strong evidence that PLWH treated with a CCR5 antagonist (i.e., maraviroc) have increased susceptibility or risk of poor outcomes to flavivirus infections.[73]

Immunocompromised states such as HIV infection and the use of trimethoprim-sulfamethoxazole (a common antimicrobial used for prophylaxis of infection in this patient population) have been associated with life-threatening infections with ehrlichiosis and Rocky Mountain spotted fever.[74–76]

Malaria

Immunocompromised travelers are at higher risk for severe malaria, and in PLWH, malaria may exacerbate HIV disease progression.[17] A review of current medications, including ART, is necessary due to the drug interactions with antimalarials.[17,18] Chloroquine, mefloquine, and primaquine can interact with protease inhibitors, while efavirenz may lower the serum levels of atovaquone and proguanil, although the clinical significance of that interaction is unclear.[18] The currently recommended first-line ART regimens, whether integrase inhibitor-based or rilpivirine-based, have no interactions with antimalarial drugs.[18] Drug interactions related to antiretrovirals can be checked on the University of Liverpool HIV Drug Interactions website (https://www.hiv-druginteractions.org/). There are limited data or recommendations for non-transplant immunocompromised patients besides PLWH.

Yellow fever

The yellow fever vaccine is a live-attenuated vaccine, and as such, is contraindicated in severely immunocompromised patients, including PLWH with CD4 <200 cells/μL, due to the risk for vaccine-associated viscerotropic disease and vaccine-associated neurotropic disease.[18]

PLWH with CD4 <200 cells/μL are strongly discouraged from traveling to areas where yellow fever is present, and those who cannot avoid such travel should be counseled on mosquito avoidance and provided with a vaccination medical waiver.[18] For PLWH with limited immune deficits (CD4 200–500 cells/μL), the yellow fever vaccine can be offered if the travel to endemic areas is unavoidable, after shared decision-making, and with monitoring for adverse events.[18] The vaccine is considered safe in PLWH with CD4 >500 cells/μL.[77] PLWH demonstrate lower seroconversion rates with lower neutralization titers.[78] The long-term response to the yellow fever vaccine depends on virologic suppression. PLWH with virologic suppression on ART achieve an immune response at 10 years comparable to patients without HIV[79] and would be recommended for a single booster at 10 years,[18,79] whereas PLWH without virologic suppression might need an earlier booster.[79] CDC recommends boosters every ten years for PLWH without contraindications.[80]

Japanese encephalitis virus

There are four types of Japanese encephalitis (JE) vaccines available in different countries. In the United States, an inactivated Vero cell culture-derived vaccine manufactured as Ixiaro is the only JE vaccine licensed for use. Immunocompromised travelers meeting the administration indications can receive the inactivated vaccine. Data is limited on the safety and efficacy of Ixiaro in PLWH,[18,46] except for one study showing lower antibody titers in infants with HIV.[81] Live-attenuated JE vaccines should be avoided in immunocompromised hosts.[82]

Dengue

Dengue in immunocompromised patients such as in stem cell and solid organ transplant recipients is associated with high rates of hospitalization, allograft dysfunction, and prolonged viremia.[83–85] Cyclosporine might be protective against severe disease with the opposite observed with tacrolimus.[83,86] PLWH exhibit CD4/CD8 ratio inversion during coinfection with dengue with evidence of apoptosis triggering in peripheral blood mononuclear cells.[87] Nevertheless, in a study of PLWH with virologic control and dengue coinfection, the clinical course of dengue infection was notable for reduced inflammation with milder progression and less vascular instability, compared to patients without HIV, attributed to a lower chemokine release from platelets in PLWH.[88]

The available dengue vaccines have not been approved in the United States for travelers visiting dengue-endemic regions. Both the

CYD-TDV (Dengvaxia) and the TAK-003 (Qdenga) are live-attenuated vaccines and are thus contraindicated in the setting of immunosuppression.[89] Dengvaxia requires serological evidence of a previous dengue infection. Qdenga might have a role for dengue-naive immunocompetent travelers visiting endemic regions where DENV-3 or DENV-4 are prevalent, pending further data on vaccine efficacy against these serotypes.[90]

Chikungunya

Chikungunya coinfection has been associated with lymphopenia and lower CD4 count in PLWH,[91] and a viral blip in an elite controller has been reported with chikungunya, but with complete recovery.[92]

The U.S. Food and Drug Administration approved a live-attenuated chikungunya virus vaccine (VLA1553, or Ixchiq) in 2023. The approval was based on immunogenicity data showing that 99% and 96% of patients developed seroprotective-neutralizing antibody levels 28 and 180 days after one dose of the vaccine, respectively.[93] The vaccine is approved for immunocompetent travelers aged ⩾18 years traveling to a country or territory where there is a chikungunya outbreak and can be considered for individuals aged ⩾65 years, particularly if they have chronic medical conditions and for persons staying for a period of 6 months or more if there has been chikungunya virus transmission among humans within the last 5 years.[65]

Antibody-containing products and vaccines

Immunocompromised patients frequently require the administration of antibody-containing preparations such as blood product derivatives and immunoglobulins. These products can interfere with the immune response of some live-attenuated vaccines but do not significantly interfere with the immune response of non-live vaccines. The administration of antibody-containing products such as specific hyperimmune globulins (e.g., hepatitis B immunoglobulin), immune globulin, and transfusion of blood products (e.g., plasma, packed red blood cells, and platelets) can alter the immune response of the MMR and varicella vaccine).[10]

Administration of antibody-containing products should be delayed for at least 2 weeks after administration of the MMR and the varicella vaccine. The administration of the MMR and the varicella vaccine should be delayed for 3 months after the administration of the hepatitis B and tetanus immunoglobulin, for 6 months after the transfusion of packed red blood cells, whole blood, and administration of immunoglobulins against hepatitis A, botulism, measles, and cytomegalovirus. The MMR and the varicella vaccine can be administered 4 and 5 months after the use of rabies and varicella antibodies, respectively. When IVIG is used, the MMR and varicella vaccines can be administered 8 months later unless a dose of 1 or 2 g/kg are used for which the interval should be 10 and 11 months, respectively.[10]

Post-exposure prophylaxis

Immunocompromised patients have lower vaccination coverage and response rates compared to the general population.[94] Knowledge about pre- and post-exposure prophylaxis in the form of vaccines, immunoglobulins, and antimicrobials is therefore crucial in providing timely and appropriate measures after exposure to selected infectious agents in this vulnerable population.

Severely immunocompromised patients should receive IVIG at a dose of 400 mg/kg up to 6 days after exposure to measles regardless of their serostatus and previous vaccination history.[95] Varicella-zoster immunoglobulin or IVIG should be administered within 10 days after exposure to the virus. The administration of IVIG or varicella-zoster immunoglobulin can prolong the average 10–21-day incubation period. Patients should therefore be monitored for up to 28 days after exposure with immediate institution of antivirals if symptoms and signs of varicella-zoster were to develop.[96]

Antibiotics are indicated, regardless of vaccination status, after exposure to diphtheria, pertussis, meningococcus, and invasive *Streptococcus pyogenes* infection.[97–100] In the same venue, immunocompromised individuals with exposure to influenza should receive post-exposure prophylaxis with oseltamivir, baloxavir, or inhaled zanamivir within 48 h of exposure and for a duration of 7 days. In the setting of continuous exposure in an enclosed setting, antiviral chemoprophylaxis can be continued for a minimum of 2 weeks and continuing up to 1 week after the last known case was identified.[101]

Conclusion

The immunocompromised traveler will continue to face challenges related to infections, in terms of risks, prevention, and management, especially as immunocompromising conditions and therapies evolve, and new infections emerge. Future studies should include or target immunocompromised patients to provide a better understanding of prophylactic and therapeutic strategies for various travel-related infections.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Joseph Sassine: Conceptualization; Investigation; Methodology; Writing – original draft.

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