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Chapter 6

The immunosuppressed traveler: infection risks with autoimmunity and immunosuppression, vaccinations, and general travel advice

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1. Introduction

People travel abroad for many reasons, to experience new places, to relax, to visit friends and relatives, for business opportunities, and for work. More and more people are traveling globally; in 2017 there were approximately 1.3 billion international tourist arrivals worldwide [1]. This growth in international travel has occurred alongside the rise of biologic drugs and other therapies for autoimmune diseases such as Janus kinase (JAK) inhibitors, as well as other forms of immunosuppression used for solid organ transplantation and treatment for malignancies. These treatments mean that those living with chronic or previously untreatable conditions are now experiencing a much-improved quality of life. Whereas previously they might have been too unwell to travel they are now able to visit a wide range of destinations and enjoy a variety of activities. Research has shown that immunosuppressed travelers follow similar travel

Infections in Systemic Autoimmune Diseases. https://doi.org/10.1016/B978-0-444-64217-2.00006-3

itineraries to nonimmunocompromised travelers and around a third visit countries with low human development indices [2]. The convergence of these trends means that there is a growing population of immunosuppressed travelers with specific travel health needs.

1.1 This chapter aims to

- Introduce the concept of risk assessment in travel and a framework for assessing the immunosuppressed traveler
- Give a brief overview of different types of immunosuppression used to treat autoimmune diseases and their mechanisms of action. Particular consideration will be given to biologic drugs, especially TNF-alpha blockers. Other forms of immunosuppression used in autoimmune conditions such as steroids and methotrexate will also be discussed.
- Discuss the implications of different forms of immunosuppression for travel vaccinations and travel-related infection risk
- Discuss vaccine preventable and nonvaccine preventable infections related to travel
- Discuss noninfectious issues applicable to all travelers including those who are immunosuppressed

The interaction between tuberculosis and immunosuppression will be discussed in a separate chapter.

2. Risk assessment and travel medicine

2.1 Defining risk

Risk may be defined as the likelihood that a person may be harmed or suffer an adverse health effect if exposed to a hazard [3]. Both the perceptions and realities of risk will be different for each individual traveler. Clinicians may also perceive risks differently based on their training and experience. For example, national malaria guidelines differ in their advice for certain countries, and this will influence the clinician's risk assessment. When considering risk it is important to weigh the possibility of harm from a travel-related disease or event against the possibility of harm from an intervention. As with all areas of medicine, it is important to remember the dictum of "primum non nocere" or "first do no harm". An example of this might be avoiding yellow fever vaccination in a significantly immunosuppressed traveler who chooses to travel to sub-Saharan Africa.

2.2 Risk assessment framework

Risk assessment is an integral part of the pretravel medicine consultation. A simple approach to start the consultation is to ask "Who is this person and

what will they be doing in this place at this time?" These areas can then be considered in more detail as follows:

2.3 Person

- Underlying medical condition
- Stability of underlying medical condition and suitability for travel
- Specific nature of immunosuppression and any resulting immune defect
- Previous vaccinations received and response to these
- Other relevant past medical history including previous infections
- Other medications

2.4 Activities

- Adventure activities, e.g., caving, diving, outdoor swimming, climbing, safari
- Business travel
- Visiting friends and relatives
- Voluntary or humanitarian work
- Animal exposure

2.5 Place

- Both countries of travel AND specific areas within countries
- Urban or rural travel
- Remote areas
- Altitude of destination

2.6 Time

- Dates and duration of travel
- Season of travel and associated risks

Once the above information has been gathered the risk of the following to the individual traveler can be considered:

- Vaccine preventable infections
- Vector-borne diseases, e.g., malaria
- Other nonvaccine preventable infections, e.g., traveler's diarrhea (TD)
- Noninfectious considerations, e.g., travel insurance and road safety

Advice should be sought from travel medicine, infectious diseases, virologists, and other treating specialists where appropriate.

2.7 Travelers visiting friends and relatives

VFR travelers are often at greater risk than other travelers and therefore merit specific discussion. They may have more compelling reasons for travel at a particular time, such as to visit sick relatives or attend funerals, weddings, and other cultural events. They may therefore be more likely to travel while pregnant or with multiple comorbidities. Lack of pretravel health care is common due to health beliefs, incomplete childhood vaccinations, and other barriers to health care such as language. Malaria is one area in which popular beliefs among VFR travelers may lead to harm. Individuals often develop partial immunity to malaria if they grow up in a highly endemic area, leading to the perception of malaria as a minor illness in adults. This partial immunity can be lost, however, if the person moves away as it depends on frequent reexposure [4]. One study showed that VFR travelers were more likely to receive a diagnosis of malaria or viral hepatitis compared to non-VFR travelers. They were also less likely to seek pretravel advice [5].

3. Types of immunosuppression used in autoimmune disease and their mechanisms of action

3.1 Defining immunosuppression

Immunosuppression is a reduction in the efficacy or function of the host immune system and may be primary or secondary in nature.

Primary immunodeficiencies are caused by a genetic defect of the host immune system.

Secondary immunodeficiencies are caused by a disease or other environmental factor that impairs the immune response. One such factor may be treatment given to a patient for a medical condition. It may either be the intended consequence of the treatment, for example immunosuppression in transplant recipients to prevent rejection, or a side effect of a treatment given for another reason, for example anti-inflammatory treatments given for autoimmune disease. The exact immune defect and resulting risk of infection depends on the specific immunosuppressive agent used. In order to understand the needs of the immunosuppressed traveler, it is important to understand the basis of their immune defect.

3.2 Biological therapies

Autoimmune diseases such as rheumatoid arthritis are characterized by persistent, abnormal inflammation. Inflammatory cytokines or "chemical messengers" play a key role in driving this inflammation, and the introduction of biological drugs that specifically target these cytokines has revolutionized the treatment of autoimmune disease. This specificity is in contrast to other traditional, "nonspecific" methods of immunosuppression such as steroids. Biological drugs have been developed that target a range of different specific inflammatory mediators including tumor necrosis factor-alpha (TNF-alpha), interleukins (IL) 1 and 6, and B and T cells.

3.3 TNF-alpha inhibitors

TNF-alpha is a cytokine that plays a key role in the immune response to infection, as well as in the pathogenesis of inflammatory disease. It is produced by activated macrophages and T-cells as a transmembrane precursor protein that is then cleaved to produce a soluble form. TNF-alpha is required for many immune processes including macrophage and phagosome activation, differentiation of monocytes into macrophages, recruitment of macrophages and neutrophils, and formation and maintenance of granulomas [6]. The importance of TNF for granuloma formation explains why patients on certain TNF-alpha inhibitors have an increased susceptibility to TB. TNF-alpha is important for the host defense against intracellular infections [7].

There are different types of TNF-alpha blockers available. Human monoclonal antibodies, such as adalimumab, certolizumab, and golimumab work by binding to TNF-alpha and preventing it from binding to its receptor, thereby inhibiting its effects. Infliximab is a chimeric antibody made from part mouse, part human antibodies. It also binds with TNF-alpha, blocking it from binding to its receptor. Etanercept is a soluble TNF-receptor fusion protein. It prevents TNF-alpha from interacting with its receptor [8] although it is only able to bind to soluble TNF-alpha unlike the other drugs which can also bind to the membrane-bound form [6]. Etanercept also has a shorter half-life than the other TNF-alpha blockers [9].

TNF-alpha blockers have been associated with an increased susceptibility to several infections including tuberculosis and nontuberculous mycobacterial infection. Invasive fungal infections such as histoplasmosis and coccidioidomycosis are also associated with TNF-alpha blockers, as are certain bacterial infections such as listeriosis and *Legionella* pneumonia. TNF-alpha blockers have also been associated with severe reactivation of hepatitis B in patients with chronic infection [6].

3.4 TNF-alpha blockers and immunization

TNF-alpha blockers may disrupt the immune response to vaccines in different ways, for example by reduced migration and maturation of dendritic cells into highly costimulatory antigen presenting cells and reduced survival of memory cells [9].

3.5 Rituximab

Rituximab is another biologic drug that has been associated with an increased risk of certain infections. It is a chimeric, monoclonal antibody that targets CD20 on B-lymphocytes leading to rapid B cell depletion. Its use has been associated with reactivation of hepatitis B, severe *Pneumocystis jirovecii (carinii)* infection, and progressive multifocal leukoencephalopathy (PML) [6].

3.6 Nonbiological drugs

3.6.1 Glucocorticoids

Glucocorticoids such as prednisolone or prednisone have been used for decades for their anti-inflammatory properties. They diffuse across the cell membrane and bind to the intracellular glucocorticoid receptor. This creates a complex that enters the cell nucleus and influences gene transcription. This mechanism of action means that steroids have a broad range of effects on the immune system in contrast to the more specific effects of the biologic drugs. One major way that glucocorticoids influence immune function is by preventing the access of neutrophils to sites of inflammation [10]. Importantly, some of the immune effects of the glucocorticoids are dose-dependent, therefore higher doses, >40 mg a day for more than a week or >20 mg a day for over 2 weeks in adults, are more likely to be associated with significant immune deficits. Systemic glucocorticoid therapy is associated with a wide range of bacterial, viral, and fungal infections.

3.6.2 Methotrexate

Methotrexate is another nonbiological therapy used in autoimmune disease. It was first developed as a chemotherapy agent and is known to act as a folate antagonist and inhibit synthesis of purines and pyrimidines. It was later introduced as a treatment for rheumatoid arthritis due to its anti-inflammatory effects. It is used at low doses for long-term therapy in rheumatoid arthritis unlike in malignancy where it is used at much higher doses. The mechanism behind its anti-inflammatory effects remains incompletely understood. It is generally thought to be safe to continue methotrexate during a mild, uncomplicated infection but it should be held in infections requiring hospital admission or intravenous antibiotics after discussion with the patient's treating specialist. It is unclear whether methotrexate is associated with an increased risk of particular infections [11] although patients taking >25 mg/week are considered significantly immunosuppressed [12].

4. Immunosuppression for autoimmunity and travel medicine

The type of immunosuppression a patient is given will affect whether they are at an increased risk of certain infections, if they can safely receive live attenuated vaccinations and whether they will mount an immune response to inactivated vaccines. Immunosuppression used to treat autoimmune disease may be limited or significant as outlined below:

4.1 Patients considered to have limited immunosuppression include [13]

- Patients taking short or low-dose steroid therapy (<20 mg/day of prednisolone or equivalent) or inhaled or topical steroids

- Patients taking methotrexate at doses of ≤0.4 mg/kg/week or azathioprine at doses of ≤3 mg/kg/day
- Travelers with autoimmune disease who are not being treated with immunosuppressive or immunomodulatory drugs, although definitive data are lacking

4.2 Patients considered to be at risk of significant immunosuppression include patients treated with the following [13]

- High-dose corticosteroids—≥20 mg per day of prednisone or equivalent when administered for ≥2 weeks
- Alkylating agents (such as cyclophosphamide).
- Antimetabolites (such as higher doses of methotrexate or azathioprine).
- Tumor necrosis factor (TNF) blockers.
- Other biologic agents that are immunosuppressive or immunomodulatory, e.g., rituximab or JAK inhibitors

4.3 General implications of significant immunosuppression

In general, patients who are significantly immunosuppressed will be at higher risk of common bacterial, viral, and fungal infections as well as certain other opportunistic infections.

5. Vaccination in the immunosuppressed traveler

5.1 General vaccine considerations with significant immunosuppression

Live vaccinations are contraindicated in travelers on significantly immunosuppressive treatment for autoimmune diseases (as defined above). This is due to the risk of developing severe or fatal infection. Inactivated vaccinations are safe to administer; however, the immune response may be impaired (Fig. 6.1).

As a general rule all travelers should be up to date with their local routine vaccination schedule as well as any specific travel vaccinations that may be required for their destination. Despite being part of the routine vaccination schedule in many countries infections such as measles remain common in parts of Asia and Africa. Decreased vaccine coverage has also led to outbreaks in developed countries, including parts of Europe and the United States. The Measles, Mumps, and Rubella Vaccination is a live vaccine and is therefore contraindicated in severely immunosuppressed patients [12].

In some rare cases it may be decided that the risk of developing a specific infection outweighs the risk from a live vaccination. This decision should be

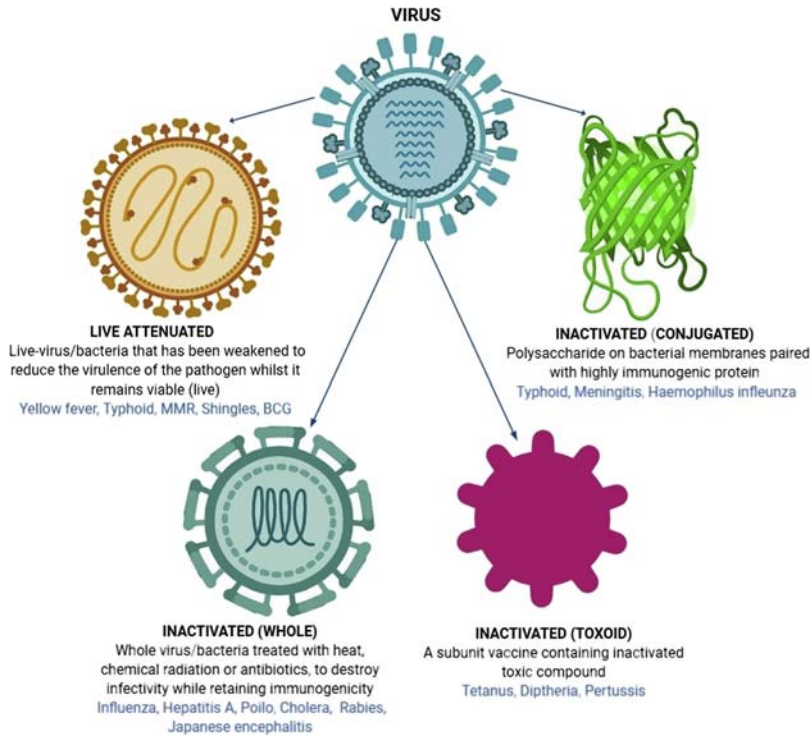


FIGURE 6.1 Type of vaccines.

made jointly by the patient's treating specialist and local virology, travel medicine, clinical immunology, or infectious diseases specialists [14].

If a patient has received a live attenuated vaccine, then ideally immunosuppressive therapy should be delayed until their immune response has been established. This is due to ongoing live virus replication after vaccination. In most cases a delay of 4 weeks is recommended. However, immunosuppressive treatment should not be delayed if it could worsen the patient's underlying condition. Specialist advice from local virology, travel medicine, clinical immunology, or infectious disease services should be sought in these circumstances [12].

5.2 Live vaccinations available in Europe [12]

- Live influenza vaccine (inactivated vaccines are also available)
- Measles, Mumps, and Rubella vaccine
- Rotavirus vaccine
- Shingles vaccine (Zostavax)
- Bacillus Calmette–Guérin (BCG) vaccine

- Oral typhoid vaccine (an inactivated typhoid vaccine is available)
- Varicella vaccine
- Yellow fever vaccine

6. Vaccine preventable, travel-related infections in the significantly immunosuppressed traveler

6.1 Yellow Fever

Yellow fever virus is a flavivirus spread by the *Aedes aegypti* mosquito. The virus is endemic in over 50 countries in sub-Saharan Africa and tropical South America. Following a bite from an infected mosquito there is a short incubation period of under a week before the onset of the illness. The classic disease has a biphasic presentation with an initial short, nonspecific febrile illness followed by a toxic phase that develops in up to 15% of patients. The toxic phase of the illness consists of fever, renal failure, hepatic failure, jaundice, hemorrhage, and cardiovascular compromise. Multiorgan failure may develop, and up to half of patients in the toxic phase die within 7–10 days [15].

All WHO member states are bound by the International Health Regulations. These are public health measures designed to reduce the spread of disease across international boarders [16]. Yellow fever is one of the only infectious diseases where a vaccination certificate may be required from travelers as a condition of entry to a country. This requirement aims to reduce the chance of viremic individuals transporting the virus and triggering a new outbreak. Guidance from the WHO suggests that one dose of yellow fever vaccination offers lifelong protection in most cases, and a booster dose after 10 years is generally not required [17].

Although an effective live attenuated vaccine is available against yellow fever, it is contraindicated in significantly immunosuppressed patients due to the risk of vaccine-associated neurotropic and viscerotropic disease [9]. Such travelers who have not been vaccinated against yellow fever should be discouraged from traveling to endemic areas. If travel is unavoidable, then they should be informed of the risk of yellow fever in their destination and the importance of strict mosquito bite avoidance measures [18]. In general, the risk of developing yellow fever is 10 times higher from travel to sub-Saharan Africa than travel to South America. If a traveler requires an International Certificate of Vaccination or Prophylaxis (ICVP) for entry to their destination, then a Medical Letter of Exemption (MLoE) may be issued instead by their treating specialist or travel clinic. This should be taken into consideration by the destination country, but patients should be aware that it may not guarantee entry [19]. Guidance on how to issue an exemption can be found here [20], and an example may be viewed here https://nathnacyfzone.org.uk/factsheet/6/medical-letter-of-exemption [21].

Yellow fever is a notifiable disease in many countries.

6.2 Typhoid

Enteric fever or typhoid is a systemic infection caused by *Salmonella enterica*, serotype *typhi,* a gram-negative bacterium. It is spread via the fecal−oral route and causes symptoms ranging from a mild fever and gastrointestinal upset to severe disseminated infection with multiorgan involvement. Severe disease occurs in around 10%−15% of cases. Other *Salmonella* serotypes such as Paratyphi A, B, and C can cause a similar clinical syndrome although disease is usually less severe. Management is with antibiotics and other symptomatic treatment if required. The disease is endemic in South Asia, parts of South-East Asia, the Middle East, Central and South America, and Africa [22]. The greatest burden of disease is found in South Asia, followed by Southeast Asia and western sub-Saharan Africa. There were estimated to be 14.3 million cases of typhoid and paratyphoid fever globally in 2017 and 135.9000 deaths; a case fatality rate of 0.95% [23].

There is currently an outbreak of extensively drug resistant (XDR) typhoid fever in Pakistan where almost two-thirds of isolates from Sindh Province were resistant to all the recommended antibiotics for typhoid fever from November 2016 to December 2018. Six travel-associated cases of XDR typhoid were noted in international travelers who had visited Pakistan in 2018 [24]. This is a reflection of the worrying rise of antimicrobial resistance worldwide.

There are two types of vaccination available in the United Kingdom, the oral live-attenuated vaccine and the polysaccharide vaccine. The oral live-attenuated vaccine should be avoided in patients on biological therapies. The polysaccharide vaccine is safe to use in immunosuppressed patients and should be given intramuscularly [22]. Studies in immunocompetent individuals estimate the efficacy of the vaccine to be between 55% and 75%; efficacy in immunosuppressed patients is likely to be lower. There are no specific data on the immune response generated by typhoid vaccination in patients on biological therapy [25]. Due to the uncertainty around vaccine response patients should be advised of the importance of following food and water hygiene measures where possible. There is no effective vaccination against paratyphoid.

Enteric fever caused by *S. typhi* or *paratyphi* is a notifiable disease in many countries.

6.3 Hepatitis A

Hepatitis A is a viral infection of the liver caused by hepatitis A virus. It is spread via the fecal−oral route and is therefore linked to poor sanitation and food hygiene. It is usually a mild infection, especially in children where the majority of infections are asymptomatic. However, the severity of infection tends to increase with age, and jaundice may occur in 70%−80% of infected adults. Fulminant hepatitis is rare and unlike hepatitis B and C there is no

chronic carrier state. The case fatality rate is generally low but is increased in those with preexisting liver disease and older adults [26]. Hepatitis A infection may be severe in immunocompromised patients [27].

Different hepatitis A vaccines are available; there is a monovalent vaccine as well as polyvalent vaccines combined with hepatitis B or typhoid. All the vaccines are inactivated and may be safely given to immunosuppressed travelers. As with other vaccinations, there may be an impaired serological response with immunosuppression. In travelers with normal immune function a first vaccine dose provides adequate protection prior to travel. A second booster dose is given at 6–12 months to provide longer-lasting immunity that can last up to 25 years or longer [26]. In immunosuppressed travelers, studies have shown that one vaccine dose does not reliably result in protection; however, a second dose provides adequate protection in the majority of patients. These travelers should therefore receive two doses of vaccine before travel. Intramuscular immunoglobulin is available and may be considered for those who do not mount a protective serological response [27].

Hepatitis A is a notifiable disease in many countries.

6.4 Rabies

Rabies is an infectious disease caused by neurotropic viruses of the genus *Lyssavirus*. A total 99% of human cases are caused by rabies virus genotype 1. Dogs are the main vector for human rabies; however, other terrestrial mammals including foxes, monkeys, and cats may also transmit the disease. Rabies is most commonly spread by the bite of an infected animal, although transmission can also occur via scratches or when the saliva of an infected animal comes into contact with broken skin or mucus membranes. Infection does not occur if the skin is intact [28].

Other lyssaviruses may cause a clinically indistinguishable syndrome to classical rabies; these are usually spread by bats. Rabies presents with an acute viral encephalomyelitis, and the case fatality rate approaches 100%, as there is no effective medical treatment once the disease has taken hold. Most rabies cases are reported in Africa and Asia, and there are estimated to be around 60,000 deaths a year worldwide [29].

Rabies cases are rare in travelers; however, animal bites and scratches are common. Travelers should be educated about the risks of rabies and advised to avoid contact with wild and domestic animals. Travelers deemed to be at higher risk of rabies, for example those traveling to high-risk areas for over a month, can be vaccinated with a preexposure course of vaccination [30]. The vaccine can be thought of as an insurance policy; although rabies is rare in travelers and the vaccine is expensive, the consequences of infection are severe. It may therefore be worth paying for extra protection from an unlikely but potentially devastating scenario.

Travelers who sustain a bite, scratch, or exposure of animal saliva to broken skin or mucus membranes should be advised to wash the wound thoroughly for 10−15 minutes as soon as possible. A suitable disinfectant should be used along with a dressing if needed. They should then be carefully and promptly risk assessed by a health professional. This risk assessment should take into account the type of animal, the health of the animal if known, the date of exposure, the country of exposure, where on the body the exposure occurred, any risk of immunosuppression, allergy status, and previous rabies vaccination status [28]. All possible rabies exposures, including contact with bats, should be discussed with local infectious diseases or virology services, and national guidelines can be used to assess the patient's overall risk level.

For nonimmunosuppressed patients preexposure vaccination primes the immune system to produce an effective antibody response following exposure. Postexposure vaccination will still be required so patients should be advised to seek medical attention promptly; however, the number of doses of post-exposure vaccine will be reduced. The available vaccines are inactivated and can be used safely in immunosuppressed travelers; however, the serological response may be impaired [30]. Advice should be sort locally as to the specific vaccination protocol in use in the relevant country.

Nonvaccinated travelers will require a longer course of postexposure vaccination. They will also require human rabies immunoglobulin (HRIG) following a significant exposure. This is infiltrated around the wound and neutralizes rabies virus at the wound site. Due to the risk of an impaired serological response significantly immunosuppressed travelers should be managed as if they are unvaccinated regardless of their vaccination history. They will require a full course of postexposure vaccination, HRIG, and antibody testing posttreatment to assess their serological response [28]. Travelers should be advised that worldwide supply of HRIG is limited and it may not be available at their destination [31].

Rabies is a notifiable disease in many countries.

6.5 Meningococcal disease

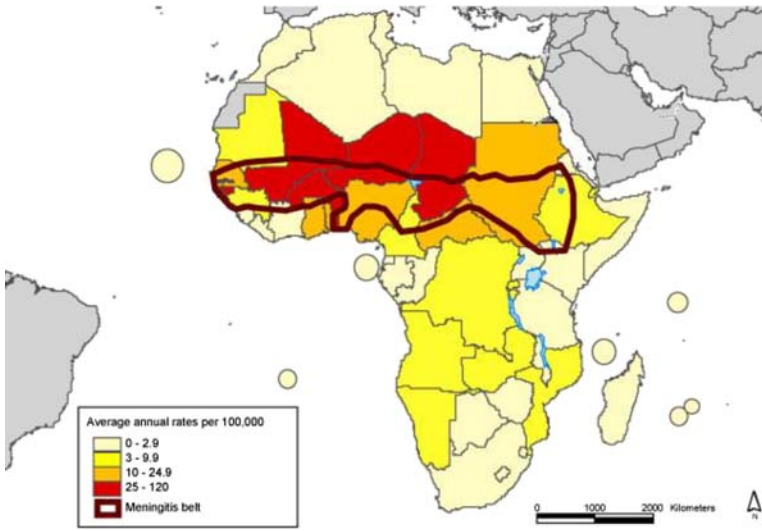
Meningococcal disease results from infection with the gram-negative bacterium *Neisseria meningitidis*. Meningococci can colonize the human nasopharynx and are often present as harmless commensals. Transmission is via the aerosol or droplet route or via direct contact with respiratory secretions. The reason that disease develops in some individuals and not others is not fully understood. The commonest presentations of meningococcal disease are meningitis, septicemia, or meningitis with accompanying septicemia [32]. There are multiple strains of *N. meningitidis*, and virulent strains carry a polysaccharide capsule. Multiple different polysaccharide capsules have been described, but only A, B, C, W-135, X, and Y commonly cause invasive disease [33].

There are different forms of meningococcal vaccine containing conjugated polysaccharides against one or more of serotypes A, W, C, and Y as well as a multicomponent protein vaccine [32]. All the vaccines are inactivated and may be administered safely to immunosuppressed patients. Meningococcal vaccination forms part of the routine vaccination schedule in many countries.

The highest incidence of meningococcal disease worldwide occurs in the so-called "meningitis belt" of sub-Saharan Africa where large seasonal epidemics occur [33]. Additionally the Islamic Hajj and Umrah pilgrimages in Saudi Arabia have been associated with outbreaks of meningococcal disease. As a result of this Saudi Arabia has made vaccination against meningococcal ACW135Y mandatory for pilgrims traveling to the above gatherings [34].

Travelers who have not been vaccinated as part of a routine vaccination schedule should be vaccinated if required following a risk assessment based on their destination, travel activities, and duration of stay. Immunosuppressed travelers should be vaccinated as per the recommendations for immunocompetent travelers [35], and they should be warned of the risk of an incomplete serological response [32].

Meningococcal disease is notifiable in many countries.



Outline of meningitis belt in Africa showing average annual attack rates [36]. *LaForce M, Ravenscroft N, Djingarey M, Viviani S. Epidemic meningitis due to Group A* Neisseria meningitidis *in the African meningitis belt: a persistent problem with an imminent solution. Vaccine 2009;27(2), B13–19. Elsevier*

6.6 Influenza

Human influenza A and B viruses cause seasonal outbreaks of influenza or "flu" worldwide. Influenza A viruses can also cause major global pandemics.

Influenza is a predominantly respiratory illness that is self-limiting in most cases; however, severe disease with complications such as pneumonia can occur. Severe cases can be life-threatening or fatal. People at higher risk of severe disease include the elderly, young children, pregnant women, those with certain chronic conditions, and immunosuppressed individuals. Influenza viruses are mainly spread by droplet transmission but may also be transmitted via touching contaminated surfaces.

Influenza has been shown to be one of the commonest vaccine preventable diseases in travelers [37]. Travelers on cruise ships and those attending mass gatherings such as the Hajj may be at particularly high risk [38]. Seasonal influenza vaccines are available, and many national guidelines advise annual vaccination for those at increased risk of severe disease, including immunosuppressed patients. Many significantly immunosuppressed travelers will therefore already have been vaccinated; however, influenza risk should still be discussed as part of the pretravel consultation. The live influenza vaccination should be avoided in significantly immunosuppressed patients. Inactivated influenza vaccines are safe to administer; however, there may be an impaired serological response [39].

6.7 Japanese encephalitis

Japanese encephalitis (JE) is caused by a flavivirus spread by *Culex* mosquitos. It is endemic in many Asian countries where it is considered a predominantly rural disease. Most infections are asymptomatic or cause a mild febrile illness; however, in less than 1% of cases it can cause severe encephalitis. This has a high case fatality rate and long-term neurological sequelae are common among survivors. Despite being the leading cause of childhood encephalitis in Asia [40] it is uncommon among travelers, although the risk depends on the type of travel, duration of stay, and itinerary [41].

Travelers to South Asia, South-East Asia, and the Far East should be vaccinated if they plan to spend a month of longer in a JE-endemic area during the transmission period [40]. There are no data on the efficacy of JE vaccination in significantly immunosuppressed patients; however, the vaccine is inactivated and can therefore be given safely. Patients should be warned of the possibility of reduced effectiveness and encouraged to follow mosquito bite avoidance measures [25].

6.7.1 Cholera

Cholera is an acute diarrheal illness transmitted by consumption of food or water contaminated by the bacterium *Vibrio cholerae.* In severe cases the disease can cause profound dehydration and death within hours of onset. The disease is associated with poverty, poor sanitation, and humanitarian crises. It is endemic in many countries in Africa and Asia and sporadic epidemics may occur [42].

Cholera is rare in travelers, but vaccination can be considered in specific groups, for example humanitarian workers. The vaccine is given orally and

consists of two doses taken 1−6 weeks apart [43]. Vaccination response in significantly immunosuppressed patients has not been studied; however, as with other vaccinations, an adequate serological response may not be achieved and patients should be advised of this [43].

Cholera is a notifiable disease in many countries.

6.7.2 Polio

Poliomyelitis (polio) is a viral infection caused by one of three serotypes of polio virus (serotypes 1, 2, and 3) [44]. Around 95% of infected individuals are asymptomatic. Symptomatic infections range from a mild illness presenting with fever and diarrhea to paralysis, which occurs in less than 1% of infections. The virus is spread by the fecal−oral route or pharyngeal spread [45].

Polio has been successfully eradicated from most parts of the world due to mass vaccination campaigns. Only three countries, Nigeria, Pakistan, and Afghanistan, have ongoing wild virus transmission [45].

Polio vaccination is part of the routine vaccination schedule in developed countries [44,45]. Additionally travelers to polio-endemic areas should be vaccinated if their last vaccine dose was over 10 years ago or if they are unvaccinated [46], although polio is extremely rare in travelers. Two vaccines are in use worldwide; a live-attenuated oral vaccine and an inactivated vaccine [45]. The inactivated vaccine is safe to use in the immunosuppressed traveler, but immunosuppressed individuals may not mount a full vaccine response and should be advised of this [44].

Polio is a notifiable disease in many countries.

7. Vector-borne infections in the significantly immunosuppressed traveler

7.1 Mosquito bite avoidance

Mosquitos, other insects and ticks, also known as arthropods, are vectors for a wide range of infectious diseases. Examples of infectious diseases spread by mosquitos include malaria as well as arboviruses such as dengue, Zika, and yellow fever. Sandflies are responsible for spreading diseases such as leishmaniasis and insects of the triatominae subfamily are vectors for Chagas Disease (CD) [47].

While chemoprophylaxis is available for some infections such as malaria, bite avoidance is a crucial part of disease prevention. Indeed for many vector-borne diseases it is the only way to prevent disease transmission. Bite avoidance is achieved via the use of repellants, impregnated bed nets, appropriate clothing, and behavioral modifications. Knowledge of the biting patterns of relevant vectors is also important. For example, the *Anopheles* mosquito, the vector for malaria, bites mainly from dusk until dawn so bed nets can be very useful to prevent disease transmission [47]. In contrast,

dengue is spread by the *Aedes* mosquito which also bites during the day so bed nets are not sufficient to prevent transmission.

N, N-diethyl-3-methylbenzamide, more commonly known as DEET, is recommended as the first-line repellant for travelers to areas where malaria and other arthropod-borne infections are endemic. Concentrations of 20%−50% are advised. Other repellants such as p-methane 3,8-diol (PMD) and icaridin are available for patients who are unable to use DEET, but high concentrations are necessary for effective bite prevention. Despite some concerns among the general public, DEET has been shown over many years to have an acceptable safety profile. Insecticide-treated bed nets are useful for travelers to malaria-endemic areas [48].

7.2 Tick-borne infections

Ticks are vectors for a number of infectious diseases including Lyme sisease, babesiosis, tick-borne encephalitis, and rickettsial infections. The disease risk depends on the tick species and travel destination. Travelers should be advised to avoid tick bites by wearing long-sleeved tops and long trousers tucked into socks when walking in grasslands or wooded areas. Clothing can be impregnated with insecticide such as permethrin. Travelers should be advised to check for ticks after outdoor activities and remove them promptly with tweezers to reduce the risk of disease transmission [47].

7.3 Malaria

Malaria is a disease of tropical and subtropical regions caused by the parasite *Plasmodium*. Over a hundred species have been described, but only *P. falciparum*, *P. vivax, P. ovale, P. malariae*, and *P. knowlesi* are known to commonly cause human infection. The disease is spread by the bite of the female *Anopheles* mosquito (Fig. 6.2). Malaria can be divided clinically into uncomplicated and severe disease; most severe malaria is caused by *P. falciparum*. An estimated 219 million cases of malaria occurred worldwide in 2017, with 92% of these occurring in the WHO Africa Region. Nigeria had the greatest disease burden worldwide, with 25% of cases occurring there. There were 435,000 deaths globally, mostly in children under 5 years of age [49].

Effective chemoprophylaxis exists for malaria and should be offered to travelers to endemic areas. The choice of agent will depend on patient preference, the patient's medical history, and their destination. Health-care professionals should consult relevant local or national guidelines for advice and be aware that these differ between countries.

Malaria should always be suspected in a febrile traveler returning from a malaria-endemic area. Diagnostic testing and treatment should be discussed with local infectious diseases specialists. Treatment depends on the infecting *Plasmodium* species and whether the patient has severe or uncomplicated disease.

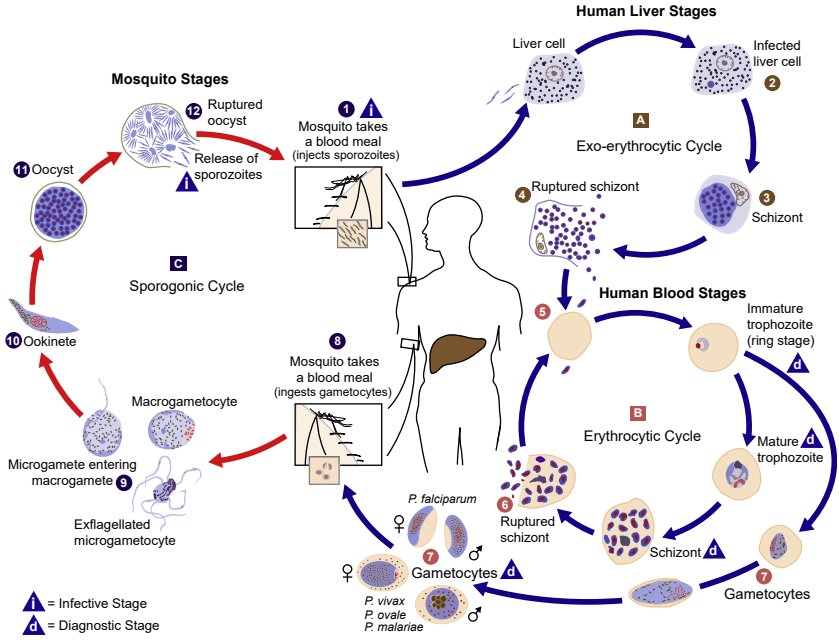


FIGURE 6.2 Malaria life cycle and primary areas of drug activity. The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female mosquito inoculates sporozoites into the human host [1]. Sporozoites infect liver cells [2] and mature into schizonts [3], which rupture and release merozoites [4]. Chemoprophylaxis medications either act at the liver stage preventing a blood-stage infection or at the erythrocytic stage of the malaria life cycle. *Adapted from the Centers for Disease Control and Prevention DPDx website.*

A British study showed that the majority of imported malaria cases in the United Kingdom were seen in people of African heritage who had traveled to visit friends and relatives. The greatest mortality, however, was seen in the elderly, tourists, and those presenting to areas where few malaria cases were seen [50].

Evidence suggests that HIV coinfection increases the severity of malaria [51]. There is no specific data on malaria infection in patients on biological therapies, JAK inhibitors, or other immunosuppression. The immunosuppressed traveler should be advised on mosquito bite avoidance and prescribed malaria prophylaxis appropriate for their itinerary and destination. Care should be taken to avoid drug-drug interactions with existing medications [35].

7.4 Chagas disease

CD is caused by the protozoan parasite *Trypanosoma cruzi* (*T. cruzi*) and is most commonly spread via an insect vector, the triatomine bug. The disease is endemic in 21 countries in Latin America, and there are an estimated 6–7 million people infected worldwide. The disease occurs in two phases.

Firstly, an acute phase following transmission that can be asymptomatic or present with mild, nonspecific symptoms. A chronic phase of infection then occurs and around 30% of people develop cardiac disease characterized by arrhythmias, cardiomyopathy, and heart failure. Sudden cardiac death can also occur. Around 10% of people develop other complications including digestive disorders such as dilatation of the esophagus and colon [52].

Although the disease was historically confined to Latin America, it is becoming increasingly widespread globally due to migration from endemic countries [53]. The disease is extremely rare in travelers, and there is only one case report of transmission in a returning traveler to Latin America in the literature [54]. It is of more relevance in migrants from endemic countries to Europe and the United States who may be commenced on immunosuppression.

Reactivation of CD in immunocompromised patients has been described, predominantly in the setting of advanced HIV infection, where it commonly affects the central nervous system causing single or multiple space-occupying lesions or a severe meningoencephalitis. Cardiac involvement or worsening of previous cardiomyopathy may also occur [55]. Data on CD in rheumatology patients treated with biological therapies or JAK inhibitors remain sparse; however, a case of relapsed CD has been reported in a patient treated with infliximab, although the patient did not develop severe symptoms and relapse was detected via a higher quantifiable PCR result [56]. One case series looked at immunosuppressed patients with chronic CD and included three patients with autoimmune disorders treated with regimens that included biologics. None of these patients suffered a reactivation or severe manifestation of their CD [57]. Although the effect of biological therapies on the course of CD remains unknown, expert opinion favors screening patients with serological testing prior to treatment if their mothers were born in endemic areas, they have lived in endemic areas for prolonged periods, or they have received a blood transfusion in an endemic country [58].

7.5 Leishmaniasis

Leishmaniasis is a parasitic infection caused by protozoa of the genus *Leishmania*. It can be divided into Old World (found in Asia, Africa, the Middle East, Mediterranean Basin, and Europe) and New World (Latin America) types. Infectious manifestations range from asymptomatic infection to cutaneous leishmaniasis (CL), mucocutaneous disease, and visceral leishmaniasis (VL). VL or kala-azar has a high fatality rate without treatment. The clinical picture depends on the infecting *Leishmania* subspecies and individual host factors. The vector for all *Leishmania* parasites is the female sand fly.

Over 90% of the global disease burden of VL is found in seven countries, Brazil, Ethiopia, Kenya, Somalia, South Sudan, Sudan, and India, although the disease may also be found in other areas worldwide including southern Europe and the Mediterranean Basin. CL is caused by various *Leishmania* subspecies.

The majority of CL cases occur in Brazil, Colombia, Peru, Algeria, Syria, Iran, Saudi Arabia, Afghanistan, and Pakistan [59].

Although the majority of VL and CL cases are found in low-income countries, two *Leishmania* subspecies, *L. infantum* and *L. tropica*, are endemic in Europe. *L. infantum* can cause both cutaneous and visceral disease and is found throughout the Mediterranean, including in Spain and Italy. *L. tropica* causes CL and is found in Greece and most likely in neighboring countries as well [60].

Leishmaniasis is a rare disease in travelers; however, it should be considered in patients with a history of travel to an endemic area and a compatible clinical presentation. Most cases of leishmaniasis in travelers are of the cutaneous form, but cases of VL and mucocutaneous disease have been reported. Latin America is the most common destination for acquisition of CL among travelers, and the Mediterranean has emerged as the main region for travelers to acquire VL. Travelers at risk of acquisition of leishmaniasis, for example adventure travelers or those traveling to rural areas in endemic countries, should be advised to follow measures to promote avoidance of sand fly bites [61]. Importantly, travelers visiting the Mediterranean may not visit a travel clinic or use bite avoidance measures as such destinations are often perceived as low risk for infectious diseases.

Immunosuppression is a well-described risk factor for developing disease following *Leishmania* infection. Coinfection with HIV and VL was first described in Europe but is now recognized in East Africa, Asia, and Brazil. Cases of VL associated with solid organ transplantation have been described. The disease may present atypically in immunosuppressed individuals or be mistaken for a flare of an underlying medical condition [62]. Europe has also seen an increasing number of leishmaniasis cases in patients treated with TNF inhibitors. One study estimated an eightfold higher risk of opportunistic leishmaniasis in patients treated with monoclonal antibodies compared to controls [63]. Both VL and CL cases have been described but a relative risk has not been definitively established.

8. Other nonvaccine preventable infections

8.1 Travellers' diarrhea, food, and water hygiene

TD is a frequent medical problem in travelers from high-income countries to lower-income countries, affecting 20%–60% of travelers to low-income regions. It can be defined as three or more loose stools in a 24 hour period with or without other symptoms of fever, nausea, or cramps [64]. TD is usually an acute, self-limiting presentation and rarely causes life-threatening disease, but it can be a significant cause of distress to travelers due to disrupted holiday plans. It may also have longer-term consequences in the form of postinfectious irritable bowel syndrome [65].

TD is spread via the fecal−oral route due to poor food and water hygiene. It is caused by a variety of different pathogens including bacteria (50%−75% of cases), viruses (5%−20%), and parasites (0%−10%) Coinfection with more than one infection occurs in 10%−15% of cases. No pathogen is identified in 10%−50% of cases [66]. Enterotoxic *Escherichia coli* is the commonest cause of acute TD globally [64].

Regions with the highest risk of TD include South and Southeast Asia, central America, and West and North Africa. South America and East Africa are also high-risk destinations for TD. Backpackers, VFR travelers, and those on all-inclusive holidays such as cruises have a higher risk of TD due to increased dietary exposure [64].

There is no strong evidence that dietary measures reduce the risk of TD [64]; however, common sense suggests that travelers should still be advised to follow the following precautions: Handwashing or use of alcohol gel after using the toilet and before eating, drinking bottled or boiled water, eating freshly cooked, piping hot food and peeled fruits, consuming pasteurized dairy products, avoiding salads, buffets, undercooked meat or seafood and food from street vendors unless cooked in front of the traveler, ensuring food it served hot and on clean cutlery [67].

The incidence of TD is not increased in patients on immunosuppressive therapies [68];however, certain food or waterborne infections can be more severe or lead to chronic disease. These include salmonella, shigella, campylobacter, giardia, listeria, and cryptosporidium [13]. Specifically invasive salmonellosis and listeriosis are more common in people on TNF inhibitors; this is thought to be due to the intracellular nature of these pathogens [7]. Additional exacerbation is common with coprescription of antacids medications, which reduce stomach acidity, allowing more bacteria to survive (Fig. 6.3). Travelers should be aware of the risk of cryptosporidium transmission from swimming pools and freshwater swimming.

Those who develop TD should be advised to maintain good hydration with regular oral fluids. Short courses of antibiotic treatment (1−3 days) taken at the onset of symptoms have been shown to reduce the duration of illness from 3 to 1.5 days [64]. The choice of regimen depends on the destination of travel. For travel to central and South America and sub-Saharan Africa fluoroquinolones, such as ciprofloxacin, are a reasonable choice of agent. For travel to South and South East Asia azithromycin is a better choice due to the increased prevalence of resistant campylobacter strains. For patients on biological agents or JAK inhibitors azithromycin would be a sensible choice of agent as it avoids the risk of tendon rupture seen with fluoroquinolones and does not interact with commonly prescribed immunosuppressants.

Significantly immunosuppressed travelers can be provided with an emergency pack of antibiotics for self-treatment of TD while abroad. They should also be encouraged to pack some oral rehydration therapy sachets, which can be easily purchased in most pharmacies and prepared with bottled water.

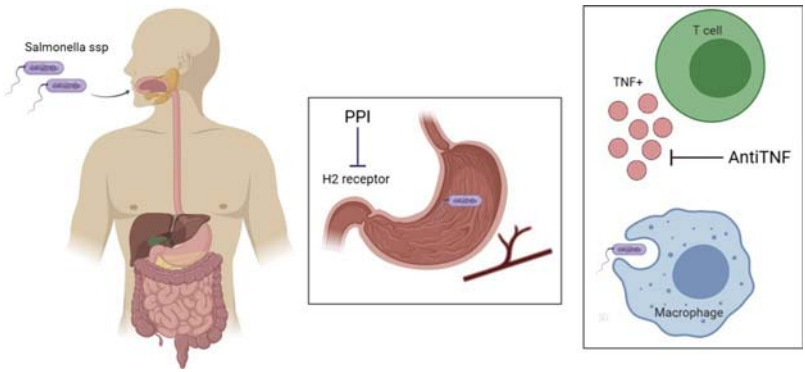


FIGURE 6.3 Salmonella infection in patients taking anti-TNF therapy and PPI. Invasive salmonella is more common in people taking TNF inhibitors, secondary to the intracellular nature of these pathogens. Additional exacerbation is common with coprescription of antacid medications, which reduce stomach acidity, allowing salmonella bacteria to survive.

These are particularly advisable for travelers at increased risk of complications from dehydration [65]. Prophylactic antibiotics may be considered for significantly immunosuppressed travelers, especially for short-term travel to high-risk countries; however, the risk of drug interactions and side effects should be considered [14].

Clinicians should be aware that travel has been associated with acquisition of multidrug resistant (MDR) Enterobacteriaceae. These bacteria produce extended spectrum beta-lactamases (ESBLs) that confer resistance to many commonly used beta-lactam antibiotics. MDR Enterobacteriaceae were initially recognized in hospitals but are now increasingly common in community settings in low- and middle-income countries. Travel has been associated with ESBL acquisition rates of 21%–51%. Travel to South Asia has the highest risk of ESBL acquisition with rates of up to 85%; other areas of Asia are also high risk. Digestive disorders, diarrhea, and antibiotic use during travel were risk factors for ESBL acquisition [69]. Antibiotic options to treat infections caused by MDR Enterobacteriaceae are limited and carriage also has implications for transmission and infection control in travelers' home countries.

8.2 Hepatitis E

Hepatitis E infection is caused by hepatitis E virus (HEV), and there are estimated to be around 20 million infections worldwide each year, with around 3.4 million symptomatic cases [70]. The highest disease burden is in Asia and parts of Africa. There are four known genotypes, 1, 2, 3, and 4. Genotypes 1 and 2 are thought to only cause human infection and are spread via the fecal–oral route. Genotypes 3 and 4 have been found in several animals

including pigs and can also cause infection in humans. In low-income countries with poor sanitation, large outbreaks of hepatitis E occur, most commonly due to genotype 1, and these are thought to be due to fecal contamination of water. Sporadic cases may occur due to genotypes 1 and 2. In high-income countries with safe drinking water sporadic cases of hepatitis E occur, mostly due to genotype 3. These are linked to eating undercooked meat, especially pork products, and can be thought of as a zoonosis [71].

HEV typically causes an acute, self-limiting illness presenting with fever and jaundice. The symptoms usually resolve after a few weeks. Pregnancy is associated with severe disease and fulminant liver failure and case fatality rates are as high as 20%−25% [71]. HEV can also cause chronic infection leading to chronic hepatitis in immunosuppressed patients. This is typically due to genotype 3. Chronic infection has been observed in solid organ transplant patients [72], as well as with other forms of immunosuppression, including a patient treated with rituximab [73]. Chronic infection in immunosuppressed patients may rapidly progress to cirrhosis [74] and treatment consists of reducing immunosuppression where possible and administration of ribavirin [75].

A vaccine has been developed against HEV but is currently only licensed in China. Travelers to areas with poor sanitation should therefore be advised to follow standard advice on food and water hygiene, especially with regards to drinking bottled water.

8.3 Strongyloidiasis

Strongyloidiasis is a parasitic infection caused by the nematode worm *Strongyloides stercoralis (S. stercoralis)*. The disease is endemic in tropical and subtropical regions throughout Latin America, Africa, and Asia. Cases have also been described in temperate regions. It is estimated that up to 100 million people are infected worldwide [76].

Infection is acquired via direct contact with contaminated soil, often when walking barefoot. It is therefore a disease of poor sanitation and poverty. Larvae invade the skin, usually of the feet, and travel via the venous system to the lungs where they are expectorated and swallowed. The larvae then hatch into adult females in the gut. These are able to reproduce asexually and release more eggs into the gastrointestinal tract. Some of these eggs hatch into larvae that are released into the stool, facilitating onward infection. Unlike most other parasites *S. stercoralis* is also able to set up a cycle of autoinfection within its original host. Some of the larvae that hatch in the gut are able to reinvade the intestinal wall, travel to the lungs and begin the cycle again [77]. This explains how *S. stercoralis* infection is able to persist for many years in the same host. Cases have been reported up to 75 years following exposure [78].

Infection with S. stercoralis is often asymptomatic in the immunocompetent host or causes only mild symptoms. A local cutaneous reaction may

occur, usually at the site of larval invasion, resulting in pruritic serpiginous or urticarial tracts. Larvae may cause respiratory symptoms such as cough or wheeze as they migrate through the lungs. Gastrointestinal infection may cause vague symptoms such as anorexia, vomiting, diarrhea, and epigastric pain that is worse after eating [77].

Immunosuppressed patients may develop life-threatening strongyloides hyperinfection syndrome. This can occur when patients with previously unrecognized chronic strongyloidiasis become immunosuppressed or when an already immunosuppressed patient develops acute infection. Hyperinfection syndrome develops due to accelerated autoinfection and typically presents as intestinal or pulmonary failure. Disseminated strongyloidiasis may occur with parasitic spread to any organ including the central nervous and cardiovascular systems. The syndrome has been well documented in patients with human T-cell lymphotropic virus type 1 infection and patients treated with steroids. Mortality approaches 100% without treatment [79]. Concurrent gram-negative sepsis may occur due to translocation of gut bacteria. Cases of hyperinfection have been observed in patients with rheumatological conditions treated with biological therapies [80,81].

Strongyloidiasis should be considered in patients with a relevant travel history or migration from an endemic area and compatible symptoms or persistent, unexplained eosinophilia. Expert opinion favors screening patients from endemic areas or with unexplained eosinophilia before starting treatment with biological therapies [58].

Diagnosis can be made via stool microscopy for ova, cysts, and parasites and a blood test for strongyloides serology. Hyperinfection may be suspected due to the presence of pulmonary infiltrates on chest X-ray and filariform larvae may be found in bodily fluids, for example on bronchoalveolar lavage. Eosinophilia may be absent [82]. First-line treatment of chronic strongyloidiasis in developed countries is with ivermectin. Treatment of hyperinfection includes ivermectin, reduction of immunosuppression where possible, and supportive care including organ support and antibiotics. An infectious disease specialist should always be consulted in the management of these patients.

8.4 Fungal infections

Travelers may be at risk of systemic fungal infections depending on their destination, season of travel, and activities. Studies have shown that although relatively rare among travelers, these infections should nevertheless be considered as potentially travel-related [83]. Caving, construction, and exposure to deserts are activities that have been associated with these diseases. They include histoplasmosis and coccidioidomycosis caused by the dimorphic fungi *Histoplasma capsulatum* and *Coccidioides*, respectively. Dimorphic fungi are able to exist as either yeasts or molds depending on the surrounding temperature. The use of biologics is associated with a small but significant risk

of fungal infections [84], particularly TNF alpha-blockers. TNF alpha has been demonstrated to play an important role in the immune response to pathogens such as *Histoplasma capsulatum* [85].

Histoplasmosis is caused by inhalation of spores from *Histoplasma capsulatum,* usually from soil contaminated by bird droppings or bat guano. Most cases in immunocompetent patients are asymptomatic. Some cases may result in acute pulmonary histoplasmosis characterized by fever, cough, chest pain, and fatigue. Most people recover without treatment, but some cases may result in disseminated disease. The commonest sites of dissemination are the central nervous system and gastrointestinal tract and the risk is higher is immunocompromised people [86]. The fungus is commonly found in the Ohio and Mississippi River valleys within the United States but also in parts of Central and South America, the Caribbean, Asia, Africa, and Australia [87].

Treatment of short-lived, mild to moderate histoplasmosis is not usually required in immunocompetent patients. Treatment of chronic histoplasmosis is with systemic antifungals, e.g., itraconazole. Severe or disseminated disease is managed with intravenous antifungals, e.g., amphotericin [88]. Histoplasmosis is one of the commonest opportunistic infections in patients receiving TNF alpha-blockers and often presents with pneumonitis and/or disseminated infection [89].

Coccidioidomycosis is caused by inhalation of spores from two species of dimorphic fungi, *Coccidioides immitis* and *Coccidioides posadasii*. These species are endemic in certain areas of the southwestern United States, Mexico, Central America, and South America. Case series suggest that between 17% and 29% of community-acquired pneumonia cases in endemic areas are due to coccidioidomycosis [90,91]. The disease can be asymptomatic or subclinical or present as a community acquired pneumonia, sometimes with accompanying cutaneous or rheumatological features. In more severe cases the infection can disseminate and spread to other areas of the body. There are estimated to be 150,000 infections per year in the United States; 50,000 of these are thought to cause an illness requiring medical attention, 10−20,000 receive a confirmed diagnosis, and 600−1000 cases are thought to lead to disseminated infection [92]. There are approximately 160 deaths per year, and autoimmune conditions such as rheumatoid arthritis, systemic lupus erythematosus, and vasculitis are more common on death certificates associated with coccidioidomycosis than on those of matched controls [93]. One case series showed that patients with inflammatory arthritis treated with infliximab are at greater risk of developing symptomatic coccidioidomycosis than those not treated with infliximab [94].

Most infections in immunocompetent hosts are either asymptomatic or self-limiting requiring no treatment. Guidelines recommend against treatment of mild disease of short duration in immunocompetent hosts. Patients with debilitating symptoms at the time of diagnosis may be started on oral antifungal treatment, e.g., fluconazole [92].

Immunosuppressed patients are at greater risk of severe pneumonia and disseminated disease. The commonest sites of dissemination are skin, bone, and meninges. Patients diagnosed with coccidioidomycosis while being treated with biological therapies should be started on oral antifungal treatment unless there are features of severe illness or dissemination in which case intravenous therapy may be indicated. Serological screening prior to commencing treatment with biologics is recommended in endemic areas [92]. Coccidioidomycosis should be suspected in travelers returning from endemic areas with compatible symptoms.

8.5 Sexually transmitted infections

Barrier contraception methods like condoms reduce the transmission of blood-borne viruses (BBVs) such as HIV, hepatitis B and C, and other sexually transmitted infections (STIs). Travelers should be advised to use condoms if engaging in sexual activity with new partners, especially if traveling to areas of high STI or BBV prevalence. However, it is important to recognize that many people will not follow this advice. For example, drug and alcohol use during travel can lead to sexual behavior that increases the risk of acquiring an infection [95].

Pre-Exposure Prophylaxis or PrEP could be considered for travelers at high risk of acquiring HIV who are unlikely to use condoms. If taken effectively, this can reduce the risk of acquiring HIV by over 90% [96], although importantly it does not reduce the risk of acquiring other BBVs or STIs.

Travelers should also be aware of the rise of multidrug-resistant STIs such as extensively drug resistant gonorrhea which have very limited treatment options [97] as such cases have been acquired from sexual contact while traveling [98] Travelers should be encouraged to have a sexual health screen on their return home if they have had sex with new partners while abroad.

8.6 Emerging infectious diseases

Human migration and travel have played a pivotal role in infectious disease emergence for centuries. For example, the arrival of smallpox in the New World with European colonization led to mass fatalities among the indigenous population who had never encountered such diseases before [99]. In the 21st century a large outbreak of Middle Eastern respiratory syndrome coronavirus (MERS-CoV) was reported in Korea. The outbreak is believed to have started with a single traveler who had recently returned from a business trip to multiple Middle Eastern countries [100].

Emerging infectious diseases are defined as infections “whose incidence in humans has increased in the past 2 decades or threatens to increase in the near future”. These can be genuinely new infections or known infections spreading to a new geographic area or population [101]. Recent examples include the

Zika virus outbreak in Latin America and the Ebola outbreak in western Africa.

The link between travel and emerging infectious diseases means it is important for health-care professionals working with travelers to remain up to date with global disease outbreaks. One useful resource is https://www.promedmail.org/.

9. Other travel considerations

Although the main focus of this chapter is vaccination and travel related-infection risks in the significantly immunosuppressed traveler, it is important to discuss other, noninfectious travel risks. These are significant causes of morbidity and mortality in all travelers.

9.1 Travel insurance

All travelers should be encouraged to take out comprehensive travel insurance. This is especially important for immunosuppressed travelers, and it is vital that they inform their travel insurance provider of their preexisting medical conditions. Failure to do so will result in the invalidation of their policy. They should also ensure that their insurance covers medical repatriation to their home country in case of serious illness abroad.

9.2 Preexisting medical conditions

All travelers should consider the implications of any preexisting medical conditions before travel. Travelers should be advised to postpone foreign travel until any medical problems are stable and well controlled. For the immunosuppressed traveler foreign travel is best delayed until both the underlying condition and the immunosuppressive treatment have stabilized.

As well as informing their insurance company, it is recommended that all immunosuppressed travelers discuss their travel plans well in advance with their treating specialist and family doctor. They should have a plan for what to do if they become unwell overseas, including where they can seek medical advice and how they would cover any costs associated with this. They should also arrange an adequate supply of their regular medications to cover the length of their trip and consider how they will transport them safely to their destination, for example if refrigeration is required. Medications should not be packed in hold luggage in case they are lost or damaged. It is advisable to carry a letter detailing the prescriptions they require from their treating specialist or family doctor [14]. It is also important to remember that certain medications are restricted or banned in other countries. Immunosuppressed travelers should consider the remoteness of their destination and whether medical care is accessible, both for emergencies and regular monitoring

including blood tests. Travelers should also enquire whether a fitness-to-fly certificate is required.

9.3 Road traffic accidents

Despite popular preconceptions between 18% and 24% of deaths among foreign travelers are attributable to injuries, significantly more than the 2% of deaths caused by infectious diseases [102]. It has been estimated that between 1.3 and 1.4 million deaths occur globally each year due to road traffic accidents [103,104], and the World Health Organization ranks road injuries as the eighth leading cause of death worldwide [103]. Additionally millions more people are injured on the roads every year. The majority of these injuries and deaths occur in developing countries. Contributing factors to road traffic accidents include excessive speed, not using a seatbelt, alcohol, lack of helmet use on motorbikes, and poorly maintained vehicles and road infrastructure [105].

The high prevalence of road traffic accidents in certain parts of the world means they are an important point of discussion in a pretravel consultation. Injuries, including road traffic accidents, are an important cause of death among international travelers, especially among younger age groups [106]. Crucially some of these deaths could be prevented by modification of traveler behavior. People may behave differently while traveling abroad and be more willing to adopt riskier behaviors than they would at home. A discussion about the importance of road safety precautions is therefore an important part of the pretravel medical consultation. Travelers should also be reminded that standards of emergency medical and trauma services vary widely throughout the world and may be lower or nonexistent in low-income countries [107].

9.4 Venous thromboembolism

The term venous thromboembolism (VTE) is used to describe deep vein thrombosis (DVT) and pulmonary embolism (PE). A blood clot forms in a deep vein (a DVT), commonly in the leg; rarely this can dislodge and travel to the pulmonary arterial system (a PE) where it can cause a life-threatening obstruction [108].

VTE can be provoked by prolonged immobility associated with any form of travel. The risk of DVT approximately doubles after a long-haul flight of over 4 hours (as well as other forms of travel associated with remaining seated for long periods). The risk increases with duration of travel and taking multiple flights in a short period. The overall absolute risk in healthy travelers remains low, 1 in 6000 in flights over 4 hours [109].

All travelers should be advised to mobilize their legs regularly during travel, ideally by walking or by flexing and extending their ankles to encourage blood flow. Patients identified as high risk of VTE should consider

the use of fitted compression socks. Low molecular weight heparin may also be considered for high-risk travellers [110] or a Direct Oral Anti-Coagulant. This can be discussed with local hematology services if desired.

Factors associated with an increased risk of travel-related VTE included obesity, use of estrogen containing contraceptives, extremes of height, and prothrombotic hematological conditions [109]. Additionally chronic inflammation associated with a wide variety of disorders such as inflammatory bowel disease and rheumatoid arthritis has been suggested as a contributing factor in the development of VTE. Finally, some immunosuppression strategies may increase VTE risk (e.g., JAK inhibition). The immunosuppressed traveler on treatment for an inflammatory disorder should therefore be encouraged to follow the above advice on remaining mobile during travel [111].

9.5 Sun exposure

All travelers should be advised of the risks from excessive sun exposure. Exposure to ultraviolet light in sunlight raises the risks of sunburn, heatstroke, melanoma, and nonmelanoma skin cancers. Travelers should therefore be advised to use an appropriate sunscreen with an SPF of at least 30 and to reapply this regularly throughout the day, especially after swimming or other exercise. They should also avoid exposure to the sun between the hours of 11a.m. and 3p.m. Use of hats, sunglasses, and clothing when out in the sun at peak times should be encouraged [112]. This advice is especially important for the immunosuppressed traveler as all immunosuppressive treatments have the potential to increase the incidence of skin cancer [113].

10. Conclusions

In summary the travel-related infection risks in the significantly immunocompromised traveler are complex and comprise vaccine preventable, vector-borne, and other nonvaccine preventable infections. A thorough risk assessment should be performed before travel and advice sought from relevant specialists. This risk assessment needs to take the patient's beliefs and preferences into account. It is also important not to neglect noninfectious travel considerations.

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