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Immunocompromised travellers

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ABSTRACT

Given a better quality of life and extended life expectancy in patients with immune suppression, the number of immunocompromised travellers is constantly growing. The aim of the article is to discuss travel-related health problems in immunocompromised patients, their most common destinations and reasons to travel, as well as complications associated with travel to regions with harsh environmental conditions. The article focuses on selected groups of immunocompromised travellers (ICTs), i.e., cancer patients, transplant patients receiving immunosuppressant agents, splenectomised patients and HIV-infected individuals. The most common infections and complications, including traveller's diarrhoea, vector-borne diseases (yellow fever, malaria, leishmaniasis, dengue, chikungunya), respiratory infections (including tuberculosis), and dermatoses were taken into account. Preventive measures dedicated to ICTs (pre-travel consultation, vaccinations, malaria chemoprophylaxis, prevention during travelling) have been also characterised.

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Key words: immunocompromised patients, travelling, tropics

INTRODUCTION

The number of domestic and international travellers is growing every year. According to the World Tourism Organisation, international tourist arrivals reached a total of 1,235 billion in 2016 [1]. The growth in international tourist movement has been estimated at 4% and more in 6 consecutive years since 2010. This fact is especially important as a large group of travellers chose as their destinations Asia and Africa, where travel-related morbidity is high [2]. According to Patel et al. [3], travelling to a wide range of destinations has become more available to increasingly diverse populations of travellers.

At the same time, the number of immunocompromised patients is constantly growing. This large and varied group of patients include those with primary immunodeficiency, malignancy or human immunodeficiency virus (HIV) infection, as well as those receiving iatrogenic immunosuppression after organ or stem transplantation, rheumatologic disorders and autoimmune diseases [3]. There are a number of other medical conditions, like diabetes, pregnancy, skin and mucosal disorders, reduced gastrointestinal acid barrier, cardiovascular prostheses and even advanced age (> 60) [4], as well as alcoholism or renal failure [5], which may cause immune deficiency and put these patients at a higher risk of infection, especially while travelling. It was estimated that the number of immunocompromised patients increased both in industrialised and developing countries [6]. This situation was caused, amongst others, by a rapid spread of HIV infections, more intense malignancy treatments (including bone marrow and solid organ transplantations) and extended life expectancy of patients with chronic diseases and malignancies in general. The widespread use of new immunosuppressive therapies in transplant patients, a growing number of malignancies as well as inflammatory and autoimmune diseases resulted in an increased number of immunocompromised patients [7, 8]. Given the higher quality of life and longer life expectancy of those patients, there are now more immunocompromised people interested in travelling.

As Dekkiche et al. [7] estimate, there is very little data in medical literature about travelling with immune suppression. Studies regarding the frequency and travel patterns amongst immunocompromised travellers (ICTs) are scarce [2]. Also, information about the real risk of infections in ICTs

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compared to other travellers is limited [9]. The studies that have been performed so far seem to be very specific or, quite the opposite, very broad. Also, the study findings are frequently mutually exclusive [7]. However, as Askling et al. [2] pointed out, immunocompromised patients do travel and they are at a much higher risk of travel-related infections and complications than healthy travellers. In addition, despite their medical condition, they do not always seek pre-travel counselling.

EPIDEMIOLOGY

Owing to better therapeutic options for immunocompromised patients, their general health is improving [7]. As they live longer and the quality of their life is incomparably better than in the past [9], they do travel more. According to Dekkiche et al. [7], chronic immune suppression is not a contraindication for travelling, even to tropical destinations. Three percent of 13,235 travels included in the American study mentioned by LaRocque et al. [10] were performed by travellers with immunocompromising conditions. In the study performed by Hochberg et al. [11], 23.3% of 15,440 travellers seeking pre-travel care were considered immunocompromised.

Destinations chosen by that group of travellers are also extremely important. In the study by LaRocque et al. [10], 98% of ICTs chose low-income or low-middle-income countries as their stamping ground. In the study by Uslan et al. [12], 26.7% of solid organ recipients travelled outside the United States and Canada and 16.2% of these travellers chose Central or South America, Asia, Africa or the Middle East as their destinations. In the American study of 267 transplant recipients, 36% of them travelled outside the United States and Canada [13]. In the study performed by Dekkiche et al. [7], 26.8% of ICTs chose South-East Asia, 17.2% travelled to South Asia and 15.2% to West Africa. The study performed by Allen and Patel [14] revealed that 53% ICTs chose Sub-Saharan Africa as their destination. Patel et al. [3] underline the importance of taking into account the specific destination chosen by ICTs — first of all, if it is rural or urban, and next, to which region or city specifically they are heading to. That data might be essential, either for pre-travel consultation or to determine travel-related morbidity.

The reason to travel is also important while discussing travel-related diseases. Travellers visiting friends and relatives (VFRs) are at a higher risk of systemic febrile diseases, parasitic infections, sexually transmitted diseases, tuberculosis as well as respiratory syndromes [15]. In the study performed by Dekkiche et al. [7], 91.4% of ICTs cited tourism or VFRs as the reason to travel. Another study reported that 43% of the ICTs went abroad for tourism purposes and 22% to visit friends and relatives [14]. According to Mikati et al. [16], immunocompromised VFRs are at a 'double epidemiological risk' of travel-related infections due to their immune suppression and behavioural and environmental risk that is inevitable while coexisting with local population and acquiring local habits.

As estimated by Askling et al. [2], ICTs are a very heterogeneous group. The Canadian Committee to Advise on Tropical Medicine and Travel (CATMAT) in its Advisory Committee Statement estimates the most important areas of interaction between immunosuppression and travel [5]. First of all, ICTs have an increased susceptibility to infections. Studies concerning infections appearing in ICTs showed that in this specific group of travellers the risk of complications is higher, as well as the rates of hospitalisation when an infection occurred [5]. It is also important to remember that not only their risk of deterioration or flare of underlying medical condition is increased, but also they are more prone to become ill due to travel-related infections [14]. The second important issue is connected with concerns about vaccinations — their safety and potentially decreased efficacy [5]. Live vaccines are associated with an elevated risk of vaccine-related diseases. Also, the traveller's immune system may not be capable of creating an efficient antibody response to a vaccination [3]. Finally, there are concerns about the use of drugs for the underlying conditions, particularly their supply while travelling as well as the potential interactions with other drugs [5]. It is especially important while considering malaria chemoprophylaxis.

Different type of immune suppression may be associated with a specific disease risk [5]. In the group of ICTs, there are different degrees of risk of infections, varying levels of vaccine immunogenicity as well as a varying risk of vaccine-related complications [2]. Immunosuppression leads to a higher risk of opportunistic travel-related diseases; however, that risk much depends on the nature of immunocompromise [17]. For example, corticosteroids affect cell mediated immunity, but not necessarily humoral immunity. Therefore, a patient under corticosteroid therapy may not be a candidate for a pneumococcal vaccination. At the same time, splenectomy may affect humoral immunity rather than cell mediated immunity, which may lead to a higher risk of infection with encapsulated organisms; this may be an indication for a pneumococcal vaccination [17]. Because of those differences every immunocompromised traveller's case should be treated individually. The degree of immunodeficiency is difficult to measure. In case of HIV-infected travellers their immunodeficiency can be defined by measuring CD4 lymphocytes. In other forms of immunosuppression there has been no specified measure to quantify it so far [5].

GROUPS OF IMMUNOCOMPROMISED TRAVELLERS

PATIENTS WITH CANCER

According to Mikati et al. [16], the prognosis for cancer patients has improved and so has the quality of their life and their ability to travel. Imunnosuppression in a cancer patient may be caused by malignancy itself or the treatment received. The impact of malignancy on the immunological system depends on the type of cancer and the treatment performed [5]. In the majority of cases, the time of the highest immune suppression is immediately after chemotherapy and/or radiotherapy [5]. Cancer patients are at a higher risk of infections during this time, especially during neutropenia, and most patients should be discouraged from travelling during that period [9]. According to Centres for Disease Control and Prevention mentioned by Mikati et al. [16], travellers are considered immunocompromised for 3 months after their last chemotherapy. However, cancer therapy varies between patients, especially in the duration and type of treatment. In general, patients treated for solid tumours have usually milder and shorter immune suppression, in comparison to patients with haematological malignancies [16]. There are some specific malignancies, such as Hodgkin's lymphoma in particular (and also non-Hodgkin's lymphoma) that are associated with a significant decrease of cell-mediated immunity which can even last after the termination of treatment. Also, some treatments, such as purine analogues therapy, may be connected with a major decrease of cell-mediated immunity. At the same time, multiple myeloma and B-cell chronic lymphocytic leukaemia are associated with major suppression of humoral immunity and higher susceptibility to some specific infections, especially with encapsulated organisms. However, there are some long-term hormonal cancer treatments, involving for example tamoxifen, that may not significantly affect the function of the immune system [5]. It is essential for the physician to get to know the detailed history of a traveller's disease and the course of their treatment while counselling them during a pre-travel consultation.

TRANSPLANT PATIENTS

Due to modern surgical techniques and effective immunosuppressive therapy, transplant patients lives have improved and so has their ability to travel [18]. Immunosuppression in solid transplant recipients varies not only depending on the transplanted organ [5], but also on the time after transplantation, the dose of immunosuppressants and the presence of acute or chronic rejection episode that may be associated with elevated doses of immunosuppressive agents [19]. According to Boggild et al. [13], the risk is higher in heart-lung, lung, liver or pancreas transplant recipients and lower after kidney and heart transplants. A small intestine transplant also requires stronger immune suppression [5]. The period of the first 6 months is the time of the highest decrease of immune competence [5, 13]. Infections during the first month after the transplant are mostly related to the surgery and the stay in the intensive care unit. The period from 2 to 6 months after the transplant is associated with the highest level of immune suppression and due to this fact the majority of opportunistic infections, such as *Herpes* virus infections (especially *Cytomegalovirus*) or *Pneumocystis jirovecii* pneumonia, are diagnosed during this period [9]. From 6 to 12 months after transplantation the risk of infections decreases [9], if the doses of immunosuppressants are at their minimum [13]. For this reason, transplant recipients should be discouraged from travelling during the first year after the transplant [9]. However, the immune suppression persists during the whole time of treatment, which means during the whole lifetime. There are some specific situations, such as chronic rejection, persistent organ dysfunction or chronic cytomegalovirus (CMV) infection that are associated with a higher immune suppression [5]. Transplant recipients should also be encouraged to consider avoiding destinations where high-level medical care is not available [17]. A patient after a transplant is at a higher risk of not only acquiring travel-related diseases, but also reactivating his/her latent infections; therefore the access to high-level medical care is essential [12]. It is also crucial for the patients under immune suppressant therapy to remember about adequate drug supply while travelling, and also taking into account time changes while travelling across time zones. Due to their increased T-cell immunity, transplant recipients, should be approached like HIV-positive patients with CD4 count below 100. The risk of intracellular infection with organisms such as *Salmonella*, *Listeria* and other fungal and mycobacterial infections may be increased [17]. In the case of stem cell transplant patients, the level of their immune suppression depends on chemotherapeutic agents used prior to the transplant, the type of the transplant — autologous (auto-HSCT) or allogenic (allo-HSCT) and the degree of graft vs. host disease (GVHD) that may be treated with immune suppressive drugs [19]. Both Auto-HSCT and allo-HSCT recipients suffer from impaired immune system functioning during the early post-transplant period, meaning first weeks to months after the transplant [19] and they are at a higher risk, especially of bacterial and fungal infections [9]. Graft-versus-host disease may put the patients at increased risk of viral infections, especially CMV, BK virus and adenovirus [20]. According to McCarthy and Mileno, allo-HSCT recipients should be approached like functionally asplenic patients during 2 years after the transplant [21]. However, even though HSCT recipients are more immunocompromised than pa-

tients after solid organ transplant during the early post-transplant period [19], their immune system gets back to normal functioning after around 2 years after the transplant if they cease the immune suppressant treatment and they do not suffer from graft-versus-host disease [5, 9].

HIV-INFECTED PATIENTS

HIV pandemic seems to be the major cause of immunosuppression worldwide [6]. Antiretroviral therapy (HAART) changed perspectives for HIV-positive patients [22], also allowing them to travel internationally [23]. HIV-positive patients' immune deficiency depends on the function of peripheral CD4 T-cells, nadir CD4 T-cell count, the presence or absence of HAART therapy and whether the HIV viral load has decreased and immunological recovery has occurred [19]. The degree of immunosuppression in HIV-infected patients may be evaluated using a CD4 cell count. Patients with over 500 cells/mm may be considered as travellers with normal immune function. Travellers with 200–500 cells/mm should be approached like patients with mild to moderate suppression. The count below 200 cells/mm is related to relatively severe immunosuppression. Patients with CD4 count below 50/mm are considered profoundly immunosupressed [5]. According to a study by Sherrard and McCarthy [24], endemic-born travellers with HIV infections, i.e. patients coming from countries where infectious travel-related diseases are endemic, are staying abroad for longer periods and also they visit their friends and relatives more often. They also visit malaria-endemic regions more frequently than non-endemic born patients. In the group of endemic-born HIV-infected patients, the prevalence of travel-related infections was found to be higher. Also, the course of travel-acquired infections may be more severe and they may be more difficult to treat in endemic-born patients [24]. It is important for the patients under HAART therapy to ensure the adequate drug supply and drug storage during their trip. It is recommended to place all medications in the hand-carried luggage to minimize the risk of losing them, as they may not be available everywhere in the world [22]. Another important problem is the risk of a travel ban or discrimination against HIV-infected travellers [5]. There are many countries with entry restrictions for HIV-positive travellers, especially those travellers willing to stay in a given country for a longer period, e.g. applying for a residence or a work visa. There are also countries with restrictions for short-term travellers or even countries with policies of deporting HIV-infected people. The list of the countries changes continuously and travel-medicine specialists should inform their patients about the possibility of such restrictions [22]. There are databases available on the Internet where travellers can verify the existence of such restrictions in the country of destination prior to travel to avoid difficulties on the border [25].

PATIENTS UNDER IMMUNOSUPPRESSANT THERAPIES

There is a huge group of patients being treated for autoimmune diseases and rheumatological disorders, such as rheumatic arthritis, inflammatory bowel diseases, psoriasis, sarcoidosis, systemic lupus erythematosus, vasculitides and many others [2, 14]. These conditions may have immunomodulatory effect themselves, but most importantly, therapies used in these diseases, either classical immune suppressant agents or new biological drugs do impair the functioning of the immune system [14]. Drugs-induced immune suppression differs, especially according to the type, dose and reason for using the medication. All the components of the immune system are functionally impaired by glucocorticoids, represented most significantly by prednisone [3, 19]. Prednisone seems to be the most commonly used immunosuppresive drug. It is prescribed in inflammatory, auto-immunological diseases and many other medical conditions. According to Askling et al. [2], from 1% to 2% of adult population use it. It has a very wide range of effects and it predisposes to bacterial and fungal infections [3]. Patients whose therapy lasts longer than 2 weeks and taking a dose equivalent to over 20 mg of prednisone a day should be approached like patients with HIV infection with a CD4 cell count below 200 cells/mm, which means that their immune suppression can be considered as relatively severe [5]. There are other widely used immunosuppresive agents. The most important are azathioprine, a purine analogue; methotrexate, structural analogue of folic acid; cyclosporine, a cyclic peptide; and tacrolimus, an agent inhibiting T-cell activation [2]. Biological agents start to play an important role in treating autoimmune and chronic inflammatory diseases. They are produced to target a specific element of immune system, like B-cells, interleukins or tumour necrosis factor alpha. The most commonly used drugs from that group of medications are anti-tumour necrosis factor (TNF)-alpha agents [2]. Travellers taking antimetabolites, chemotherapeutics, alkylating agents, immunomodulators or TNF blockers are generally considered as patients with severe immune compromise [3]. The majority of available data about travellers under biological therapy is about anti-TNF-alpha agents. Patients under that kind of therapy may be at a higher risk of developing skin infections. In the Dutch study, travellers with compromised immunity system were found to be at an increased risk of skin infections, fatigue and abdominal pain. There were also cases of cutaneous leishmaniasis in this group of patients [9]. Also, travellers taking TNF-blockers are more prone to re-activate a tuberculosis infection as well as to develop a primary infection [5].

SPLENECTOMISED PATIENTS

Travellers after splenectomy are prone to infections with encapsulated organisms [5, 9]. The major risk is *Streptococ-*

cus pneumoniae infection; however, infections caused by *Neisseria meningitidis, Haemophilus influenzae* and *Capnocytophaga* are also common. The risk is at its highest level during the first two years after the splenectomy. However, the elevated risk of these infections remains for the lifetime [5]. It is essential for splenectomised patients to receive adequate vaccinations prior to travel. Asplenic patients should have a supply of antibiotics while travelling to enable quick empirical treatment of febrile diseases which may be caused by encapsulated organisms [9, 17]. In a study on the group of Danish children it was proved that a combination of pneumococcal vaccine and early penicillin therapy in febrile diseases reduced the risk of fatal sepsis [5]. It is important to remember that a risk of acquiring infections is associated with underlying conditions in asplenic patients. It is increased in patients with haematological diseases or those with suboptimal immunisation. Splenectomised patients are at a higher risk of developing severe malaria as their ability to clear *Plasmodium* parasites is impaired. Also, they may develop a severe illness if infected by *Babesia* [9].

MOST COMMON INFECTIONS AND RISKS OF COMPLICATIONS

TRAVELLERS' DIARRHOEA

Travellers' diarrhoea is the most common travel-acquired illness. Usually, it is a self-limiting disease [2]. However, it can even be life-threatening to ICTs. The disease may lead to bacteraemia, metastatic seeding as well as altered intestinal absorption. Due to changes in the intestinal intake, the absorption of oral immunosuppressive agents may also be altered [26]. The risk of developing travellers' diarrhoea is definitely higher in transplant patients [5]. This is associated with a higher risk of compromised renal function as well as increased toxicity of immunosuppressant agents due to dehydration [5, 18, 26]. Immunocompromised patients are recommended to seek medical assistance if the diarrhoea persists for more than 1–2 days and is accompanied with fever, vomiting and/or bloody stools. Prophylactic agents are rarely recommended for ICTs. If they are prescribed, they should only be used for a short period of time. Also, immunocompromised patients ought to have a supply of antimicrobial agents in case travellers' diarrhoea occurs. The most common drug used as empiric treatment is fluoroquinolone. In some cases, azithromycin is also used [26]. In her study Hochberg et al. [11] reported of 66.8% of ICTs successfully treated with ciprofloxacin and around 30% cured with azithromycin. However, it should not be omitted that azithromycin may cause a rise in cyclosporine and tacrolimus levels, which is especially important in transplant recipients. Antimotility agents may delay the clearance of the toxins from the intestines. Medications containing bismuth may also be prescribed as a therapy; however, it should not be forgotten that Supportive Oligonucleotide Technique (SOT) recipients with diminished renal function may be at an increased risk of salicylate toxicity from bismuth subsalicylate metabolism. Taking into account an increased risk of water-borne diseases, infections caused by *Coccidia*, giardiasis and microsporidiosis should be considered as a potential cause of refractory diarrhoea in ICTs [26].

ARTHROPOD-BORNE DISEASES

Vector-borne diseases include those transmitted by mosquitoes, sand flies, triatomes and ticks [3]. Malaria and dengue are considered the most prevalent travel-related arthropod-borne illnesses [27]. Malaria, however, is the most common reason of febrile illnesses in travellers [28]. There is no evidence that the prevalence of arthropod-borne diseases is more common in ICTs than in other groups. However, the course of the illness, if acquired, may be more severe. This is particularly true for malaria, leishmaniasis and Chagas disease [3]. The review cited by Rello et al. [9] found that up to 45% of malaria cases in transplant recipients met at least one of the criteria for severe malaria. It is also important that malaria may be transmitted with the organ from the donor to the recipient, without any history of travelling [27]. It was proved that in HIV-positive travellers severe malaria occurs more frequently [3]. HIV infection may be connected with recurrent malarial parasitaemia, more frequent reinfections as well as a more severe course of malaria. At the same time, recurrent malaria may lead to a decrease in CD4 cell count in HIV-infected travellers, also in those under antiretroviral therapy [29]. It is also important to highlight that there is a higher risk of severe malaria in splenectomised patients due to the impaired clearance of intraerythrocytic parasites [5, 9]. All of the travellers choosing endemic regions as their travel destination should receive malaria chemoprophylaxis. Travellers with diminished immune response are at a risk of acquiring dengue and chikungunya viruses as they are often found amongst travellers. There is little evidence of increased severity of dengue or chikungunya amongst ICTs [3]. However, there have been several reports of severe dengue in immunocompromised patients [9]. According to Patel et al. [3], Chagas disease and leishmaniasis may disseminate in immunocompromised patients, especially HIV-infected, as well as transplant recipients [3]. Chagas disease, either as a reactivation of a latent infection or transmitted from the donor organ may be associated with increased mortality [30].

PULMONARY DISEASES AND SYSTEMIC FUNGAL INFECTIONS

Respiratory tract infections are one of the most common travel-related health problems [31]. Of all travellers with

medical conditions included in the study by Wieten et al. [4], 30% suffered from a self-reported respiratory disease. Influenza may be the most prevalent travel-related infection. It also increases the risk of pneumonia of bacterial origin, especially that caused by *S. pneumoniae* and *S. aureus*. Every immunocompromised patient should be vaccinated with a yearly influenza vaccination, as well as with a pneumococcal vaccination, as this can help reduce the severity of symptoms and decrease mortality associated with respiratory infections in immunocompromised patients [2]. According to Ericsson [17], HIV-positive patients are at a higher risk of acquiring a respiratory tract infection. The risk of *Pneumocysitis jirovecii* does not seem higher while travelling. As Rello et al. [9] estimate, the risk of tuberculosis is elevated in immunocompromised patients; however, the risk of the travel-acquired tuberculosis has not been determined. The risk is connected with the reason to travel. Intense contact with local population, inevitable while working in the health sector or while VFRs, is associated with a significantly higher risk of acquiring tuberculosis. Amongst immunocompromised patients, those with impaired cell-mediated immunity, HIV-infected patients as well as those taking TNF-alpha blockers, seem to be at an elevated risk of developing tuberculosis [5]. It is important to screen these patients for latent tuberculosis infection after visiting endemic regions to identify the patients at a higher risk of developing active tuberculosis [9]. For example, Bhadelia et al. [29] recommend that in HIV-positive patients a tuberculin skin test should be performed prior to travel and 6 months after return. Tuberculosis skin test, however, may have a decreased sensitivity in individuals with impaired cellular immunity [5]. Immunocompromised patients are at a risk of acquiring fungal infections, such as for example histoplasmosis, coccidioidomycosis and penicilliosis, while travelling [26]. These infections are potentially associated with increased severity and mortality in immunocompromised patients [9]. Sometimes, travel-acquired fungal infections may reveal, for example, a HIV infection, as fungal infections are one of the most common opportunistic diseases [32]. Fungal infections may occur as a consequence of inhalation or skin inoculation and in both cases it may disseminate, due to the impaired immunity system. It is crucial to remember that a fungal infection acquired while travelling may present as an acute infection or as a reactivation many years after travelling [33]. Some of these infections may have a long incubation period [9]. Due to that fact, a case of potentially severe pneumonia, with no confirmed bacteriological cause that may be accompanied by dissemination signs such as cytopoenia or skin lesions, should make a physician consider a travel-acquired fungal disease as a potential diagnosis even long time after travelling [33]. It is important that, as Ericsson estimates, some fungi have geographical distribution so travelling to certain destinations may be connected with an increased risk of certain fungal infections, which should not be omitted in differential diagnosis. For example, travelling to North America and some parts of Central and South America may be connected with a higher risk of coccidioidomycosis infection. Travelling to Latin America may put an immunocompromised traveller at a higher risk of acquiring paracoccidioidomycosis and choosing South-East Asia as a destination may be a reason to take into consideration *Penicillum marnefeii* as a cause of infection in differential diagnosis [17].

SKIN DISEASES

Skin exposure may also be the source of risk. *Strongyloides*, an insect penetrating intact skin, may lead to hyperinfection syndrome in immunosuppressed travellers, especially in those under corticosteroidal therapy [3]. It may be affiliated with higher mortality in immunocompromised patients [9]. However, it is not common in post-transplant patients due to cyclosporine's anti-helminthic activity [5]. Also, there is a risk of acquiring *Leptospirosis* after direct skin contact with infected rodent urine. The disease may cause not only fever but it can also lead to renal and liver failure [3]. In immunocompromised patients, it may have a severe course and be associated with elevated mortality [32]. As mentioned before, fungal infections may occur after skin inoculation. It may lead to diverse primary mucosal, cutaneous, and subcutaneous infections. In the group of immunocompromised patients, lesions may be more extensive than in other travellers [33]. As mentioned before, patients under anti-TNF treatment are at an elevated risk of developing skin infections in general [9]. Transplant recipients are at a higher risk of skin cancer, associated with the intensity of sun exposure. It is important for these patients to use sun protection — hats, sunglasses, protective clothing as well as sun-blocking agents with high factors [26].

PREVENTION OF IMMUNOCOMPROMISED TRAVELLERS

PRE-TRAVEL CONSULTATION

Allen and Patel highlight that ICTs need specialized pre-travel advice in order to address the risks associated with travelling. The pre-travel consultation should take place several months before potential departure [14]. A structured approach should vary depending on a patient's individual immunocompromised state. According to the study amongst 267 post-transplant patients in the United States and Canada, 37% travelled abroad and 66% sought pre-travel consultation with their transplant doctors. However, despite having sought pre-travel advice, only 5% received vaccination against hepatitis A before travelling to endemic regions [13].

This shows that specialists need education and guidance on pre-travel medical care of immunocompromised patients. According to Askling et al. [2], the consultation should by performed by a travel medicine specialist in collaboration with a relevant specialist. Doctors and specialised clinics which take care of immunocompromised patients should emphasise the need for pre-travel advice [5]. Interventions and guidance should be adequate to each traveller's immunocompromise state. Patel et al. [3] created a detailed check list of pre-travel advice that involve 5 most important aspects, which obligate a physician to assess traveller's health, assess the risk of exposure, administer vaccines and relevant counselling, administer medical prophylaxis and provide medical care and counselling [3].

VACCINATIONS

Before vaccinating an ICT, the physician should take into account the mechanism and degree of each patient's immunosuppression. It is essential to choose the type of vaccination needed, predict the efficacy of vaccination and assess the potential need of revaccination. The destination, risk of exposure, duration of travel and activities performed while travelling are also very important while considering immunization. It must be remembered that the response to vaccination and the duration of immunity may vary amongst immunocompromised patients, also depending on the type of vaccine used [3]. Live vaccines are generally contraindicated in travellers with immune suppression [2, 3]. These vaccines may cause vaccine-related disease in patients under mild or high immune suppression. If possible, a live vaccine should be administered to patients a month before the planned beginning of immunosuppressive treatment or at least 3 months after the termination of therapy [2]. In general, inactivated vaccines are considered safe; however, their efficacy may vary depending on the immune system's functioning and may not always be fully effective. The time of vaccination should also be wisely considered. It is important to vaccinate the patient early to achieve full immunity before the trip and to allow time to administer boosters to the patient if needed [3].

In cancer patients, the response to the vaccine is the most effective when it is administered prior to chemotherapy or radiotherapy or several months after the termination of therapy. Hormonal cancer treatments should not affect the immunological response to the vaccination [5]. The situation may vary in transplant recipients. Their immunological response to the vaccine may be diminished if an organ failure occurred prior to transplantation. The effectiveness of the vaccination as well as the duration of immunity may be suboptimal, especially during the first 6 months after the transplant. When the primary vaccination is performed before the transplant and then boosted after it, the response to the vaccine seems to be higher. That group of patients should be advised, if possible, to get vaccinated at least six months after transplantation [5]. Importantly, HBV-specific immunity is transferred to the recipient of stem cell transplant if the donor was vaccinated.

In the case of travellers taking corticosteroids and other immune suppressive agents, vaccines should be postponed one month after the discontinuation of tumour necrosis factor inhibitors or corticosteroid therapy [3]. In the case of biological treatment, the time after therapy termination may be even longer, for example, several months to 1 year [3] or 6 to 12 months after rituximab therapy [5]. Patel et al. [3] highlight that in different situations, if needed, vaccinations should be postponed until the immunosuppressants can be administered at lower doses or discontinued altogether. In HIV-infected patients, there are vaccines that may cause a slight elevation in HIV viral load. However, the increase is not considered clinically significant [29].

As mentioned before, routine vaccinations, including annual influenza and pneumococcal vaccination, should be offered to that group of travellers [3]. If the patient is not a candidate for vaccination, they should reconsider their travel destinations in order to diminish the risk of travel-related diseases. According to Patel et al. [3], it is especially important while considering travelling to regions where live vaccine-preventable diseases are endemic, for instance, Sub-Saharan Africa or South America, where the risk of yellow fever transmission is high. In the case of transplant recipients or those under high-dose immunomodulating therapy, these destinations should be avoided for at least one year. Travelling to regions with ongoing outbreaks should be strongly discouraged in that group of travellers in general [3].

MALARIA CHEMOPROPHYLAXIS

All travellers choosing malaria-endemic regions as their destination should receive chemoprophylaxis, chosen according to the Centres for Disease Control and Prevention (CDC) guidelines. For ICTs, it is essential to take possible drug interactions into account while choosing the antimalarial drug regimen. In cancer patients it is important to remember that mefloquine may increase the concentration of calcineurine inhibitors. At the same time, it is safe for patients with renal failure, which should be taken into account in post-transplant patients. Doxycycline may decrease the concentration of mycophenolate [3]. Atovaquone/proguanil seems to be safe in the majority of cases; however, the high cost of the medication may limit its use. Some antimalarial agents, particularly chloroquine, but also mefloquine or atovaquone/proguanil, may cause an increase of cyclosporine, sirolimus and tacrolimus concentration. Due to that fact, transplant recipients should consider starting

malaria chemoprophylaxis several weeks prior to travel in order to monitor the concentration of these drugs and find an optimal dose of an antimalarial agent [5]. In HIV-infected patients it should not be forgotten that antiretroviral medications, especially protease inhibitor, for example ritonavir, may interact with other drugs. Ritonavir may increase the concentration of atovaquone. At the same time, atovaquone can increase zidovudine concentration. Ritonavir increases quinine concentration and it inhibits the metabolism of lumefantrine, which is a component of *Coartem*, an antimalarial drug widely used in Africa. There is a higher risk of life threatening cardiac arrhythmias in patients taking these two drugs simultaneously [5]. Mefloquine may cause a decrease in ritonavir concentration. Doxycycline is probably safe [22]. Atovaquone/proguanil may be a good choice in patients who are under therapy including non-nucleoside reverse transcriptase inhibitor. Atovaquone and protease inhibitors have limited interactions as well [29].

PREVENTION DURING TRAVELLING

In the study performed by Bialy et al. [34], 65.7% of 105 ICTs reported behaviours which may have put them at a higher risk of infectious diseases. The risk behaviours included eating food from unreliable sources or unsafe sex practices, also without barrier precautions. Due to this fact, it seems highly necessary to provide international travellers with full information regarding health and safety precautions to be followed while travelling. Food and water precautions are particularly important in this group of patients. Travellers are recommended to drink bottled, boiled or filtered water only. Food should be thoroughly cooked and eaten immediately after preparation. Undercooked meat, fish, seafood and shellfish put a traveller at a risk of many viral, bacterial and parasitic infections. Buffet style dining should be avoided. Fresh fruits that can be peeled seem to be save. Unpasteurised milk products and food containing raw eggs may also put a traveller at a risk of infections [3]. It is essential to use insect repellents containing diethyltoluamide several times a day in order to avoid diseases transmitted by mosquitoes, ticks, sand flies and chiggers. It is also advised to wear clothes covering arms and legs. Immunocompromised travellers should avoid walking barefoot and swimming in freshwater reservoirs because of a potentially elevated risk of infecting abrasions or transmission of parasitic illnesses, such as the already mentioned *Strongyloides* and *Leptospira* infections, which may lead to severe complications. These patients should also avoid caving and outdoors activities to minimise the risk of fungal infections [3]. Travellers should remember to use barrier precautions during sex. It is essential, especially for HIV-infected travellers, not only to reduce the risk of transmission of other sexually transmitted infections, but also to avoid the acquisition of another HIV strain [17]. 23% of HIV-infected travellers studied by Salit et al. [23] reported casual sex with new partners while travelling abroad and only 58.1% of them confirmed a regular use of condoms. The study findings suggest that international travellers have little knowledge and awareness of health risk factors and health precautions.

CONCLUSIONS

Given a better quality of life and extended life expectancy in patients with immune suppression, the number of ICTs is constantly growing. There are some connections between this medical condition and travelling. The main areas of consideration are the elevated susceptibility to infections, various health risks and potentially decreased efficacy of vaccinations, but also the issue of drug supply while travelling as well as potential drug interactions. In the group of immunocompromised patients, the most common travel-related diseases may be associated with a more severe course and more serious complications. Pre-travel counselling performed by a travel-medicine doctor in collaboration with a relevant specialist is essential in ICTs. Interventions and guidance should be adequate to each traveller's immunocompromise state and their general health. Due to that fact, every case should be considered individually.

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