REVIEW

The medically immunocompromised adult traveler and pre-travel counseling: Status quo 2014

Helena H. Askling a,b,*, Virgil A.S.H. Dalm c

a Karolinska Institutet, Dept. of Medicine/Solna, Unit for Infectious Diseases, SE 17176 Stockholm, Sweden
b Dept. of Communicable Diseases Control and Prevention, SE 118 91 Stockholm, Sweden
c Department of Immunology, Erasmus MC, ’s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands

Received 20 February 2014; received in revised form 16 April 2014; accepted 24 April 2014
Available online 6 May 2014

KEYWORDS
Immunocompromised; Travelers; Vaccination; Pre-travel; Counseling

Summary  International travel is increasing among a growing number of medically immunosuppressed patients regaining life-activity due to efficient drugs. Adequate pre-travel advice for this group of patients requires not only a travel-medicine expert but a relevant specialist as well, so that a personalized plan can be made concerning vaccinations and other prophylaxis. Inactivated vaccines can generally be prescribed during immunosuppressive therapy; the risk of inducing an exacerbation of the underlying disease is minimal and even though the post-vaccination antibody response will often be impaired, it will possibly benefit the patient by means of inducing a milder course of the disease. Live vaccines are generally contraindicated and if the risk of getting the disease in a particular country is high, the potential risks must be carefully discussed with the patient. It is essential to try to prevent infections in this group of patients who are more vulnerable to serious complications caused by the immunosuppression. The aim of this review was to summarize the available literature on immunosuppressive drug mechanisms and evidence on pre-travel-vaccinations, malaria prophylaxis as well as drugs preventing tourist diarrhea. The immunocompromised conditions/drugs used in these conditions that are covered include solid organ transplantations (SOT), hematopoietic stem cell transplantations, splenectomy, and chronic inflammatory diseases in adults. HIV and pediatric patient populations are not included.

© 2014 Elsevier Ltd. All rights reserved.
Background

Over one billion international tourist arrivals were reported world-wide in 2012, which is a near tripling of the annual rate in two decades. Travel to countries with developing economies, such as those in Africa and Asia, has particularly increased over this time period [1]. Concurrently, there has been a rise in the number of persons undergoing solid organ transplantation [2], receiving hematopoietic stem cell transplantation [3], and being prescribed biologics and other immunosuppressive medications for autoimmune diseases [4]. Together these trends have created an increase in the exposure of immunocompromised patients to travel-associated infectious pathogens.

There is limited medical literature about the frequency and travel patterns of immunocompromised travelers (ICTs), about infection rates among them and about the care provided by travel-medicine specialists. However, based on the available data we can see that: 1. they do travel, 2. they do not always seek pre-travel advice, and 3. they are at higher risk for travel-related complications. In a recent multicenter U.S. study involving 18 travel clinics, 3 percent of 13,235 travel visits involved patients with an ‘immune system condition’ [5] and within a consortium of Boston-area travel clinics, 4.2 percent of travelers were considered immunocompromised [6]. Of U.S. solid organ transplant recipients, 27 percent reported travels outside the U.S. or Canada [7]. In a European study of kidney transplant recipients, 34 percent of the responders had traveled outside Western Europe (WE) and Northern America (NA); 22 percent of these travelers had not sought pre-travel health advice [8]. Studies on infections among ICTs have revealed that they are at higher risk for complications with high rates of hospitalization when illness occurs [8,9]. A prospective case–control study of splenectomized individuals revealed suboptimal immunization coverage as well as suboptimal malaria prophylaxis [10].

ICTs form a heterogeneous group of patients with varying degrees of risk for travel-related infections, varying levels of vaccine immunogenicity, and varying degrees of risk for vaccine-related complications [11]. There is a gap of knowledge in how to deal with the increasing group of patients treated with biologics and other immunosuppressants with respect to travel-related vaccines as well as malaria prophylaxis treatment and other pre-travel medical concerns. This review investigates the scientific basis for pre-travel advice for the growing group of medically immunocompromised non-HIV adult travelers. The conditions/drugs used for these conditions that are covered include solid organ transplantations (SOT), hematological stem cell transplantations, splenectomy, and chronic inflammatory diseases in adults. Also, a short overview is presented of the mode of action of various immunosuppressants, followed by a review of the literature on travel-vaccinations, malaria prophylaxis and other pre-travel medical concerns in relation the immunocompromised conditions described above.

Immunosuppressive drugs

Classic immunosuppressive drugs

Prednisone was originally isolated in 1950 and was used for the first time in 1954, in clinical studies in inflammatory conditions like rheumatoid arthritis [12]. Since then, prednisone has become one of the most important anti-inflammatory drugs and nowadays, oral corticosteroids are being used by 1–2 percent of the total adult population [13]. Prednisone affects virtually every cell type involved in immune and inflammatory responses and its use leads to lymphopenia, monocytopenia, reduced lymphokine, cytokine, prostaglandin and nitric oxid formation, impaired phagocytosis, decreased proliferation and migration of lymphocytes and decreased chemotaxis and migration to sites of inflammation of monocytes and macrophages [14]. Due to these broad effects, use of this anti-inflammatory drug is strongly associated with a higher susceptibility for bacterial and fungal infections [14–17]. Because of these and other unwanted effects like development of osteoporosis, diabetes and skin atrophy amongst others, steroid-sparing immunomodulatory agents have been developed and introduced in everyday clinical practice in the past decades.

One of the first steroid-sparing agents was azathioprine (1954), a purine analog. Azathioprine competitively interferes with nucleoid acid metabolism and consequently, inhibits B- and T-lymphocyte proliferation [18,19]. Azathioprine also interferes with the interaction of T-lymphocytes and macrophages in antigen-presentation. In vaccine responses azathioprine may therefore interfere with B-cell proliferation, antibody production and T-cell sensitization, potentially reducing normal responses.

Methotrexate is a structural analog of folic acid. By inhibiting the synthesis of nucleic acids and cell proliferation methotrexate inhibits proliferation of both T- and B-cells [20].

Cyclosporine, a cyclic peptide, and tacrolimus, a macrolide immunosuppressant produced by soil bacteria, both inhibit T-cell activation via interaction with interleukin (IL)-2, a cytokine that is essential for adequate T-cell activation [21]. In this way these compounds interfere with T-cell dependent B-cell responses and may thus hamper vaccine response as well.

Biologics

‘Biological drugs’ are proteins produced with biological methods (opposed to chemically synthesized) to target a specific component of the immune system. There has been a dramatic increase in their use over the last decade due to broadened indications for use in many autoimmune diseases and chronic inflammatory conditions such as rheumatoid arthritis (RA), inflammatory bowel diseases (IBD) and psoriasis. Targets of these biologics include interleukins (e.g. anti-IL1β), B-cells (anti-CD20) and tumor necrosis factor-alpha, (TNF-α). Anti-TNF-α drugs are by far the most
widely used biologics and therefore also the ones most studied in relation to vaccination. TNF-α is a pro-inflammatory cytokine produced by macrophages, T-cells, B-cells and dendritic cells. It plays a key-role in controlling intracellular bacterial infections (e.g. *Mycobacterium tuberculosis*, *Listeria monocytogenes*), fungal infections (e.g. *Histoplasma capsulatum*) and constitutes an important factor in the natural course of chronic viral infections (e.g. hepatitis B, hepatitis C, HIV). TNF-inhibitors (TNFis) effectively block the development of the inflammatory cascade. Among TNFis there are both receptor inhibitors (etanercept) and monoclonal antibodies. The latter are either chimeric/humanized (infliximab, certolizumab-pegol) or human (adalimumab, golimumab). Monoclonal antibodies are produced by identical immune cells and have monovalent affinity i.e. they bind to the same epitope. For an overview see Fig. 1. Using biologics in the treatment of patients with chronic inflammatory diseases has been a revolution and a success story for formerly disabled individuals. When treated with a TNFi, many of them regain their former life-activity, which often includes traveling to countries where pre-travel prophylaxis has to be considered.

Vaccines

General recommendations for each vaccine are summarized in Table 1.

Indications for immunocompromised travelers

In general, immunocompromised travelers are considered to have the same risk of getting specific travel-related disease as immunocompetent. However, immunocompromised patients have a higher risk to get an infection and the consequences of the disease can be much more severe. This implicates that the *indications* for vaccination are the same for immunocompromised patients but the *recommendation* of pre-travel vaccination is even more imperative since it can prevent disease or at least reduce severity of the course in this vulnerable population.

Safety

Inactivated vaccines are considered to have the same safety-profile in immunocompromised patients as in immunocompetent persons, with usually mild adverse events. Furthermore, there is no evidence that inactivated vaccines cause a flare-up of the autoimmune or chronic inflammatory disease [22–25]. Live attenuated vaccines (e.g. yellow fever, BCG and MMR), form a potential risk for vaccine-related disease in case of moderate or high immunosuppression. Therefore, live attenuated vaccines are generally contraindicated. If there is a high risk for obtaining the disease in the country of destination, change in travel destination should be considered and the patient must be carefully informed about the risk for disease if travel is still undertaken. For live vaccines, it is advised to adequately vaccinate the patients — if possible — one month prior to intended start of immunosuppressive therapy or at least three months after termination of treatment. The latter is dependent on the drug used; in case of biologics the immunomodulatory effect of the drug used can be very long e.g. 6–12 months for rituximab. There is a fairly wide discrepancy in national recommendations concerning use of live vaccines and time-interval to immunosuppressive drugs [26]. The discussion is facilitated by a close contact with the doctor who is familiar with the

**Table 1** Summarized general recommendations for pre-travel vaccination of medically immunocompromised individuals. More detailed information is found in each separate text section.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumococcal</td>
<td>Yes but independent of travel</td>
</tr>
<tr>
<td>Influenza</td>
<td>Yes annually, ensure before travel if available</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Ensure 2 doses before travel or gamma globulin if time-span to short</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Evaluate antibody response. Consider enhanced immunogenicity by using combination vaccine (hepatitis A + B)</td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Yes if indicated</td>
</tr>
<tr>
<td>Rabies</td>
<td>Ensure protective neutralizing antibody titers after a 3-dose schedule</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Yes if indicated. Use inactivated vaccine. Avoid live oral vaccine.</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td></td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Contraindicated during immunosuppressive therapy.</td>
</tr>
<tr>
<td>BCG</td>
<td>Contraindicated during immunosuppressive therapy.</td>
</tr>
<tr>
<td>MMR</td>
<td>Contraindicated during immunosuppressive therapy.</td>
</tr>
</tbody>
</table>

Immunoglobulin might be considered.

---

Fig. 1  "Biologics" — an overview of the most common used drugs.
patient, underlying conditions and related drugs. Therefore thorough pre-travel evaluation and counseling is essential.

Immunogenicity vs. effectiveness or efficacy

An important limitation of available studies on vaccine response in immunosuppressed patients is that the end-points of these studies are always antibody titers, which alone give no information on efficacy of vaccination in preventing infections. Due to small sample sizes of those studies and the rareness of diseases events, from these studies it can not be derived whether or not antibody titers result in a relevant proxy for protection against disease [27]. In general it has been shown that compared to immune competent persons, immunocompromised patients demonstrate a less significant increase in antibody titers after vaccination. Still, the cellular immunity, of which we know little in most studies, might be enough to prevent severe disease in patients with an inadequate antibody response compared to patients that have not been vaccinated (see studies for each vaccine below).

Inactivated vaccines

Pneumococcal vaccine

Pneumococcal disease contributes to a significant proportion of world-wide mortality. Although corticosteroids are widely used, not much is known on the efficacy of vaccines in patients on steroid treatment. In a study of patients receiving bone marrow transplantation, steroid treatment was associated with poor antibody responses to pneumococcal polysaccharide vaccination [28]. In general it is recognized that the pneumococcal vaccines — both polysaccharide and conjugate — do induce a significant humoral response, albeit to a lesser degree and at a lower level when under steroid treatment, compared to healthy subjects [29]. Also in kidney transplant recipients receiving calcineurin inhibitors (cyclosporine A or tacrolimus) and prednisone a significant increase in antibody levels upon polysaccharide pneumococcal vaccine vaccination was found [30]. On the other hand, the use of methotrexate leads to impaired antibody response to the 7-valent conjugate pneumococcal vaccine in RA-patients [31]. In patients who had an initial increase in antibody levels, upon treatment with methotrexate post-vaccination antibody levels decreased significantly in 1.5 years, declining to levels before vaccination [32].

In RA-patients using TNFis only, pneumococcal vaccination response has been shown to be similar to healthy controls, both polysaccharide and conjugate vaccine. However, patients on methotrexate in combination with a TNFi, have impaired responses [31,33–36]. The persistence of antibodies after pneumococcal conjugate vaccination was significantly decreased in older patients and patients with high disease activity and long duration of RA [32]. One study of IBD-patients treated with TNFis showed a decreased antibody response compared to healthy controls, after the polysaccharide vaccine [37]. The effect of abatacept on pneumococcal vaccination was investigated in healthy controls and showed a decreased antibody response [38]. Neither certolizumab-pegol nor tocilizumab-treated RA-patients had an impaired antibody response after pneumococcal polysaccharide vaccination [39,40]. This was also shown with the 7-valent conjugate vaccine for tocilizumab but the antibody response was impaired for the RA-patients treated with abatacept or rituximab [41].

Recommendation: Pneumococcal vaccine is not a specific travel-related vaccine. It should instead be administered to all iatrogenic immunocompromised patients. Recommendations on type of vaccination (polysaccharide vaccine vs. conjugate vaccine), dosing and timing differ widely between various countries [26] and national guidelines should be followed. With respect to travel-related vaccination, one should assure that a patient has received a pneumococcal vaccine according to national guidelines prior to travel.

Influenza vaccine

Influenza vaccine has a protective effect concerning severity of disease and related mortality [42,43]. A study of patients with Systemic Lupus Erythematosus (SLE) treated with prednisone, demonstrated a blunted immune response [44]. A similar impaired response has also been demonstrated in patients (renal transplant recipients and juvenile dermatomyositis) on azathioprine, mycophenolate or cyclosporine, [45–47].

Both trivalent inactivated (TIV) and H1N1-vaccines have been shown to elicit a fairly good response in patients treated with TNFis. Several studies showed a lower, but still protective antibody titer compared to a healthy control-group [48–54]. Two studies showed an antibody response similar to the control-group [35,55]. When adding methotrexate to the treatment the antibody response was weaker [35,50,51,53–55].

Recommendation: Annual influenza vaccination is recommended for all immunocompromised patients. They should be informed to seek advice prior to travel for optimal timing of the annual vaccination. If the destination is in the opposite hemisphere, appropriate influenza vaccination is recommended.

Hepatitis A vaccine

Hepatitis A is a fecal-oral transmitted virus that is still endemic in many parts of the world where there are poor hygienic conditions. Advanced age and immunosuppression increase risk for complicated disease and death [56]. In healthy individuals, the inactivated vaccine is effective for pre-travel prophylaxis with one dose only [57]. In 78 solid organ transplant recipients (39 liver and 39 kidney recipients), vaccination against hepatitis resulted in seroconversion in 24 percent of kidney recipients 41 percent of liver recipients after a primary dose (compared to 90 percent in healthy controls). After a booster dose, seroconversion was described in 72 percent and 97 percent respectively (100 percent in healthy controls). Moreover, the seroconversion rate was inversely associated with the number of immunosuppressive drugs (steroids, azathioprine, cyclosporine) [58]. Remarkably, after 2 years of follow-up, the proportion of patients still seropositive declined to 26 percent in renal transplants and 59 in liver transplants, while all healthy controls remained seropositive [59].

A retrospective evaluation of patients with different conditions and immunosuppressive drugs demonstrated a
poor anti-HAV antibody response after one dose of hepatitis A vaccination, and the use of TNFis was associated with significantly less seroprotection rates than obtained in healthy individuals [60]. This was confirmed in a prospective study with a homogenous group of RA-patients treated with TNFis and/or methotrexate. The negative effect was reinforced by adding methotrexate but also true for treatment with methotrexate alone [61]. These data imply that a single dose of hepatitis A vaccine as a pre-travel prophylaxis will not protect ICTs and especially those treated with both TNFis and MTX.

**Recommendation:** In this vulnerable group of patients, gamma globulin alone, or in combination with hepatitis A vaccine at the same time, should be considered if time does not allow two doses with a six months interval before travel.

**Hepatitis B vaccine**

Hepatitis B virus is transmitted via blood or sexual contact. Few studies have examined the effects of immunosuppressive therapy on hepatitis B vaccination response in adults. In a study of RA-patients treated with different rheumatic drugs but not TNFis (methotrexate 77 percent) 68 percent responded serologically after 3 doses of hepatitis B vaccine [62]. Two studies on IBD-patients also showed poor response to hepatitis B vaccination being particularly weak in patients with long-term disease, low serum albumin levels and those on corticosteroid therapy [63,64]. In two small studies patients (IBD and spondyloarthrisis) treated with TNFis have been shown to have a poor antibody response to hepatitis B vaccination [65,66].

**Recommendation:** In ICTs hepatitis B serology should be checked before vaccination, to exclude chronic infection. After the recommended 3-dose vaccination schedule, anti-Hbs titer should be measured. Patients should be revaccinated when the initial antibody response is absent or suboptimal (anti-Hbs <10 mIU/mL). The hepatitis A and B vaccination combination has been shown to be more immunogenic in healthy individuals [67] and can be a good alternative as well, although it has not been evaluated.

**Meningococcal vaccine**

Meningococcal disease is rare but severe. Despite modern intensive care mortality rates are very high. There are both monovalent type C conjugate as well as multivalent vaccines available. Vaccination is indicated for splenectomized patients, for students on exchange programs in countries where this is recommended in the national program as well as for pilgrims to Saudi-Arabia and for those who travel to the so-called ‘meningitis-belt’ the Sahel region in Africa. Indications may differ between countries and may also include other groups. Little is known about the effectiveness of meningococcal vaccine in immunocompromised adults.

**Recommendation:** Inactivated meningococcal vaccine is indicated as for healthy travelers and depending on national recommendations. What type of vaccine should be used should be discussed with a travel-medicine expert. For splenectomized individuals with travel plans meningococcal vaccination should always be recommended [10].

**Rabies vaccine**

No data could be found to support management of pre-exposure rabies vaccination in immunocompromised patients.

**Recommendation:** Due to the serious nature of rabies disease and the possibly impaired vaccine response in immunocompromised patients, pre-exposure prophylaxis should, if possible, be postponed until the immunosuppressive condition is resolved. When this is not feasible, the rabies-virus neutralizing antibody response should be determined 2–4 weeks following vaccination with three doses to assess the possible need for an additional dose of the vaccine [68].

Revaccination should be an alternative but always evaluated by post-vaccination antibody titers [69].

**Typhoid vaccine**

Typhoid-fever is caused by an invasive infection with Salmonella typhi. Vaccination is recommended for travelers going to areas with low hygiene and/or longer trips especially to the Indian subcontinent. There are no experimental data on safety and efficacy of typhoid vaccines in non-HIV immunocompromised conditions dealt with in this review.

**Recommendation:** The inactivated typhoid vaccine is currently recommended for immunocompromised patients whereas the live oral vaccine is contraindicated.

**Japanese encephalitis vaccine**

Japanese encephalitis is caused by a mosquito-borne flavivirus. Mortality and morbidity are high in endemic settings but the incidence among travelers is low [70]. Pre-travel vaccination might be considered when traveling to certain areas and trips beyond 3–4 weeks to certain parts of Asia. Inactivated Japanese encephalitis vaccine is recommended in 2 doses with a four week interval but no specific data exist on the immunogenicity and safety in immunocompromised patients. It is however likely that immunocompromised patients will have less of an antibody response to the vaccine compared to healthy controls.

**Recommendation:** Until more data gets available that show otherwise, inactivated Japanese encephalitis vaccine should be recommended for immunocompromised patients traveling to certain areas and trips beyond 3–4 weeks to certain parts of Asia.

**Live attenuated vaccines**

**Yellow fever vaccine**

Yellow fever — a mosquito-borne flavivirus — is present in tropical regions of South America and sub-Saharan Africa. Clinical disease varies from a mild, undifferentiated febrile illness to severe disease with jaundice and hemorrhagic manifestations [71]. There is no specific antiviral treatment available for Yellow fever, hence prevention is critical to lower disease risk and mortality. The currently available 17D vaccine is a live attenuated vaccine [72]. Although no specific data exist on the use of Yellow fever vaccine in
patients on immunomodulatory and immunosuppressive therapies, these persons are presumed to be at an increased risk for Yellow fever vaccine-associated serious adverse events, and the use of live attenuated vaccines in these persons is contraindicated according to the package insert for most of these therapies [73]. Interestingly, very recently it was reported in a cohort of 34 patients on steroid therapy (prednisone or equivalent 7 mg/day) that all subjects tested had specific neutralizing antibodies after 17D vaccine administration and only an increase in local reactions when compared to healthy controls was described, while no serious adverse events were reported [74]. Moreover, in a small cohort of solid organ transplant recipients (n = 19), who received 17D vaccines inadvertently, no important side effects were found. Immunosuppression varied widely with different drug combinations: azathioprine (7 patients), cyclosporine (8), deflazacort (1), mycophenolate (10), prednisone (11), sirolimus (3), and tacrolimus (4) [75]. Unfortunately, no data were available on vaccine immunogenicity. Both studies demonstrated that Yellow fever vaccine could be administered safely in these patients groups, but due to the small number of patients large-scale studies are warranted prior to extending these findings to the rest of the transplantation population.

Recommendation: Live attenuated vaccines should be avoided in immunocompromised patients and these patients should be strongly discouraged from traveling to destinations where the Yellow fever vaccine is indicated. Live attenuated virus vaccines can be administered after cessation of immunosuppressive therapy. The proposed interval between discontinuation of therapy and vaccination differs between 2 and 12 weeks, depending on national guidelines and half-life of the immunosuppressive drugs used [26]. Close collaboration between the travel-medicine expert and the drug-prescribing clinician will be required to form a sound advice and plan for treatment/vaccination.

Bacillus Calmette Guerin (BCG) vaccine

BCG is a live attenuated vaccine to prevent tuberculosis, most effectively in children and the disseminated form. Its use is in immunocompromised patients is generally contraindicated [76].

Measles—mumps—rubella (MMR) vaccine

The WHO elimination goal of the measles is one of several reasons to consider MMR-vaccine as a travel-vaccine and to check pre-travel immunity if not known already. The American continent is declared measles-free, but at the same time Europe has experienced huge measles-epidemics during the last years [77]. Thus, Europe has been the continent most often responsible for travel-related measles outbreaks. MMR-vaccine is a live attenuated vaccine and as such generally contraindicated in immunocompromised patients. Recently, it was shown that low dose methotrexate did not interfere with the generation of long-lived virus-restricted T-cells and protective levels of virus-specific IgG antibodies after MMR vaccination in juvenile idiopathic arthritis patients. Moreover, no adverse effects were reported [78,79]. These studies were however too small to advice MMR vaccination in immunocompromised patients in general and further studies are warranted.

Recommendation: MMR-vaccines are generally contraindicated in immunocompromised patients. For patients with high risk of exposure to measles short-term immunoglobulin therapy could be an option. Both for pre- and post-exposure prophylaxis.

Medical malaria prophylaxis

The importance of protection against Plasmodium falciparum malaria infection is the rationale supporting medical prophylaxis and is the same for all travelers. There are no studies dealing with the issue of non-HIV-immunosuppressive drugs and malaria prophylaxis. Immunosuppressed patients should use malaria prophylaxis as healthy people when traveling to areas where it is indicated. Concerning mefloquine there is the possible induction of the cytochrome CYP3A4, which can be of importance for patients using other medication. Depending on the drug used, interactions should be investigated. There are two main and equally effective prophylactic alternatives to mefloquine, namely atovaquone/proguanil and doxycycline. Malaria prophylaxis is especially important to splenectomized individuals given their inability to clear intra-erythrocytic parasites. These patients will become severely ill when infected with malaria [10].

Other medical concerns

Travelers’ diarrhea

Travelers’ diarrhea (TD) is the most common disease acquired by travelers [80,81]. In most healthy travelers, TD is a self-limiting, mild to moderate illness. In immunocompromised travelers, TD may be complicated by bacteremia, metastatic seeding and altered intestinal absorption and metabolism of immunosuppressive medications [82,83]. Therefore, ICTs should be instructed well: in addition to replacing fluid losses antibiotic therapy should be strongly considered. Commonly recommended antibiotic treatments include fluoroquinolones (ciprofloxacin or levofloxacin), azithromycin, or rifaximin [11]. Antibacterial chemoprophylaxis may be beneficial for shorter stays. Chemoprophylactic antimicrobial options also include fluoroquinolones, azithromycin, and rifaximin [84]. Travelers who are prescribed chemoprophylaxis, particularly rifaximin since it is not effective against invasive pathogens such as Shigella spp. and Campylobacter spp., should also carry a fluoroquinolone or azithromycin for self-treatment of breakthrough TD. Although studies on the use of probiotics to prevent TD have had mixed results [85–87] they are generally not recommended in heavily immunocompromised patients.

Other antibiotics to carry along?

Simple skin and soft-tissue infections, urinary tract infections, and vaginal yeast infections are common and can occur at any time in both immunocompetent and immunocompromised travelers. One study showed a higher frequency of skin-infections in immunocompromised travelers [88]. Since in ICTs, mild infections may progress quickly to
more severe disease, individuals with a history of these infections may be instructed to carry antimicrobial agents for empiric self-treatment and should be advised to seek prompt medical support when an infection is suspected. Splenectomized travelers are prone to encapsulated bacterial infections and should be instructed to use antibiotics [10].

**Counseling the relevant specialist**

Prior to travel, we recommend that ICTs consult their specialist before departure. Organ transplant recipients are recommended not to travel during the first year post transplant or during periods of intensified immunosuppression [89]. In a study among patients with IBD, the most common medical issue during travel was exacerbation of their IBD, not a travel-related disease [90]. Since medical care may not be easily accessible or reliable when traveling, it is critical that underlying autoimmune diseases are well controlled at the time of departure. Ideally, the issue of future travel should be discussed already when an individual is diagnosed with a chronic inflammatory disease or other diagnosis with planned immunosuppressive treatment. Vaccination should be considered pre-treatment to obtain an optimal serologic response prior to immunosuppression. Of course, in patients with high disease activity, it might be of importance to treat the patient immediately and the vaccination issue is not a priority. However, in cases with time to plan initiation of immunosuppression, future travel plans and vaccinations should be brought up in a structured way to avoid missed opportunities.

**Information about seeking health-care**

ICTs should be provided a list of resources for identifying high-quality healthcare facilities at their travel destination and should consider purchasing evacuation insurance prior to travel (Table 2). Travelers who have obtained travel health insurance or evacuation insurance often have access to a 24-h hotline to assist identifying sources of healthcare while traveling. Of note: health facilities and personnel associated with consulates and embassies are not available to care for non-staff international travelers. ICTs should carry a sufficient supply of necessary medications, which should be carried in the hand luggage, not in the checked-in luggage. Those requiring needles and syringes should carry a letter of medical necessity from their health care provider.

**Conclusion**

To conclude, pre-travel counseling of the medically immunocompromised patient should be given by a travel-medicine expert in collaboration with the relevant specialist. The activity of the disease, the drugs used and the level of immunosuppression must be related to all the usual pre-travel advice issues such as the itinerary, time of travel, accommodation and activities. The patient should be carefully informed about the relevant risks of disease, whether vaccine-preventable or not, and the importance of preparing insurance. Also it should be stressed that in case of symptoms, immediate contact with health-care providers is of utmost importance, in order to avoid a ‘patient’s-delay’. Inactivated vaccines can generally be prescribed during immunosuppressive therapy, without risk of flare-up of the disease, however the post-vaccination antibody response will often be impaired. Live vaccines are generally contraindicated. There are many diseases one cannot be vaccinated against and ICT may present with more vague symptoms compared to the non-ICT. It is therefore very important that adequate diagnostic work-up is done quickly when an ICT returns home with symptoms. Further studies are warranted that focus on clinical outcome after vaccination of immunocompromised patients to determine whether vaccination with inactivated vaccines leads to reduction of disease and/or prevent worse outcome.

Preventing infectious diseases is pivotal in ICTs as they are more vulnerable to serious complications. Inactivated vaccines should be given when indicated, because even though the vaccination might be less effective in terms of antibody response, it probably does protect against a more severe course of disease in the patient.

**Funding**

None.

**Conflict of interest**

Helena H. Askling: Payments for lecturers; speakers from Abbott Laboratories 02-032011. Participation in travel-medicine meetings; 50% of travel expenses, conference fees and accommodation paid by either Crucell or GlaxoSmithKline Foundation once annually 2007–2011. No personal payment.

Virgil Dalm: None declared.
Acknowledgment

Brian Schwartz and to C.E.F. (Kiki) van Bilsen.

References


The medically immunocompromised traveler


