Travel and the immunocompromised host

Christopher P Conlon

Increasing opportunities for travel and advances in medicine mean that immunocompromised patients may venture to potentially risky parts of the world. This article examines the risks faced by such travellers. Some limitations of standard travel vaccines are discussed and suggestions are made as to how best to advise such travellers.

Medical advances in the past few decades have resulted in significantly increased numbers of survivors for a variety of conditions that were previously fatal. Many such people survive at the cost of an impaired immune system, whether because of immunosuppressive drugs after transplantation or because of cancer chemotherapy. In addition, there are now large numbers of people with human immunodeficiency virus (HIV) infection whose lives have been transformed by better medical care and new antiretroviral drugs. The past two decades have also seen an enormous increase in international travel and it is likely that many of those with immune impairment will want to travel. This article explores the risks faced by different groups of people with immunodeficiency when they travel and outlines how these risks can be managed.

The most important immune defects that affect the sort of advice given to travellers are those affecting T lymphocyte function, as may occur following organ transplantation or with HIV infection. Impaired T cell function will make responses to many vaccines unreliable and may make the use of live vaccines potentially dangerous. However, other conditions, such as splenectomy, may affect polymorph function, B lymphocyte function and other aspects of the humoral immune system. As well as impairing vaccine responses these immune defects can make the traveller more susceptible to endemic infections in other countries.

An important aspect of advising immunocompromised travellers is education about the risks of their particular journey. They should know how these risks should be avoided, with advice about drinking water for example, and they should be instructed about when to seek help. It is useful for the traveller to carry details of any medicines they are taking and to have a letter from their physician outlining their medical problems and containing contact details should the physician's advice be needed. Travellers should take adequate quantities of prescribed medicines, as they may be impossible to obtain at their destination.

HIV INFECTION

HIV infection produces a complex immunodeficiency dominated by an increasing defect in cell-mediated immunity but including defects in phagocytic function and humoral immunity. The defects become more marked as the CD4 lymphocyte count declines and the HIV viral load rises. People with HIV are particularly prone to infection with intracellular pathogens, such as mycobacteria and viruses, but also handle encapsulated bacteria, such as the pneumococcus, poorly. In recent years the inevitable decline of immune function over time has been dramatically altered by the introduction of highly active antiretroviral therapy (HAART), complex treatment regimens involving three or more drugs that have clearly led to better survival for patients with HIV and AIDS.

Numerous data show that the response to vaccinations in people with HIV is suboptimal both in levels of antibodies obtained and durability of the antibody response (Opravil et al, 1991). It is also clear that responses are particularly poor in patients with advanced HIV disease (Kroon et al, 1994). There are also theoretical concerns that the use of live vaccines in patients with HIV may be hazardous and this has been documented with measles vaccine (Centers for Disease Control, 1996) and with bacille Calman–Guérin (BCG). There is also the risk that oral polio may lead to chronic virus excretion and the possibility of

Dr Christopher P Conlon is Consultant Physician in Infectious Diseases, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford OX3 9DU

reversion to wild type strains that can cause poliomyelitis. Although the World Health Organization has recommended yellow fever vaccination in asymptomatic HIV infection, there are no data to support the safety (or efficacy) of this approach. Most physicians caring for people with HIV would be reluctant to give live yellow fever vaccine to patients with CD4 lymphocyte counts below 500/mm^3 and would offer waiver letters for immigration purposes. In general, live vaccines should be avoided in this patient population.

Killed or polysaccharide immunizations are safe and although their efficacy may be reduced in HIV-positive recipients, they should normally be offered to those travelling abroad. Many patients may also be offered pneumococcal vaccine as part of routine HIV care and this may be offered pre-travel. However, there are no efficacy data. Recent studies have shown that the response to hepatitis A vaccines is adequate for short-term protection in those with HIV but the durability of the response is not known (Hess et al, 1995). Patients needing polio vaccination should receive the parenteral (Salk) vaccine and those requiring typhoid should receive the parenteral vaccine, not the live, oral vaccine.

Some studies have shown that immunization of HIV positive individuals can cause a transient rise in HIV viral load. However, these increases are small and short-lived and are probably not clinically significant (Glesby et al, 1996). This phenomenon has also been shown in patients receiving HAART following hepatitis A vaccine and influenza vaccine. In general, patients can be reassured that the risks of non-live vaccines are minimal but should be reminded that their efficacy is uncertain, even in those receiving HAART. However, those on HAART may obtain better responses than untreated patients (Kroon et al, 1998).

There are no data to suggest that those with HIV are at increased risk of malaria, so standard malaria advice should be given. There are no actual or theoretical examples of interactions between antimalarial drugs and the drugs used in HAART. However, proguanil is a folate antagonist and this may theoretically be additive if other drugs, such as co-trimoxazole, are given concurrently. In addition, mefloquine has rare but well-documented neuropsychiatric side-effects and mild cognitive impairment has been documented with HIV infection, so this drug should be used with circumspection in some patients. The author's own practice is to prescribe this drug for 3 or 4 weeks before travel in an attempt to identify any problems before the individual goes to the tropics.

There is no evidence to show that those with HIV infection are more prone to travellers' diarrhoea but those who do get diarrhoea may be severely affected. Infections with salmonella may be more likely to result in bacteraemia. The coccidian parasite cryptosporidium is more common in the tropics and may present special problems as people with HIV often fail to clear this parasite and develop debilitating, chronic diarrhoea. Because of these risks, travellers with HIV should be given specific advice concerning food and water safety.

Finally, some infections are only endemic in certain geographical locations and may be encountered for the first time by an HIV positive traveller. Such infections, for example *Penicillium marneffei* (a fungus endemic in parts of South-East Asia), may be acquired when abroad and subsequently present as a clinical problem some time later at home. Thus, physicians caring for patients with HIV must take a good travel history in any patient presenting with a new clinical problem.

ASPLENIC TRAVELLERS

The spleen has an important role in removing bacteria and parasitized red cells from the circulation. It also produces proteins, such as properdin and tuftsin, that play a role in complement activation and opsonization respectively. Splenectomy has been estimated to carry a lifetime risk of overwhelming sepsis of up to 5%, although the risk is probably highest in the first 2 years after splenectomy and higher in children than in adults (O'Neal and McDonald, 1981). Most of the risk seems to be an increased susceptibility to pneumococcal infection although other encapsulated bacteria, such as *Haemophilus influenzae* and *Neisseria meningitidis*, may pose a risk. Those patients who undergo splenectomy for haematological disease, such as Hodgkin's lymphoma, may be at greater risk of infection than those who have splenectomy following trauma. There is no evidence that splenic tissue left in the peritoneal cavity following surgery provides any useful splenic function. Patients with sickle cell disease and some other haemoglobinopathies are functionally asplenic.

Asplenic individuals respond poorly and unpredictably to polysaccharide vaccines (Jakacki et al, 1980). Antibody levels are lower than in normal hosts and wane more rapidly. Nevertheless, they may provide some protection for the short-term traveller. The author would normally offer pneumococcal and meningococcal immunization to asplenic travellers along with routine travel immunizations. There is no evidence that these vaccines or live vaccines

carry any increased risk in this patient population. Asplenic travellers should also be given a course of an antibiotic, such as amoxycillin, to take if they become ill abroad and should be advised to seek medical help as soon as possible.

Patients without spleens are known to be susceptible to overwhelming infection caused by *Babesia* species, a red cell parasite that occurs along the eastern seaboard of the United States and some parts of northern Europe (Gorenflot et al, 1998). Asplenic travellers to these regions should be advised to avoid tick bites. Theoretically they may also be prone to severe malaria in the tropics but there are, surprisingly, no data to confirm this. Such patients should be given standard antimalarial advice and chemoprophylaxis but should be advised to seek treatment early or to self-treat empirically with oral quinine if febrile in a malaria endemic country. They may want to avoid travelling to areas, such as coastal West or East Africa, where transmission rates of malaria are high.

TRANSPLANT RECIPIENTS

Transplant recipients must take immunosuppressive medication to prevent graft rejection. Drugs such as cyclosporin or tacrolimus have profound effects on T lymphocytes. Azathioprine also affects T cells and impairs neutrophil function. Steroids are also part of the immunosuppressive regimen and increase the risk of infection, primarily through their effect on neutrophils. These patients are at particular risk from intracellular pathogens, such as viruses, mycobacteria and fungi.

Patients with transplants are less likely to respond to immunization than normals and the responses are weaker and less durable (Versluis et al, 1986). There is no evidence to suggest that immunization leads to a greater risk of graft rejection. However, because of the T cell impairment these patients have, there is a risk that the administration of a live vaccine, such as yellow fever or polio, may lead to disease with the vaccine strain. Thus live vaccines should be avoided. Inactivated, parenteral polio vaccine can be used if required and travellers to countries requiring yellow fever vaccination should be provided with a waiver letter after consultation with the embassy of the country to be visited.

Malaria advice for transplant recipients does not need to be different from normal. There are no known interactions between antimalarials and the usual immunosuppressive regimens. Renal transplant recipients need to be reminded of the risks of dehydration in hot climates or if they get travellers' diarrhoea. All transplant recipients probably carry an increased risk of bacteraemia if they have gastroenteritis caused by salmonella or campylobacter. It may be prudent for these patients to carry a quinolone antibiotic, such as ciprofloxacin, for use as empiric treatment for travellers' diarrhoea.

There is an increased frequency of skin cancers in transplant patients and the risk may be increased by exposure to sunlight (Cowen and Billingsley, 1999). Those who travel to the tropics should be given specific advice concerning hats, sunblocks etc.

Patients who have undergone bone marrow transplantation have a more severe immunosuppression than solid organ recipients and are functionally asplenic. Some may have poor neutrophil numbers and function for many months post-transplant. Live vaccines should be avoided and those that do travel should have a standby course of antibiotics in case they develop a fever abroad.

CANCER CHEMOTHERAPY

Some haematological malignancies will lead to immunosuppression in addition to that caused by the therapy to cure them. Solid organ tumours may lead to more subtle immune defects. It is known that these patients respond less well than normal to immunizations following cancer chemotherapy and that the poorest responses are in those with primary haematological malignancies (Gross et al, 1985). It would be expected that the responses to travel immunizations would also be poor. Live vaccines should be avoided until at least 3 months after the end of chemotherapy. Standard malaria advice is appropriate for this patient group.

Patients with chronic lymphocytic leukaemia (CLL) or with myeloma are functionally antibody deficient and will not make a useful response to immunization. Although there is some evidence that intravenous immunoglobulin (IVIG) can protect patients with CLL from infection (Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukaemia, 1988), it is probably more reasonable to provide such patients with some antibiotics to use empirically if they become febrile when abroad or to give them regular prophylactic antibiotics.

STEROID THERAPY

There are increasing numbers of people taking high dose steroids and other immunosuppressive drugs, such as methotrexate and cyclophosphamide, for connective tissue diseases and other immune-mediated disorders.

These patients usually have defects in their cell-mediated immunity and have weaker responses to immunizations (McDonald et al, 1984). They should be managed in the same way as those who have received solid organ transplants. Patients with systemic lupus erythematosus should be counselled about skin photosensitivity.

OTHER CHRONIC MEDICAL CONDITIONS

Patients with chronic renal failure or chronic liver failure are at increased risk of infection and may not respond as well as normal to immunizations. In addition to standard travel immunizations, it may be sensible to offer these people influenza and pneumococcal vaccines to try to reduce the risk of respiratory disease. However, there are no data to show that this approach is effective. Travellers' diarrhoea may lead to severe and serious dehydration in these patients so they should be advised about food and water safety and may be offered antidiarrhoeal agents and empiric antibiotics.

Patients with renal impairment may accumulate proguanil, an antimalarial that is renally excreted (Tattershall et al, 1987). This may lead to folate deficiency. Patients with a creatinine clearance below 50 ml/min should take half the normal proguanil dose after the first 4 weeks of prophylaxis and all patients with renal impairment should take folic acid supplements if taking proguanil. Mefloquine is metabolized in the liver and is safe for those with renal failure but should be avoided in those with liver impairment. Mefloquine is also potentially toxic for those with cardiac rhythm disturbance and should be avoided in these patients.

CONCLUSIONS

There are few absolute contraindications to travel for people who are immunocompromised. However, each case should be assessed and an individual risk–benefit analysis made after discussing the proposed itinerary. The biggest infective risks for any traveller are travellers' diarrhoea and malaria. The immunocompromised traveller should have these risks carefully discussed and should be advised as to how to minimize the risks.

In general, live vaccines should be avoided because of the risk of dissemination of the vaccine strain, with possible clinical disease as a result. Other vaccines are generally safe but physicians and their patients should understand that they may not offer full protection and that revaccination at shorter than normal intervals may be required. All patients should be given letters to carry outlining their medical history and should know how to access help if they become ill abroad. Illnesses presenting after returning from their travels should be investigated in the light of a thorough travel history. **HM**

KEY POINTS

- Immunizations in the immunocompromised patient are generally of lower efficacy and the protection less durable than in normal hosts.
- Live vaccines should generally be avoided in the immunocompromised traveller.
- Standard malaria advice is usually appropriate but expert advice should be sought in renal or hepatic impairment.
- Travellers' diarrhoea represents an increased risk for the immunocompromised, who may benefit from the provision of empiric treatment for this common problem.

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Centers for Disease Control (1996) Measles following measles-mumps-rubella vaccination in a patient with HIV infection. *MMWR* **45:** 603–6

Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia (1988) Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia: a randomized, controlled clinical trial. *N Engl J Med* **319:** 902–7

Cowen EW, Billingsley EM (1999) Awareness of skin cancer by kidney transplant patients. *J Am Acad Dermatol* **40:** 697–701

Glesby MJ, Hoover DR, Farzadegan H, Margolick JB, Saah AJ (1996) The effect of influenza vaccination on human immunodeficiency virus type 1 load: a randomized, double-blind, placebo-controlled study. *J Infect Dis* **174:** 1332–6

Gorenflot A, Moubri K, Precigout E, Carcy B, Schetters TP (1998) Human babesiosis. *Ann Tropical Med Parasitol* **92:** 489–501

Gross PA, Gould LA, Brown AE (1985) Effect of cancer chemotherapy on the immune response to influenza virus vaccine: Review of published studies. *Rev Infect Dis* **7:** 613–18

Hess G, Clemens R, Bienzle U, Schonfeld C, Schunck B, Bock HL (1995) Immunogenicity and safety of an inactivated hepatitis A vaccine in anti- HIV positive and negative homosexual men. *J Med Virology* **46:** 40–2

Jakacki R, Luery N, McVerry P, Lange B (1980) *Haemophilus influenzae* diphtheria protein conjugate immunization after therapy in splenectomized patients with Hodgkin's disease. *Lancet* **ii:** 450–3

Kroon FP, van Dissel JT, de Jong JC, van Furth R (1994) Antibody response to influenza, tetanus and pneumococcal vaccines in HIV seropositive individuals in relation to the number of CD4+ lymphocytes. *AIDS* **8:** 469–76

Kroon FP, Bimmelzwaan GF, Ross MT, Osterhaus AD, Hamaan D, Miedema F, van Dissel JT (1998) Restored humoral immune response to influenza vaccination in HIV-infected adults treated with highly active antiretroviral therapy. *AIDS* **12:** F217–223

McDonald E, Jarrett MP, Schiffman G et al (1984) Persistence of pneumococcal antibodies after immunization in patients with systemic lupus erythematosus. *J Rheumatol* **11:** 306–8

O'Neal BJ, McDonald JC (1981) The risk of sepsis in the asplenic adult. *Ann Surg* **194:** 775–8

Opravil M, Fierz W, Matter L, Blaser J, Luthy R (1991) Poor antibody response after tetanus and pneumococcal vaccination in immunocompromised, HIV-infected patients. *Clin Experimental Immunol* **84:** 185–9

Tattershall JF, Greenwood RN, Baker LRI, Cattel WR (1987) Proguanil poisoning in a hemodialysis patient. *Clin Nephrol* **28:** 104

Versluis DJ, Beyer WEP, Masurel N, Wenting GJ, Weimar W (1986) Impairment of the immune response to influenza vaccination in renal transplant recipients by cyclosporine, but not azathioprine. *Transplantation* **42:** 376–9