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Infectious Complications of Transplant Tourism

Michele I. Morris[1] · Elmi Muller[2]

Abstract

Purpose of Review To outline the impact of transplant tourism on the type and severity of post-transplant infections that may be seem in returning transplant tourists. This review outlines infections that might be expected and provides recommendations on screening tests that may assist in the diagnosis and management of such patients.

Recent Findings Transplant tourists may develop unusual or resistant infections that pose a public health risk in their home country.

Summary The practice of transplant tourism is associated with a significantly increased risk of surgical and infectious complications after transplant. Returning transplant tourists require a thorough evaluation for active and latent infections. Transplant centers must be vigilant for new and emerging pathogens in this population.

Keywords Transplant tourism · Commercial transplant · Donor-derived infection · Pre-transplant screening

Introduction to Transplant Tourism

It is estimated that about 10% of organ transplants in the world occur through transplant tourism [1]. Travel for transplantation is the movement of persons across jurisdictional borders for the purpose of obtaining a transplant. Travel for transplantation becomes "transplant tourism" if it involves trafficking in persons for the purpose of organ removal and/or trafficking in human organs; or if the resources (organs, professionals, and transplant centers) devoted to providing transplants to patients from outside a country undermine the country's ability to provide transplant services for its own population. Many patients who travel for a transplant are also involved in a commercial transaction, buying a kidney in a country where living donors are exploited [2].

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✉ Michele I. Morris
mmorris2@med.miami.edu

Elmi Muller
Elmi.Muller@uct.ac.za

[1] Division of Infectious Diseases, University of Miami Miller School of Medicine, 1120 NW 14th St., Suite 842 (R-21), Miami, FL 33136, USA

[2] Division of General Surgery, Department of Surgery, Groote Schuur Hospital, University of Cape Town, Observatory, Cape Town 7925, South Africa

Geography of Transplant Tourism

Transplant tourism is now illegal in most countries in the world, though historically such procedures have been performed on US residents in at least 35 other countries [3]. Through the efforts of organizations such as the Transplantation Society, the International Society of Nephrology, and the Declaration of Istanbul Group, the geography of transplant tourism is changing as governments and law enforcement agencies become engaged in limiting this practice [4]. Historically, the major destination countries for transplant tourism have included China, India, Pakistan, Iran, the Philippines, Egypt, Turkey, and Iraq [5]. Patients who travel for transplant may be recent immigrants or have a personal connection to the region they travel to for transplant, either through relatives in the country or a shared ethnicity with the region [6, 7].

Increased Infection Risk in Commercial Transplantation Settings

Solid organ transplantation has always been associated with an inherent risk of infection, which may be donor-derived or

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due to post-transplant reactivation or exposure in the setting of immunosuppression. Improvements in post-transplant immunosuppression have now evolved such that post-transplant hospitalization is more frequently associated with infectious complications than acute rejection [8]. Such infectious complications occur even after transplants performed by experienced surgeons working in optimal conditions with strict adherence to sterile technique and infection control. Careful donor screening and judicious use of antimicrobial prophylaxis reduce the risk of post-transplant infection in established centers.

Transplant tourists lack such benefits when they travel outside of their country of residence for the purpose of obtaining a living or deceased donor transplant through unofficial or unrecognized transplant centers. In the case of transplant tourism, donor screening is inconsistent and unstandardized. In general, the living donors used for transplant tourism come from low socio-economic groups and are more likely to have infections such as tuberculosis, viral hepatitis, HIV, malaria, and other bloodborne pathogens. This could be because these donors have limited access to healthcare prior to donation [9], increasing their risk for subclinical or latent infections which are potentially transmissible through organ transplantation and may reactivate in the immunocompromised recipient.

Surgical wound infections are frequently reported and may be caused by unusual organisms that cannot be isolated with routine bacterial culture. Transplant tourists may not be well enough to return to their home country early post-transplant, placing them at increased risk for exposure to infections endemic to the destination country. Such infections may be challenging to diagnose when returning travelers present for medical care in their country of residence, where the diseases may be rare and the signs and symptoms altered by post-transplant immunosuppression. Culture positive organisms may be multidrug resistant or have unusual susceptibilities reflecting the patterns of the foreign transplant center. Essential culture data, if obtained, may not travel with the transplant tourist when they return leading to poorly controlled or recurrent infections that may be an infection control and public health risk.

While it can be challenging to accurately measure the outcomes of transplanted patients who received their organs through a process of transplant tourism, published case reports and case series clearly document a significantly increased risk of infectious complications when compared with legal transplantation performed in the recipient's country of residence. A recent review of the literature noted an infection rate of 45–54% in transplant tourists in comparison with a rate of 5% in non-tourist transplant recipients [5]. One single center in South Korea observed an 85-fold increase in infectious diseases diagnosed in overseas kidney transplant recipients when compared with recipients transplanted at their center [10]. The cause of this dramatic difference in infectious complications is multifactorial, with contributing factors including surgical skills and operating room conditions, inadequate donor screening and selection, and the absence of recipient prophylaxis.

Transplant tourists previously denied transplant in their home country due to comorbidities or psychosocial reasons may also be at increased risk of post-operative infection. The reasons why a person was denied a transplant in his/her home country might not be known to the center performing a commercial transplant and this might result in devastating complications for the transplant recipient.

Etiology of Infectious Complications

Infections can be classified as donor-derived or non-donor derived. The timeline for detection of donor-derived infections could be well after the transplant took place, or it could be detected early after the transplant. It is also possible for solid organ recipients to experience a re-activation of an infection that was experienced before the transplant took place. Furthermore, infections can be community-acquired, hospital-acquired, or opportunistic. Patients who are the victim of transplant tourism activities are at increased risk for donor-derived infections as well as for new community-acquired or hospital-acquired infections in the center where they receive the transplant (Fig. 1).

Lastly, the recipient's risk for reactivation of a previous infection or opportunistic infection might also be increased, depending on the pre-transplant screening and post-transplant prophylaxis prescribed at the transplant center and how long the patient remains at the transplant center where he/she traveled to.

Donor-Derived Infections

Bacterial Infections

Donor-derived bacterial infection is usually suspected in the first 4–6 weeks after the transplant, though mycobacterial infections may become symptomatic later in the first year. When the immunocompromised recipient receives an organ colonized or infected with a transmissible pathogen, there is increased risk to develop systemic symptoms and clinical infection secondary to this event. This risk is increased if the infection is not identified and treated early with appropriate antimicrobials. In the case of transplant tourism, it is especially important to consider the risk of transmitting multidrug-resistant bacterial organisms such as New Delhi metallo-beta-lactamase-producing organisms that may be rare and difficult to eradicate using antibiotics available in the recipient's home country [11]. Infections with these organisms carry a high risk for sepsis and death.

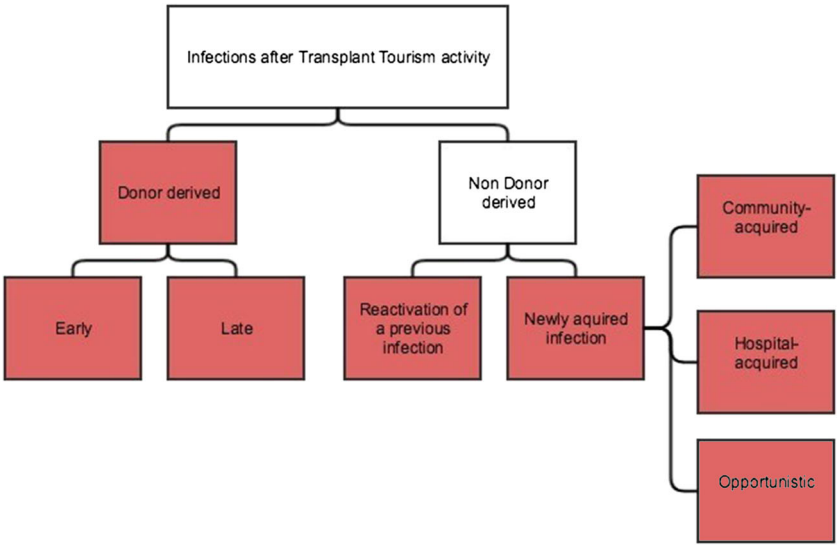

Fig. 1 Increased infectious disease risk after transplant tourism activity. Red blocks represent an increased risk compared with patients who do not travel for a transplant

Transmission of Viral Pathogens

The assessment of the epidemiological risk for certain viral infections in living donors is mandatory in most countries. Chronic viral infections like cytomegalovirus (CMV), human immunodeficiency virus (HIV), and hepatitis B and C (HBV, HCV) are known to be transmissible via the organ allograft. CMV represents the most common infection among recipients of solid organ transplants. Donor CMV screening is the standard of care in established transplant centers and is used to guide the duration of recipient CMV prophylaxis or pre-emptive monitoring post-transplant. CMV infection can present as asymptomatic viral replication or CMV disease, which can range from a mild viral syndrome to tissue-invasive end organ disease [12]. As CMV prophylaxis, diagnostic testing, and treatment are likely to be absent in commercial transplant centers, the risk for this infection is significantly increased [13]. Paid organ donors may not be screened for transmissible viruses such as HIV and hepatitis B and C, greatly increasing the risk of preventable infections with associated morbidity and mortality for organ transplant recipients [14–16].

Arboviral infections may also be transmissible through organ transplantation. In the literature, a 4–6-month donor deferral had been recommended for potential donors with suspected or confirmed Zika viral infection [17, 18]. Donors with recent Chikungunya infection should be deferred for at least 30 days [18]. Commercial transplant centers are often located in countries with a high incidence of rabies, yet living donor evaluations may be minimal or non-existent and exposure risk for such transmissible infections is unknown. Transplant tourists are therefore at risk of infection with a diverse group of viral pathogens, either because of insufficient screening or failure of the transplant center to defer the donor operation.

Transmission of Other Latent Donor Infections

Living donors may harbor other latent infections such as *Histoplasma*, *Coccidioides immitis*, *Mycobacterium tuberculosis*, and strongyloidiasis based on their previous epidemiologic exposures [19]. The increased risk for patients who travel for transplant is the result of absent or poor screening policies in centers who provide commercial transplantation. In endemic areas, all donors should be screened for tuberculosis by purified protein derivative or interferon-γ release assay, but this is not likely to happen when a commercial transplant takes place [20]. Tuberculosis infection in transplant recipients is a challenging condition to treat with many drug interactions in an immunocompromised patient [21]. The patient who travels for a transplant puts him/herself at significant increased risk for infection when deciding to undergo this procedure [6].

Newly Acquired Infections in the Recipient

Bacterial Infections

Early post-operative bacterial wound infections are likely attributable to poor operating room conditions and lack of sanitation as well as the technical expertise of surgeons employed in illegal transplant operations.

Bacterial pathogens are the most frequent cause of pneumonia after transplantation. Early after transplantation, recipients are at higher risk for nosocomial infection. The most commonly encountered pathogens during this period are gram-negative bacilli (*Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*), but gram-positive cocci such as *Staphylococcus aureus* or *Streptococcus pneumoniae* and even opportunistic pathogens like *Legionella pneumophila*

and non-tuberculous mycobacteria may cause infection. Little is known about the specific infecting organisms in commercial transplant centers as information is obtained from the cultures of returning travelers who often have received empiric antimicrobial therapy prior to presenting for care in their home country.

Patients with bacterial infections have an increased risk to develop systemic symptoms, including sepsis and septic shock. Urinary tract and pulmonary infections are common and prognosis in immunocompromised patients is similar to non-immunosuppressed patients if treated early and correctly but can be dismal in a commercial transplant setting where the diagnosis might either be missed, or treatment might be inadequate.

Clinical diagnosis can be more difficult in immunocompromised patients as they are usually slower to respond to pathogens by signs of inflammation and fever. Radiological investigation including CT scans, nuclear medicine studies, and MRI might be useful tools for the clinical decision maker. These tests are unlikely to be available in commercial transplant settings.

Fungal Infections

Commercial transplant recipients are also at increased risk for invasive fungal infections (IFIs). The surgical site and organ allograft are frequently involved, though many of these cases progress to disseminated disease by the time they are diagnosed in the recipient's home country. This unusual presentation often early post-transplant may reflect the lack of sterile conditions at the time of organ procurement, transport, and implantation [22]. A 2-year retrospective review of 198 renal transplant recipients in Oman reported that 8% of returning transplant tourists (13/162) were found to have IFIs, most commonly *Aspergillus* and *Mucorales* species, compared with no IFIs in patients transplanted in Oman [23]. Outcomes in the commercial transplant recipients with IFI were poor, with death due to septic shock in 23% and nephrectomy required in 10 of 13 infected cases for allograft infarction and wound infection. Correct diagnosis usually requires histopathology and/or culture. Management often requires a multidisciplinary team approach with combined antifungal and surgical therapies.

Parasitic Infections

Parasitic infections like malaria are endemic in regions of the world that are known to be sites for commercial transplantation. Clinical diagnosis can be more difficult in immunocompromised patients as they may manifest few signs and symptoms of infection. Clinicians who manage returning transplant tourists may not always recognize infections with *Trypasosoma*, *Strongyloides*, *Schistosoma*, *Babesia*, and *Plasmodium* species that can be seen in this population, resulting in a significantly higher risk for complications [24].

Viral Infections

Community-acquired respiratory virus infections like influenza are among the most common serious infections acquired via exposure during travel [25]. Vaccine immunogenicity for influenza in immunocompromised patients is low. The incidence of respiratory failure due to respiratory syncytial virus, adenovirus, and parainfluenza is higher in immunocompromised patients. Transplant travelers are at risk for vaccine preventable infections such as measles and varicella if not appropriately immunized pre-transplant. Recommended pre-travel counseling and immunization are rare among immunocompromised travelers, and unlikely to occur prior to travel in patients seeking organ transplantation overseas [26]. If a patient does disclose their plans to travel for transplant, appropriate pre-transplant vaccinations should be offered if the patient cannot be convinced to re-consider due to the associated morbidity and mortality risks [27].

Recommended Minimum Screening in All Patients Who Return After Receiving a Transplant Abroad

Regardless of the health status of the transplant recipient at the time of presentation in their home country, a minimum set of basic screening tests are recommended. Additional testing should be performed if patients have evidence of a post-operative wound infection or if they have signs or symptoms of infection including fever. Testing recommendations may be modified based on the country of origin of the organ donor, if known, as well as the location of the transplant procedure. Published guidelines may assist in identifying the likely infecting pathogens based on the geographic exposure of the returning transplant tourist [28].

All patients should undergo a detailed history and physical examination, with careful review of all medical information they can provide regarding their transplant care. Information they share regarding the health status of their organ donor should be reviewed but may not be accurate. Standardized post-transplant screening should proceed regardless of any donor test results presented. It is important to remember that commercial transplant donors are generally members of marginalized groups; hence, their overall health may not reflect the epidemiology of their country of origin. In addition, the donor's country of birth may not be the transplant center location, and the complex migration patterns and exposure risks of disenfranchised organ donors mandate consideration for

all potentially transmissible pathogens. Such donors are more likely to have had previous exposure to tuberculosis, HIV, syphilis, hepatitis viruses, and arthropod-borne infections then more affluent residents of the region.

Minimum Screening Tests That Should Be Performed at First Presentation of the Recipient in Their Home Country

i. Serology for HIV, hepatitis B, and hepatitis C (repeat within 28 days of donation in living donors)
ii. CMV IgG
iii. Epstein-Barr virus IgG
iv. HIV-1/2 antibody or 4th generation HIV antigen/antibody assay
v. Hepatitis B surface antigen and core antibody; consider NAT
vi. Hepatitis C NAT
vii. Syphilis screening
viii. Toxoplasma IgG
ix. Blood, urine, and sputum cultures as clinically indicated

Recommended Additional Screening

i. Tuberculosis screening (purified protein derivative or interferon-γ release assay)
ii. Testing based on geographic location of transplant
    a. *Strongyloides* antibody
    b. *Trypanosoma cruzi* antibody
    c. *Histoplasma* antibody
    d. *Blastomyces* antibody
    e. *Coccidioides immitis* antibody
    f. Hepatitis E antibody
iii. Testing based on epidemiologic exposures
    a. *Brucella* antibody
    b. *Cryptococcus* antigen
    c. West Nile virus antibody
    d. Arboviral serology or PCR if available
    e. Molecular diagnostic testing for malaria, *T. cruzi*, and other parasites as indicated

Serologic tests perform poorly in transplant recipients with deficient antibody response early post-transplant, so close clinical monitoring and molecular diagnostics may be required to diagnose unusual infections. Early involvement of referral laboratories and expert resources such as the US Centers for Disease Control is recommended when appropriate.

Timing of Presentation Post-transplant

The timing of the initial presentation of returning transplant tourists post-operatively varies greatly depending on the policy of the recipient's home country and their state of health post-transplant. Some patients may be delayed in returning due to early post-transplant medical complications that limit their ability to travel or require a prolonged hospital stay or readmission abroad. Others may present very early after surgery due to post-operative complications that become apparent during travel or upon arrival in their home country. Legal requirements for the reporting of suspected transplant tourism vary, but in most cases, a transition of care will ultimately occur and medical professionals local to the recipient's region will assume the responsibility for post-transplant management. Medical records from the transplant procedure should be obtained and reviewed, but may be incomplete or inaccurate.

Public Health Impact of Transplant Tourism

The returning transplant tourist frequently presents with significant medical and surgical complications, disproportionately burdening their home country's medical system when compared with patients transplanted legally [29]. This may limit the country's ability to safely provide transplant care to their own residents, particularly when transplant tourists return with unusual and transmissible infectious diseases. It is known that medical tourism contributes to the worldwide spread of multidrug-resistant organisms [30]. Potentially lethal pathogens such as New Delhi metallo-beta-lactamase-1-producing gram-negative bacteria and *Candida auris* may be brought into the healthcare system in the body of a returning transplant tourist. Outbreaks of infection may be initiated by the introduction of infection during the initial medical care of patients transplanted abroad [31]. Rigorous infection control procedures should be implemented when such patients are evaluated, though unfortunately the history of commercial transplant may not be apparent at the time of patient presentation.

Concluding Recommendations

Transplant outcomes in returning transplant tourists are much poorer than those transplanted in their home country, due primarily to infectious complications and an increased risk of acute rejection [10]. Overseas transplant recipients require expensive medical care and may spread infection when they return to their home country. Guidelines for the management of patients returning after transplant abroad exist, but an organized global response by the international medical and law enforcement community is needed to

prevent this dangerous illegal practice [4, 32]. Transplant professionals have a responsibility to educate their patients about the risks of transplant tourism. In addition, clinicians who care for transplant recipients must maintain their vigilance in order to recognize the pattern of unusual post-transplant complications that may identify such patients as returning transplant tourists.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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