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Review Article

Post-Transplants Infections: A Brief Review

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Abstract

Organs transplant had carried a great hope to patients with end organs damage; nevertheless, with the great advancement in the therapeutics and with the institution of new and strong immunosuppressive medications, the acute rejection rate had declined significantly over past decades particularly at the first-year post-transplant. But the consumption of these potent immunosuppressive agents had led to appearances of several opportunistic infections such as cytomegalovirus, Epstein-Barr virus (EBV), BK, parasitic and fungal infections which had emerged extensively. Moreover, the rate of new cancers had increased extensively, owed to the oncogenic influences of these agents.

Keywords: BK; Chagas Disease; CMV; EBV; Fungal Infections; HBV; HCV; Transplant Recipients; Tuberculosis

General Background

Infection is the principal cause of morbidity and mortality in transplant populace. It is a great challenge to identify post-transplant infection at early stage, owed to suppressed immunity level which makes the characteristic signs and symptoms of infection such as fever, rigors and others are unusual till advanced disease; hence an early diagnosis with specific institution of antimicrobial therapy is crucial. Moreover, utilization of special tests including certain invasive diagnostic techniques is often mandatory to reach an accurate diagnosis in prompt timing [1,2].

Risk of Infection

Clinicians have to balance between the risks of infection owed to immunosuppressant medication versus the risk for acute rejection. Unfortunately, there is no concurrent single assay that can predict patient susceptibility to infection, hence the use of prophylactic therapy is based on patient's history, lab results and the susceptibility of each individual to get the infection. Epidemiological Exposure: could categorize in to 4 groups: donors-related, recipients-related, nosocomial, and community-acquired infections [1].

Donor-related Infections: certain infections such as tuberculosis, CMV, and *T. cruzi* can remained dormant inside the donor cells and transmitted thereafter to the recipient, hence pre-transplant organs screening for such infections is essential. Moreover, bacteraemia or viremia can be easily missed at the time of organs procurement leading to invasive recipient's dissemination. Additionally, more unusual infections have been transmitted from the deceased donors and were reported, including rabies, HIV, choriomeningitis virus and West Nile viral infection. The prognosis of transplant recipients with such disseminated infections are poor owed to depressed immunity level, leading to rapid disease progression, permanent neurological sequels and death. Unfortunately, screen-

ing of transplanted organs for such infection is constrained by the current techniques and by the brief time frame amid which organs from deceased donors can be utilized. Conversely and for special circumstances, organs from donors with certain determined pathogens might be accepted for particular recipients with well explained situation and recipient agreement, depending on the insistence of the transplant besides accessibility of related treatments. For instances; organs from hepatitis B virus infected donors with positive anti-HB core Ag are presently transplanted to few patients who had received the vaccines or were infected earlier with the virus, providing availability of HBV antiviral therapy. Utilization of HCV infected organ is debatable and should be held in reserve (if needed) for infected HCV individuals. It is advisable to evade using organs from infected deceased donors with encephalitis, rash, unexplained fever or untreated infections [1,2].

Recipient-related Infections: The impacts of donor-related or recipient-related infections such as Tuberculosis are strongly seen in the endemic regions. Any acute and current infective process affecting potential candidates must be treated prior to transplant surgery to avoid any disseminated infection post-transplant owed to suppressed immunity [1,2].

Nosocomial Infection: Patients may get nosocomial, antimicrobial resistant pathogens while they are waiting to get transplanted. Such pathogens as *MRSA, vancomycin res. enterococcus, Clostridium difficile, azole-resistant candida, aspergillus,* can grow aggressively at post-transplant period causing different clinical profiles, ranging from mild infection of the wound, and catheters to severe fulminant infection such as severe pneumonia or sepsis.

Community acquired Infections: simple and undetected infections in the normal individuals may cause catastrophic infection in the transplant recipients, such as *nocardia, aspergillus, C. neoformans*, and respiratory viral infection [1,3].

Immunosuppression Net Status

Immunosuppression net status denotes all causes which add to patient's risk of having infections. Main risk factors include type, dosage and overall period of immunosuppression. Immunosuppressant's levels are the measurement frequently practiced to monitor therapy with an aim to balance between the risk of graft rejection and side effects of medications. However, such measurements are considered as old and crude methods which need to be replaced ultimately with sensitive assays to allow patient individualization and probably minimization of immunosuppression [1].

Timeline of common infectious pathogens in transplant recipients

Infective pathogens can frequently be distinguished on the premise of the time interim from transplantation to clinical presentation. For instance, overwhelmed infections at the first month post-transplantation usually related to surgical procedures, including urinary tract infection (mainly with E. coli), wound and vascular line infection and pneumonia, while the following 1-6 months have excessive risk of viral and opportunistic diseases, related to the increased immunosuppressive dosages. Thereafter the risk of infection reduces significantly with subsequent reduction of immunosuppressant's medications. Nonetheless, transplant recipients still at persistent risk of community acquired infections in addition to chronic viral infections such as HCV and CMV as well as opportunistic pathogens. Severe infections with unusual organisms suggests over immunosuppression or exposure, particularly following acute rejection or escalation of immunosuppressant's therapy [1-5] (Figure 1).

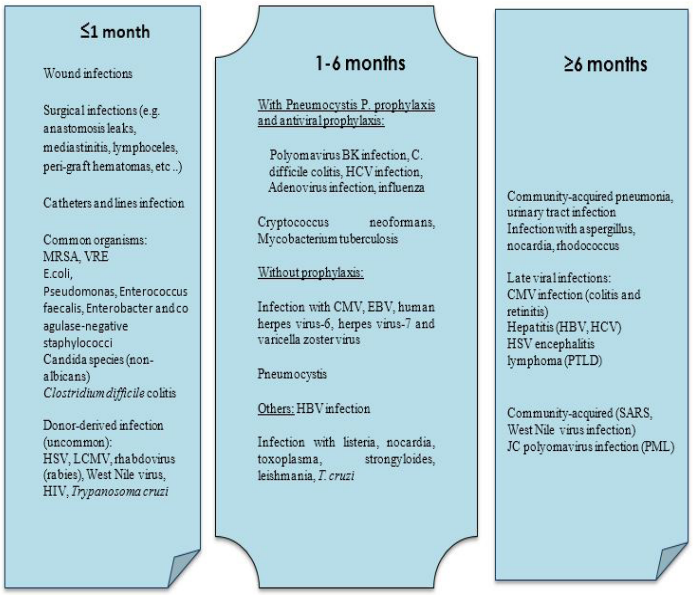

Figure 1: Chronological association between post-transplant period and common infectious pathogens.

Common Infections in Transplant recipients

Prompt diagnosis is crucial in immunocompromised patients, often requires invasive diagnostic methods. The most diagnosed infectious pathogens are bacteria (in 45.9%), viruses (40.6%), fungi (12.5%), and protozoa (1%). The most well-known viruses are CMV in 31.5%, HSV 23.4%, and varicella-zoster virus in 23.4% (2,6).

Post-Transplant Surgical Infections

Incisional wound infections is not uncommon, and the most often isolated pathogens are *E.coli, Pseudomonas, Enterococcus faecalis, Enterobacter, staphylococcus aureus* and *coagulase-negative staphylococci* . Risk factors were diabetes and sirolimus therapy. Surgical wound infection requires early debridement combined with antibiotics, organ involvement or adjacent cavities need to be excluded [6]. Moreover, kidney and pancreatic recipients might have lymphoceles, peri-graft hematomas and

urinary fistula complicating surgery. Liver recipients might have complicated intra-abdominal infections such as intra-abdominal abscesses, hepatic abscess, biliary infections (leakage, stricture), hepatic artery thrombosis, internal bleedings and peritonitis, these infections mainly caused with bacterial organisms (in 50% of the cases) and can leads to significant morbidity and mortality [5,7]. Heart recipients are at risk of acquiring mediastinitis and infections at aortic suture lines, resulting in mycotic aneurysms, while lung recipients might develop disturbance at bronchial anastomosis. The frequently elaborated pathogens are staphylococcus and gram-negative bacteria's. Treatment involves wound debridement and antimicrobial therapy for 3 to 6 weeks [5].

Gastrointestinal Infections

Gastrointestinal complaints are frequently reported in transplant recipients (in 51 to 68%) ranging from mild to severe, 15% of those might necessitate radiological, endoscopic examination or even surgical exploration [8,9]. Abdominal pain is commonly reported complaint in 20-61% of the cases, followed by dyspepsia (52%), diarrhoea (40-51%) and nausea (34%). CMV and *C. difficile* are the frequently recognized organisms in the pathogenesis of infectious post-transplant diarrhoea. However, if diarrhoea persisted despite excluding those, then more extensive and sophisticated approaches ought to be considered. There are several reported cases with unusual pathogens such as *rotaviruses, enteroviruses, adenoviruses, EBV, Cryptosporidium* and others. Other differential diagnoses of post-transplant diarrhoea consist of intestinal ischemia, diverticulitis, malignancy, inflammatory bowel disease (whether de-novo or a flare up of pre-existing disease) and PTLD [5,10,11].

C. Difficile Associated Diarrhoea (CDAD) can be suspected in transplant recipients with frequent hospital admissions, prolonged antibiotics courses and with intense immunosuppression. Clinically it might present with severe diarrhoea (absence of diarrhoea carries poor prognosis) and leucocytosis that can be the only diagnostic clue. Rarely patients can have acute abdomen or inflammatory pseudotumor. Diagnosis is through analysis of fresh stool samples for the presence of *C. difficile* toxins. Additionally, the organisms can be proven on rectal swabs. Management is by cessation of the antibiotic therapy when possible. Patients with severe diarrhoea can be treated with oral vancomycin with or without IV metronidazole. 10-25% of the CDAD responders might have a relapse (within 3 to10 days following discontinuation of therapy) and they do respond to another systemic antibiotic course [10-15]. Alternatively, immunosuppressant's such as MMF, cyclosporine, tacrolimus and sirolimus are altogether known to cause diarrhoea. A systematic approach ought to be followed before deciding any dose reduction [5,16]. Regardless the cause, diarrhoea is related to inferior renal allograft outcomes and can escalate the risk of graft loss and patient death [16].

Urinary Tract Infections are the most well-known infections necessitating hospitalization in renal allograft recipients, followed by pneumonias, postoperative infections and sepsis. Female recipients are at high risk of infection; other risk factors consist of deceased donors, recurrent Pre-transplant history of UTI, ureteric stents, prolonged catheterization, kidney-pancreas transplant with bladder drainage and intense immunosuppressive status [3,5,17]. Escherichia coli appear to be the commonest culprit in such cases, however, unusual pathogens like *Mycoplasma*, *tuberculosis,* BK and JC viruses should be kept in mind [5]. All UTIs involving renal allograft recipients are considered complicated, hence a standard antibiotic therapy should be given for 7–14 days. However, there is no international agreement for the management of asymptomatic bacteriuria, though randomized prospective trials suggested that treatment more than a year does not prevent symptoms to appear [18]. The current standard post-transplant prophylaxis consists of trimethoprim-sulfamethoxazole for 6-12 months post transplantation. Patients allergic to trimethoprim-sulfamethoxazole should be considered for an alternative prophylaxis [3].

Managing fungal UTIs is a complicated issue in the transplant recipients and further attention should be given to drug interactions between immunosuppressive medications and antifungal therapy particularly CNI and mTOR inhibitors. Furthermore, radiological imaging should be done to exclude the presence of fungus balls, abscesses, and other urological anomalies that may demand surgical intervention or prolonged therapy [3,5].

CNS Infection in transplanted individual is considered as an acute medical crisis. There are wide ranges of causative pathogens, including *HSV, JC virus, listeria and C. neoformans*. Once suspected, treatment should have started empirically as early as possible, while waiting other results, like blood culture, CSF analysis (including HSV-PCR and *Cryptococcus*-antigen) and imaging studies. Nevertheless, non-infections CNS causes needs to be considered, like lymphoma and calcineurin inhibitors toxicity [1].

Cytomegalovirus Infection

Cytomegalovirus can exhibit either a direct intracellular affect in the transplant recipients, or might prompt an invasive disease. Invasive disease commonly emerges amid first year following completing of prophylactic therapy and shown clinically as neutropenia, thrombocytopenia, fever, lymphadenopathy, chorioretinitis, meningoencephalitis, pneumonitis, gastro-intestinal signs (gastritis, ulcers, colitis and bleeding), hepatitis and pancreatitis. CMV can occur in the transplanted recipients as a consequence of primary infection, re-activation, or viral super-infection. Primary infection or seroconversion, are the severe ones and occurs when sero-negative transplant recipients get the organ from sero-positive donor. Quantitative analytic tests are crucial in diagnosing and managing CMV disease. It consists of molecular-based analyses (PCR) and antigen detection. Negative tests do not exclude the

diagnosis of active CMV infection. Presence of ulcers in the endoscopy is highly suggestive of the disease; in such cases PCR is an accurate technique for detection of CMV in the gastrointestinal mucosa even if PCR is negative in the blood [1,3,5,19].

Both pre-emptive treatment and antiviral prophylaxis reduces the risks of acquiring cytomegalovirus disease. Furthermore, prophylactic therapy with antiviral can avoid different viral infection like HSV, EBV, human herpes virus-6, herpes virus-7 and varicella zoster virus and reduces the complications of HCV and PTLD [20,21]. Majority of centers offer prophylactic therapy intended for the initial 3 to 6months post-transplant, with acyclovir, valacyclovir, ganciclovir, valganciclovir and rarely, CMV hyperimmunoglobulin. Heart and lung transplants will require prolong prophylaxis course. Nevertheless, recipients taking valganciclovir or ganciclovir are at risks of myelosuppression, hence close monitoring of blood counts is required. Ganciclovir resistance is rare, but it might occur secondary to CMV UL54/or UL97 genes mutation. Cytomegalovirus syndrome and invasive disease warrant therapy with intravenous ganciclovir, though recent data analysis with the use of oral valganciclovir therapy is promising [1,3,22].

Epstein–Barr Virus is responsible mainly for PTLD, a specific group of lymphoproliferative diseases, with high mortality rate of 40 to 60%, affecting mostly recipients with SOT [23]. Risks for PTLD development consist of acquiring graft from infected EBV-seropositive donor in to EBV-seronegative recipient, other risks include CMV co-infection, Anti-lymphocyte antiserum and allograft rejection [23,24]. Quantifiable viral-load assay, antigen tests and histologic examination through specific EBV-RNA stains can all assist in identification and management of PTLD disease [24]. In the polyclonal type, reducing immunosuppressive medications alone might prompt disease reversion; however, it may subject individuals to rejection. An aggressive illness necessitates alternate managements, including anti-CD20 antibodies, chemotherapy, surgery and radiations (for CNS disease). T-cell immunotherapy are still under on-going trials and sirolimus emerges is an option against PTLD; however, additional data are required to confirm its role as a protective agent [24-26].

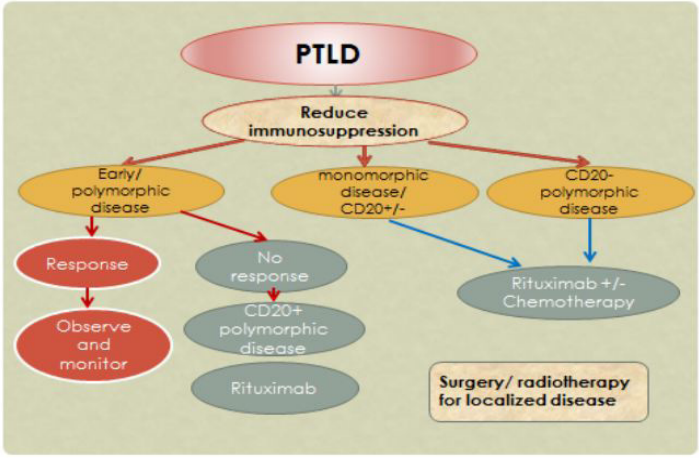

Figure 2: Diagrammatic illustration for PTLD management.

BK-Polyoma viruses BK virus has been linked to nephropathy and ureteral strictures in transplant recipients. Diagnosis depends on identification of viral nucleic acids in serum and urine. Unfortunately, there is no efficient antiviral treatment for polyoma-viruses; however, diminishment in immunosuppressive medications might help in management. Medications such cidofovir, leflunomide and intravenous immune globulin are used widely; however, none of these drugs have been approved to be effective in the treatment of polyomaviruses [1,3,27,28].

JC-Polyoma virus has been linked to progressive-multifocal leuko-encephalopathy. Similar to BK virus, has no effective eradicative therapy (1,3).

Varicella zoster infection

VZV has a prevalence of 3-10% in transplant populations and approximate mortality rate of 34% in patients with disseminated disease [28,29]. It can manifest either as a primary disease (chickenpox or varicella) demonstrated clinically as vesicular eruptions on the head, trunk or extremities, or as a herpes zoster (shingles), manifested as a painful unilateral vesicular rash taking a characteristic dermatomal shape, that might get disseminated

leading to fatal outcomes. Time of onset is between 2 to 92 months post-solid organs transplant. Male gender, intensity of immunosuppression, escalation of immunosuppressant's following acute rejection episode, MMF therapy, higher CNI level are altogether viewed as a risk factors for VZV infection [28,29]. Vaccination with live attenuated varicella vaccine ought to be prescribed to all sero-negative patients before transplantation, however, VZV vaccine ought to be avoided if transplant is expected within 4-6 weeks. Ganciclovir as CMV prophylaxis can protect against infection with VZV/HSV in the early post-transplant period [28,29].

Infected patients should start oral acyclovir as earliest as possible to avert viral dissemination in addition to reduction in MMF dosage. If A VZV-seronegative transplant patient had exposed to an infected individual with varicella, then he/she must receive varicella immune globulin within 96 hrs. from contact (if accessible). If VZIG is not accessible, or the patient presented after 96 hours, then acyclovir might be used as prophylactic therapy [28,29].

HCV Infection

HCV replication might increase substantially in the immediate post-transplant period regardless to virus genotypes. Post-transplant HCV might manifest clinically as trivial rises of serum transaminases that recover with lessening of immunosuppression. Approximately 20%–50% of affected individuals might have normal liver enzymes with unusual histological pictures; therefore, protocol liver biopsies every 6 to 12 months might be necessary for post-transplant assessment. Liver cirrhosis was estimated to be 5%-21% at 3 to7 years post-transplant. Acquirement of HCV disease post-transplantation has poor prognosis with rapidly progressive course [3,28,30]. Glomerular lesions depicted in renal transplant individuals incorporate cryoglobulinemia, non-cryoglobulinaemic membranoproliferative GN and membranous GN. HCV infected recipients ought to be examined for proteinuria at regular intervals, and those detected to have new onset proteinuria must have kidney biopsy (3,30). Potential transplant candidate with HCV infection should be treated prior to transplantation based on liver histology. Interferon has variable successful rate (ranges from 20% to 90%) according to HCV genomes. Ribavirin should be avoided in advance kidney disease since it may induce acute haemolytic anaemia, while there is lacking evidence on the use of protease inhibitors in renal failure patients [3,30].

Post transplantation, HCV infected recipients must be managed in consensus with herpetologist or infectious disease specialists. Interferon therapy is not an option in transplant recipients since it increases the risk of allograft rejection [1,2,28]. The ideal immunosuppressant's in HCV-infected kidney transplants is indefinite. Induction with OKT3 and anti-thymocyte globulin has been linked to progressive liver disease. Tacrolimus is associated with higher incidence of post-transplant diabetes mellitus as compared to cyclosporine; additionally, these patients are prone to glomerulopathy with significant proteinuria. Oppositely, sirolimus were found to reduce liver fibrosis in liver transplant recipients [31], though this effect is not prominent in renal transplant recipients with HCV.

HBV Infection

Chronic HBV Patients with cleared viremia can be considered for transplant. However, they require close monitoring post-transplantation. Unfortunately, detection of HBV liver disease post-transplant can be challenging since liver enzymes levels may not precisely reflect the disease status. Sequential monitoring of HBV-DNA on periodic intervals (3 to 6 months) is necessary and raised virus loads suggest imperviousness to treatment [3,28]. Seven therapeutic selections are available and approved for management of chronic hepatitis B: IFNa, pegylated IFN, lamivudine, entecavir, telbivudine, tenofovir, and adefovir [3,28]. IFN is not recommended in transplant recipient, and patients on Lamivudine can develop resistance to therapy, therefore KDIGO guidelines suggests using tenofovir or entecavir which have a lower rate to drug resistance compared to lamivudine.

On the premise of current information, it is suggested that antiviral therapy should started at the time of transplants, regardless of HBV-DNA level, to overturn virus replication and avert liver fibrosis [3]. Replication of the virus has been associated with the net status of immunosuppression and not to any individual drugs; therefore, it is advisable to maintain HBV allograft recipients on the lowest possible immunosuppressive dosage. HBsAg-positive renal allograft receivers ought to be screened for hepatocellular carcinoma with annual hepatic sonography besides a-fetoprotein level measurements [3,28].

HIV Infection

HIV was viewed in the past as a contraindication to transplantation; however, latest evidences propose that selected HIV candidates can have successful transplantation with acceptable survival rates, if they met the following criteria's: the infection is well controlled with imperceptible viral loads and CD4 counts > 200 cells/ml, and in the absence of active infections or malignancies [3,28]. It is desirable (if possible) to evade using protease inhibitors, for their known interactions with immunosuppressive drugs. However, the decision of anti-retroviral drug ought to reflect HIV sensitivity results and to be agreed upon with the patient's HIV physicians [3,28]. Monoclonal anti-IL2 receptor antibodies, for example daclizumab /basiliximab, have been appeared to raise the CD4 levels, hence can be used as induction agents. Mycophenolate was found to reduce HIV replication in vitro while tacrolimus is desirable over cyclosporine as for reducing the rejection risk. HIV renal transplant patients should receive lifelong Pneumocystis prophylaxis with trimethoprim-sulfamethoxazole [3,28].

Human Herpes-virus 6, Human Herpes-virus 7

HHV-6 and HHV-7 belongs to Beta-herpesvirinae subfam-

ily, genus Roseolovirus. Viruses can remain dormant in the host tissues following primary infection, and get reactivated in the presence of immunosuppressive therapy. Clinically may manifests with fever, rash, myelosuppression, hepatitis, pneumonitis and encephalitis. Moreover, HHV-7 may act as a co-factor for HHV-6 and CMV reactivation, and both HHV-6 and HHV-7 may act as co-factors for the pathogenesis of CMV disease and acute rejection [3,28]. Viruses can be detected through qualitative and quantitative molecular tests, by tissue immunohistochemistry, and/or blood mononuclear cell culture. Treatment includes reduction in immunosuppressive dosage besides ganciclovir therapy. Cidofovir and foscarnet have additionally been used [3,28].

Human herpes-virus 8 (HHV 8)

belongs to Gammaherpesvirinae subfamily, and has been linked to Kaposi's Sarcoma, primary effusive lymphoma, and Multicentric Castleman's Disease (lymphoproliferative disorder). Treatment for Kaposi's Sarcoma incorporates immunosuppression reduction and cytotoxic chemotherapy. Sirolimus can be used in such cases owed to its antineoplastic characteristics besides being antirejection therapy [3,28].

Pneumonitis and Pneumocystis infection

it is less seen currently owing to the use of pneumocystis P. prophylaxis. Can manifests clinically with dyspnea, severe hypoxemia, and cough that develop despite absence of clinical or radiological findings. There is no specific characteristic radiological pattern in the immunocompromised patients. Computed tomography is valuable in defining the extent of the disease and also bronchoscopic examination for microbiological testing. Non-infectious cause's needs to be considered in the differential diagnosis such as sirolimus induced pneumonitis [1,5].

Mycobacterium tuberculosis

Tuberculosis incidence is variable amongst kidney allograft recipients, contingent upon the endemicity of the infection in their nations, while it ranges 0.5% in North America it can scopes to 15% in India and Pakistan with a mortality of 6.1% and allograft survival rate of 97% at 1year. Tuberculosis usually occurs at the initial 9 months post-transplant (0.5 to 13 months). Risk factors for early tuberculosis include non-renal allograft, acute rejection, OKT3/anti-T cell antibodies use and past exposure to M. tuberculosis [3,32,33]. TB in immune-suppressed patients has different clinical profile than in the normal populace. Extra-pulmonary involvement and disseminated infection appears more prominent in transplant population affecting nearly one third of the cases compared to 15% of the normal individuals [3,5,32,33].

Tuberculosis in transplant recipients is suspected on clinical back ground. Neither tuberculin skin assessment nor IFN-g release tests are appropriate for the determination of current infection. Occasionally, biopsy might be necessary for microbiological analysis. Management of active tuberculosis in transplant patients must consist of four-drug regime; isoniazid, rifampin, pyrazinamide, and ethambutol, all for the initial 2 months, followed with rifampin and isoniazid alone for the next four months. Extrapulmonary involvements (bone, joint and CNS infection) may necessitate a longer period [3,5,32,33]. Rifampin can activates the CYP3A4 pathway; therefore, it reduces CNI and mTOR inhibitors levels significantly, and aggravates rejection risk, hence frequent monitoring of dugs levels is recommended [35]. Rifampin might be replaced in some patients with fluoroquinolones, however, it is necessary to do susceptibility analysis on all segregated mycobacterium bacilli to confirm the suitability of the chosen therapy. Role of Isoniazid as prophylactic therapy in transplant recipients is still arguable [34,35].

Chagas Disease

Chagas disease is a striking concern in North, Central and South America with 7.7 million people being tainted in 18 countries. People migrated from endemic zones had prompted significant increment in the number of infected populace in non-endemic places, which unfortunately had deferred the diagnosis and identification of Chagas disease due to lack of awareness and inexperience of health care providers in the required management resulting in appearance of fatal cases of Chagas disease post cardiac transplantation [36]. Heart is the essential reservoir for *T.cruzi* pathogens in infected patients; therefore, cardiac transplant from infected donors will prompt transmission of the disease and may cause recipient's death, therefore utilization of cardiac allografts from infected seropositive donors is not advisable. Alternatively, non-cardiac allografts (such as liver and kidneys) might be considered and have reasonable outcomes, however, *T.cruzi*-PCR monitoring should be done periodically and can detect disease re-activation before appearance of signs and symptoms [36].

Chagas cardiomyopathy is no more considered as relative contraindication to cardiac transplant, and grafts survivals is not inferior to cardiac-transplantation done for other reasons. Benznidazole is the treatment of choice for Chaga disease, other available agent is nifurtimox, though both does not cure chronic *T.cruzi* pathogens. Other medication noted to have antitrypanosomal activities are posaconazole and allopurinol, but they are under on-going clinical trials [36]. Myocarditis secondary to Chaga reactivation could be misdiagnosed as allograft rejection which if managed with increased immunosuppression can prompt extensive dissemination, cardiac biopsy with histopathological examination might be necessary in such cases and can detect intracellular T.cruzi-amastigotes; moreover, it will identify the degree of fibrosis, tissue necrosis, position and the extent of cellular infiltrate. Considering the high risk of Chaga disease reactivation, several centers had recommended prophylactic anti-trypanosomal therapy in all cardiac transplant patients [36].

Distinction between acute Rejection and Infectious Complications

In majority of transplant cases, infection is easily distinguishable from rejection based on clinical data, timing of infection, patient signs and symptoms and laboratory tests. Moreover, cultures, viral loads, imaging, Procalcitonin (particularly in lung transplant recipients), Acute Phase Proteins (APPs) such as C-Reactive Protein (CRP) or Serum-Amyloid A (SAA), ImmuKnow assays, all have demonstrated some role in differentiating infection from rejection episodes, however, their roles are still questionable and in some cases allograft infection may bear a resemblance to rejection. In such cases allograft biopsy with clinic-pathological correlation might be necessary to distinguish these two entities. Recognition of tissue deposition of complements parts (particularly C4d) by IHC/ IF is the basic component of indicative criteria for ABMR. Furthermore, antigens detection to infectious organisms in allograft biopsy specimens has a pivotal role in the accurate diagnosis and proper therapy for tissue-invasive infection in transplant patients [1,37-41].

Commonest Infections Among Transplant Travellers and Preventive Measures

Prior to international travel, organ recipients must meet with their transplant team to decide any potential risks related to each country going to visit. It is advisable to avoid travelling to developing countries for at least 3-6 months post-transplant and following treatment of acute rejection episodes, owed to severely suppressed immunity at that period

Traveller's Diarrhoea

Diarrhoea is a common among travellers to developing countries (affecting 10-60%), and it might be life-threatening to immune-compromised patients. Prior to travel, organ recipients must be educated in appropriate food and water precautions. They should be warned to drink boiled or bottled water and other beverages and to avoid direct drinking of water from wells and lakes (as it might be contaminated with cryptosporidium or giardia), and avoid food sold by street sellers and raw foods (except fruit and vegetables that can be peeled) and unpasteurized dairy products (as it might be contaminated with Listeria or E. coli). Moreover, Immune-compromised travellers must carry some antimicrobial drugs for possible use in acute emergencies. Fluoroquinolones are the ideal choice for empirical usage in case of travellers' diarrhoea (alternatively, azithromycin can be given, but with caution if patients taking cyclosporine/ Tacrolimus, hence the drug level might be transiently increased) [1-4,42-44]. Transplant recipients with severe refractory diarrhoea, particularly if accompanied with fever, vomiting and/or bloody stools, must seeks medical physician.

Respiratory Infections

Respiratory diseases are the second common infection influencing travellers. All transplant recipients ought to get pneumococcal vaccines and annual influenza vaccination. Transplant recipients are at greater risk for invasive fungal infection, and ought to dodge activities, for example, spelunking and excavating, exercises that have been related to *Cryptococcus neoformans* or endemic fungi [1,42].

Malaria and Other Arthropod-Borne Disease

Malaria and dengue fever are the most common arthropod borne disease among travellers. Malaria prophylaxis should be given based on traveller's destinations. Choloroquine is the first-line Malaria prophylactic agent for individuals traveling to endemic areas with chloroquine-sensitive malaria, however, it might increase cyclosporine levels, and therefore periodic cyclosporine monitoring is needed. On the other hand, transplant travellers to areas endemic for choloroquine-resistant malaria, three main prophylactic options are present: atovaquone/proguanil, mefloquine and doxycycline [42-44]. Prophylactic medications ought to be begun few weeks preceding travel to allow immunosuppressant's level monitoring prior to travel and to be rechecked again after returning from journey and stopping prophylaxis. In addition to malarial chemoprophylaxis, transplant recipients should be advised on approaches that can limit insect bites, such as evading mosquitos, particularly during dusk and dawn when mosquitoes that transmit malaria are most likely to bite and to use insect's repellents, protective wears and bed nets. Such protection will also reduce other insect borne illnesses (e.g. Chikungunya) [42-44].

Sun Exposure and Skin Exposure

It is advisable for transplant travellers to have protective measures such as wearing sunglasses, caps, protective clothing and applying sun blockers creams to minimise sun rays concentration and exposure and avoid walking barefoot or swimming in freshwater, which can put them at increased risk for abrasions, infections, and parasitic disease [44-46].

Sexually Transmitted Diseases

Travellers need to use barrier precautions when engaged in sexual encounters.

Vaccination is generally less effective in the presence of immunosuppression and has limited immunological protection period. Moreover, live vaccines are contraindicated post-transplantation, since it might lead to disseminated infection in immune-compromised patients. Hence the need for vaccination ought to be assessed before transplantation. Examples of these vaccines are influenza (live attenuated), Measles, Mumps, Rubella (MMR), varicella, rota virus, activated poliomyelitis vaccine and BCG. Immune globulins should be considered for susceptible individuals travelling to endemic areas. A minimum of 4 weeks between live-virus vaccine administration and transplantation is suggested [1,3,42-45]. On the other hand, Pneumococcal vaccination is suggested each 3-5 year, while influenza immunization is suggested

yearly. Additional vaccinations are prescribed accordingly to patients traveling to endemic areas where certain diseases are present [1,3].

Travel Vaccines

When possible, vaccination for travel should be started several months before the trip, to allow time for possible additional boosters and serologic evaluations. Hepatitis B vaccine might be suggested for certain transplant patients, incorporating those with new sexual partners while traveling, and those going to live in endemic countries.

Hepatitis A vaccines

Hepatitis A vaccine is less efficient in transplant patients. However, if the trip planned in advance with sufficient time before travel, and the transplant recipients are no less than a year post-transplant and on modest immunosuppressive dosage, then it might be valuable to be vaccinated with two vaccine doses of 6-12 months separated. Conversely, if the transplant individual does not have enough time, then ought to be given intramuscular immunoglobulin before travelling. Immunoglobulin's can provide 85 to 90% protective effect; however, such effects can persist only for 3-6 months [42-45].

Tetanus, Diphtheria and Pertussis

Though tetanus is rare among travellers, however, all adults including SOT recipients should have a tetanus booster dose before traveling. Diphtheria is common in poor areas with 5–10% mortality among normal hosts, despite therapy. Patients vaccinated more than 10 years before travel should be revaccinated before entering an area in which diphtheria is endemic or resurgent. The incidence of pertussis has been increasing worldwide over the last 20 years; as 90% of pertussis still occurs in developing countries, it is important to ensure that all travellers including SOT recipients are protected. A newer a cellular adult vaccine for pertussis is available, in combination with tetanus and diphtheria (Tdap). Although administration of Tdap has not specifically been studied in SOT recipients, given the risk and consequences of developing pertussis in travellers, a single dose of Tdap should be given to adult travellers who have not recently received Tdap [42-45].

Typhoid Fever: Immune-compromised patients are at great risk of developing severe complications with typhoid infection; hence they must be vaccinated prior to travelling to endemic places. There are 2 available vaccines for typhoid fever; TyphimVi® (Aventis Pasteur SA), which is a polysaccharide inactivated vaccine, and Vivotif® which an oral attenuated live vaccine. The live attenuated oral typhoid vaccine should be avoided in immune-compromised patients.

Meningococcal disease: is associated with high mortality rate. The meningococcal immunization is a quadrivalent polysaccharide (against N.meningitidis A, C, Y, W-135), and indicated for people going by territories with a flare-up of intrusive meningococcal disease brought on by a sero- group incorporated into the vaccine. Confirmation of vaccination is compulsory for Muslim travellers to Saudi Arabia for hajj or umra. The vaccine effects tend to decline over the initial 6-12 months following vaccination and revaccination might be required for a new travel [42,43].

Rabies

Rabies vaccine is an injectable inactivated virus. Only individuals expecting intense animal exposure, and those on long-term (≥30 days) travel and plans to be far from medical care should receive rabies vaccine. All travellers with a potential rabies exposure should receive post-exposure prophylaxis, starting with immediate cleansing of the wound with soap and water. Those who have not previously been immunized should receive multiple doses of intramuscular vaccine, plus rabies immune globulin (HRIG) (20 units/kg), half at the site and half intramuscular. Those who have received pre-exposure prophylaxis receive two more doses on days 0 and 3 and no HRIG. Since SOT recipients may not mount adequate antibody responses to the rabies vaccine (titers >0.5 IU/mL are considered adequate), some recommend administration of HRIG following animal's exposure [42-46].

Yellow fever

Yellow fever vaccine is a live attenuated virus and must not be given to solid organ recipients. Ideally transplant recipients must avoid countries where the yellow fever is endemic.

Japanese encephalitis

JE vaccine is a killed viral vaccine with high efficacy of 80 to 90%. Vaccination against JE should be considered for travellers to areas of Asia endemic with JE [42-45].

Bacille Calmette-Guerin and tuberculosis

Bacille Calmette-Guerin (BCG) is a live, attenuated strain of *M. bovis*, and is used to prevent tuberculosis, especially in infants and children, however, BCG is contraindicated in SOT recipients because they can develop disseminated BCG. There are no specific approaches to prophylaxis other than wearing appropriate masks in health care settings in endemic regions [44].

Conclusions

- Any acute and active infection affecting transplant recipients must be eliminated prior to transplant surgery.
- Advanced and sensitive techniques such as immunoassays, microbiological assays and others, may permit titration of immunosuppression, hence decreasing mortality rate from infection and malignancy, however, these techniques are still under development.
- Routine post-surgical antimicrobial prophylaxis depends on

the organ transplanted and local epidemic organisms, and has to be adjusted based on cultured colonized organisms.

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