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Infections after Solid Organ Transplantation

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ABSTRACT

Solid organ transplantation has continued to evolve over past 60 years with invent of newer immunosuppressive medication and ever-advancing battery of tests for immune compatibility. The development of cardiovascular disease, malignancy and infection pose a significant threat to long-lasting graft and patient survival. The source of infection could be the donor, recipient, hospital or community. Various methods can be used for the prevention of infection including vaccination, universal prophylaxis and pre-emptive treatment. The signs, symptoms and laboratory features of infection in transplant recipients can be subtle or even absent. Therefore, diagnosis requires a high index of suspicion and the proactive use of imaging, tissue biopsy and/or culture for confirmation. The natural history of infections in immunosuppressed is rather aggressive. The pattern of infection has changed with the use of universal prophylaxis and pre-emptive treatment. The goal of treatment is to maintain an acceptable graft function and excellent patient survival with the use of minimal immunosuppressive medication. Novel methods for precise quantification of the net state of immunosuppression will help in individualizing treatment regimen. In this narrative review, we revisit this important topic in solid organ transplantation and provide an evidence-based guideline for the management of such complications.

Keywords: Immunosuppression, Infection, Transplantation, Prophylaxis, Vaccination

Abbreviations: CMV: Cytomegalovirus; HSV: Herpes Simplex Virus; EBV: Epstein Barr Virus; HIV: Human Immunodeficiency Virus; HTLV: Human T Lymphotrophic Virus; VZV: Varicella Zoster Virus; NODAT: New Onset of Diabetes after Transplantation; PTLD: Post Transplant Lymphoproliferative Disease; LCMV: Lymphocytic Choriomeningitis Virus; HHV 6: Human Herpes Virus 6; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; VDRL: Venereal Disease Research Laboratory; MRSA: Methicillin Resistant *Staphylococcus aureus*; VRE: Vancomycin Resistant Enterococcus; TMP-SMX: Trimethoprim Sulfamethoxazole

INTRODUCTION

Transplantation remains the treatment of choice for end-stage organ dysfunction such as end-stage renal disease and chronic liver disease [1]. It has evolved over the past 60 years with invent of newer immunosuppressive drugs and advanced immunological test. Cardiovascular disease, malignancy and infections are common complications of solid organ transplantation which can lead to graft loss. Transplant recipients are at increased risk of opportunistic infection due to the immunosuppressed state. Indeed, about 70% of kidney transplant recipients experience one episode of infection within the first three years [2]. According to the

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United States Renal Data System (USRDS), there has been a steady increase in the hospitalization rate for infection from 5.9% per 100 patient years in 2001-2003 to 6.5% per 100 patient years in 2004-2006. Recognising an infection in transplant recipients may be difficult due to the atypical presentation [3]. Furthermore, the response to treatment may be suboptimal due to the rapid progression of underlying disease. Infection can also increase the risk of allograft rejection, cardiovascular events, new onset of diabetes after transplantation (NODAT) and post-transplant lymphoproliferative disorder (PTLD).

Risk of Infection

The risk of infection after transplantation varies according to the degree of immunosuppression. The early transplant period is characterised by a higher risk due to the relatively high net state of immunosuppression. Reliable assays to quantify the net level of immunosuppression are still largely experimental. Contrary to conventional belief, it seems that the mortality rate related to sepsis is lower in the solid organ transplant recipients compared to the general population albeit a higher overall risk of bacteraemia and sepsis [4]. The lower mortality may be attributed to more timely management and blunted inflammatory response in the transplanted individuals. The interplay of three factors namely determines the severity of the infection; the infective agent, environmental exposure and host factors **(Figure 1)**. Infections in a transplant patient can be donor-derived, recipient-derived, nosocomial or community acquired. Indeed, the transplanted organ may be a source of infection to the recipient [4].

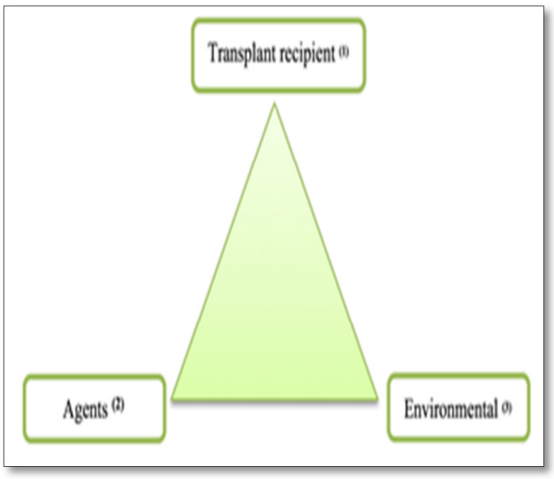

Figure 1. Epidemiological triad of infection in transplant recipient.
(1) Transplant recipients as immunosuppression, organ dysfunction, surgery and comorbidity
(2) Agents as bacteria, virus, fungi and parasite
(3) Environmental as hospital exposure and community exposure

The aetiology of these infections could be viral, bacterial, fungal or parasitic **(Table 1)**. Most often these infections are latent in the transplanted organ. Although donors undergo comprehensive screening prior to organ donation, many infections are difficult to detect especially when depending on antibody detection alone. Also, some viral infections have a window period for detection. In this regards, nucleic acid testing allows earlier detection. Screening for the pathogen **(Table 2)** and exclusion of donors with recent symptoms or laboratory abnormalities remains the mainstay for preventing donor-derived infections.

Table 1. Donor derived infections in solid organ transplantation.

Viruses	Bacteria
• The Herpes Family: Herpes simplex virus (HSV 1 and 2), Cytomegalovirus (CMV), Epstein Barr virus (EBV), Human herpes virus 6 (HHV 6) and Varicella zoster virus (VZV) • Hepatitis B and C • Human Immunodeficiency Virus • Human T-Lymphotropic Virus (HTLV) I and II • West Nile virus • Rabies • Lymphocytic Choriomeningitis Virus (LCMV)	• Bacterimia at the time of donation • Multidrug resistant organisms (e.g. Carbapenem resistant Enterobacteriaceae, Vancomycin resistant enterococcus) • Mycobacterium tuberculosis • Non-tubercular mycobacteria • Meningiococcus • *Treponema pallidum*
Fungi	**Parasites**
• Candida species • Aspergillus • Endemic mycosis (*Histoplasma capsulatam*, *Coccidoides* spp., *Cryptococcus gattii*) • *Cryptococcus neoformans*	• *Toxoplasma gondii* • *Trypanosma cruzi* • *Plasmodium falciparum* • Babesia • *Strongyloides stercoralis* • Leshmaniasis

Table 2. Donor screening test.

Donor Screening
Epidemiological history
Serological tests for HSV, EBV, CMV, VZV, HBV, HCV, HIV and VDRL
Microbiological testing of blood and urine
Specific serologic testing, nucleic acid assays or antigen detection based on epidemiologic factors and recent exposure (e.g. Toxoplasmosis, West Nile virus, HIV, HCV)

Recipient evaluation must include screening for all potential infectious diseases **(Table 3)**. Most common recipient related infections are latent viral infection, endemic fungal and parasitic infection. Common latent viral infections include the herpes simplex virus (HSV), CMV, Varicella zoster virus (VZV), hepatitis B virus (HBV), hepatitis C virus (HCV), human papillomavirus (HPV) and BK polyomavirus. Pre-transplant screening and treatment can prevent recipient-related infection. Recipients with HBV or HCV can be treated with antiviral drugs either before transplant or after transplant.

Table 3. Recipient screening test.

Recipient Screening
Epidemiological history
Vaccination history
Serologic testing for HSV, EBV, CMV, VZV, HBV, HCV, HIV and VDRL
Tuberculin skin test and Interferon Gamma Release Assays (IGRAs)
Microbiological testing of blood and urine
Specific serologic testing, nucleic acid assays or antigen detection based on epidemiologic factors and recent exposure (e.g. Toxoplasmosis, West Nile virus, HIV, HCV)

HIV infection was traditionally considered as an absolute contraindication for transplantation due to the concern of accelerated disease progression. However, the recent improvement in long-term outcome of HIV infected patients and studies demonstrating excellent results with organ transplantation have prompted many centres to evaluate their policies. Several studies have shown a comparable patient and kidney transplant outcome in HIV positive and HIV negative recipients [5]. However, results are inferior among transplant recipients who are co-infected with HCV [5]. In addition, HIV positive recipients are at increased risk of rejection and malignancy [6]. There are no established criteria for selection of HIV positive recipients, but most centres prefer recipients with low viral load (<20 copies/ml), CD4 count of >200 cells/μL and on stable anti-retroviral therapy regimes for at least six months [7].

Nosocomial infections can be associated with drug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant Enterococcus (VRE), Carbapenem-resistant Enterobacteriaceae and fluconazole-resistant Candida species [8,9]. Prolonged ventilator support, decreased lung function, ischemic graft tissue and stents are amongst the risk factors contributing to hospital-acquired infections [10]. These pathogens can infect surgical sites, fluid collections such as hematomas or transplanted organs resulting in prolonged hospitalization [11].

Community-related infections are generally commoner in the late post-transplant period. Common infection includes respiratory tract pathogens and endemic fungal infection such as Aspergillus, Nocardia or Cryptococcus [12].

Prevention of Infection

There are various approaches which can be employed to prevent post-transplant infections. These include vaccination, universal prophylaxis and pre-emptive therapy. In the ideal circumstance, transplant recipients should undergo vaccination against common viral and bacterial diseases before transplantation **(Table 4)**. The Infectious Disease Society of America (IDSA) recommends a minimum waiting period of four weeks between live virus vaccine and transplantation [13]. Live vaccines (such as varicella) are generally contraindicated in the post-transplant period due to the risk of disseminated disease. Also, seroconversion after vaccination may be suboptimal in transplant recipients compared to the general population [14]. Inactivated vaccines are considered safe after transplantation, although there has been some concern about the possibility of triggering organ rejection [15,16].

Surgical prophylaxis before transplant depends upon the type of organ transplanted and local epidemiologic factors. For instance, in kidney transplantation, antimicrobial agents that provide coverage for skin flora and gram-negative bacilli are generally recommended. Antifungal prophylaxis is individualized based on the risk and epidemiologic factors such as past exposure to broad-spectrum antibiotics, prolonged stay in ICU and prolonged use of total parenteral nutrition. Fungal infections particularly related to non-albicans Candida and Aspergillus species are more common in lung and liver transplants [19].

Table 4: List of vaccine for solid organ transplant recipients [17,18].

Vaccines given before or after transplant	Vaccines given before transplant
• Inactivated seasonal influenza (yearly) • Pneumococcal polysaccharide vaccine • Conjugated pneumococcal vaccine • Hepatitis A • Hepatitis B • Inactivated polio • Diphtheria • Tetanus • Menigiococcus • Pertussis • *Hemophilus influenza* • Japanese encephalitis • *Salmonella typhi* Vi • Malaria, Chikungunya, Dengue, Rabies, Yellow fever	• Measles • Mumps • Rubella • Varicella • BCG

The American Society of Transplantation guidelines published in 2013 recommends that patients with risk factors for invasive fungal infection should receive fluconazole (400 mg daily) or a lipid formulation of amphotericin B (3 to 5 mg/kg intravenously daily) as postoperative antifungal prophylaxis [20]. The echinocandins (micafungin, anidulafungin) are alternative options for antifungal prophylaxis [21,22]. Intravenous amphotericin in a weekly dose may also be considered for such high-risk patients [23].

The majority of transplant recipients should receive trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis for 3 to 6 months [24]. This antibiotic combination is effective against *Pneumocystis jirovecii* pneumonia (PCP), *Toxoplasma gondii*, *Isospora belli*, *Cyclospora cayetanensis*, Nocardia, Listeria and common respiratory, urinary, gastrointestinal pathogen [24]. In the pre-prophylaxis era, the incidence of PCP was relatively high (10-15%). The introduction of TMP-SMX prophylaxis has virtually eliminated PCP in the post-transplant period [25,26]. The usual dose of TMP-SMX is 480 mg once daily or 960 mg thrice weekly. Few high-risk individuals such as lung transplant recipients may extend TMP-SMX prophylaxis beyond one year. Alternative options for antibiotic prophylaxis in case of proven TMP-SMX allergy include dapsone, atovaquone and pentamidine, though they are less effective and have narrow spectrum of activity [27].

Strategies for prevention of post-transplant cytomegalovirus (CMV) infection include universal prophylaxis and pre-emptive therapy. In universal prophylaxis, the transplant recipient deemed at risk is given antiviral agents such as valganciclovir for a definitive period after transplantation, usually 3 to 6 months. In pre-emptive therapy, the organ recipient is monitored with sensitive quantitative assay for CMV at periodic intervals and treatment is initiated in the presence of a significant viral load [28]. Both strategies are equally effective, although universal prophylaxis is generally easier to perform and well tolerated. Additionally, some evidence suggests a reduced rejection rate and reduced incidence of PTLD [29]. Compared to placebo, prophylaxis with acyclovir, valacyclovir or ganciclovir significantly reduces the risk of CMV disease, CMV infection and all-cause mortality [29]. The preferred drugs for CMV prophylaxis are ganciclovir and oral valganciclovir although high dose oral acyclovir and valacyclovir are also effective [28]. Occasionally, valganciclovir prophylaxis can lead to bone marrow suppression and delayed onset primary CMV disease [30].

In addition to the above measures, the patients themselves have a crucial role in the prevention of post-transplant infections. It is recommended that transplant recipients maintain good personal hygiene, avoid close contact with people having contagious infections, avoid drinking unsafe-water, avoid undercooked meat and avoid unpasteurized dairy produce [12].

Changing the Pattern of Infection

Organ transplantation has evolved over the years with newer immunosuppressive drugs. Induction immunosuppression has resulted in lower incidence of acute rejection and better short-term graft survival. However, their use has been associated with a higher incidence of viral infections such as CMV and a higher incidence of bacterial infections [31].

A small number of non-infectious post-transplant complications can mimic opportunistic infections such as sirolimus induced pneumonitis [32]. Pattern of infection after transplant varies with time and can be divided into early, intermediate and late transplant periods. The early period is predominantly characterized by donor-derived or hospital-acquired infections. Common infections include surgical site infections or catheter-related infections. The intermediate period is primarily characterized by viral infections in patients on antibiotic prophylaxis, while the late period is frequently associated with community-related infections commonly seen in the general population or endemic fungal infections (**Table 5**).

Table 5. Pattern of infection after transplantation.

Early transplant period (<1 month)	Late transplant period (>6 months)
• Infection with anti-microbial resistant species - MRSA, VRE, Candida species, CRE • Aspiration • Catheter infection • Wound infection • Anastomotic infection • *Clostridium difficile* colitis • BK virus infection, adenovirus, influenza, Cryptococcus infection • Mycobacterium infection	• Community acquired pneumonia, urinary tract infection, atypical moulds, Mucor species, Nocardia • Late viral infections – CMV colitis, Hepatitis (HBV, HCV), HSV encephalitis, JC virus infection

Evaluation for Infection

Infections in transplant recipients often present with minimal symptoms or absent laboratory features. The diagnosis requires a proactive approach including radiological investigations such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). The gold standard for diagnosis is microbiological culture and biopsy, although this is not always clinically feasible. Tests based on serological analysis may not be useful in the post-transplant period. The use of nucleic acid testing (NAT) provides earlier and more reliable diagnosis. NAT can be performed on various types of clinical specimens based on the diagnosis. Commonly used specimens for diagnosis are blood, sputum, urine, CSF and sputum. NAT involves multiple steps including extraction of nucleic acid from the cell by manual and automated technique followed by amplification. The final nucleic acid sequences are read by different methods including polymerase chain reaction (PCR), real-time PCR, microarrays and sequencing (Sanger and next-generation).

COMMON INFECTION IN TRANSPLANTATION

Cytomegalovirus infection (CMV)

CMV, a member of the beta herpes virus group **(Figure 2)** and is one of the commonest infections seen in solid organ transplant recipients. Active CMV infection is defined as detection of CMV replication in the blood regardless of whether signs or symptoms are present. CMV disease is defined as the presence of detectable CMV in a clinical specimen accompanied by other clinical manifestation [17]. CMV exerts a direct effect on the various organs and has indirect effects secondary to immune phenomena. Invasive CMV disease usually manifests in the first year of transplant, frequently with non-specific symptoms such as fever, leucopenia and elevated liver enzymes [33]. Secondary immune phenomena can manifest as allograft injury, reactivation of EBV, new onset of diabetes after transplant or opportunistic infection. CMV reactivation can up-regulate histocompatibility antigens or adhesion molecules resulting in cytokine release and graft rejection [34-36]. Transplant recipients can develop primary CMV infection, reactivation or super-infection when transplanted with a seropositive donor.

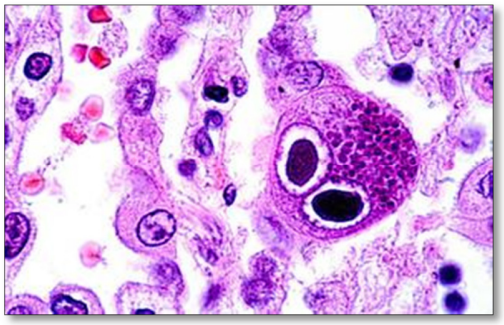

Figure 2. CMV infected cell showing classic intranuclear inclusion with "owl eyes" pattern.
Reprinted courtesy of Wiedbrauk DL, PhD, Scientific Director, Virology & Molecular Biology, Warde Medical Laboratory, Ann Arbor, Michigan

CMV disease can be prevented by either universal prophylaxis with valganciclovir or preemptive therapy based on regular monitoring of CMV viral load. Also, universal prophylaxis may be useful in preventing herpes simplex virus, varicella-zoster virus, EBV, human herpes virus 6 (HHV6) and human herpes virus 7 (HHV7) [37]. Most transplant centers give universal prophylaxis for 3 to 6 months and up to 1 year in heart and lung transplantation. CMV can be diagnosed by quantitative polymerase chain reaction (PCR) and antigen detection assays. However, PCR may be negative in a few cases of invasive disease despite the presence of histological lesions.

Treatment includes intravenous ganciclovir in severe diseases such as colitis or pneumonitis followed by valganciclovir. Duration of therapy depends upon documentation of cure with molecular assays and evidence of healing of an injured organ such as colonic ulcers. With extensive use of universal prophylaxis ganciclovir resistance is becoming common due to a mutation in UL97 gene or UL54 gene. Ganciclovir resistance can manifest as slowly responsive or relapsing infection [38].

Polyomaviruses BK and JC

Human polyomaviruses, such as the BK and JC virus are highly seroprevalent in humans but appear to cause clinical disease only in immunosuppressed patients. BK polyomavirus **(Figure 3)** is associated with infection of renal allograft and can present with asymptomatic viruria, interstitial nephritis, ureteral obstruction and hemorrhagic cystitis [39-43]. BKV can also present with progressive graft dysfunction. Diagnosis is usually confirmed via nucleic acid testing of blood and/or urine. However, a definitive diagnosis requires positive immunostaining on graft biopsy. JC virus is associated with progressive multifocal leukoencephalopathy (PML) in immunocompromised individuals. Treatment requires reduction of immunosuppression especially the anti-proliferative drugs. Many consider BK replication as a reliable sign of over-immunosuppression. An array of anti-viral drugs has been used in the treatment of BK virus including cidofovir and leflunomide, but none of these is of proven value.

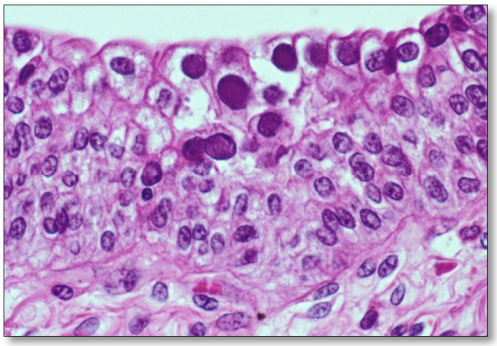

Figure 3. Urothelial cells showing intranuclear BK virus inclusion bodies with scant inflammation [27].

Epstein Barr virus and post-transplant lymphoproliferative disorder (PTLD)

Epstein-Barr virus (EPV) belongs to the herpes virus group and is spread by close contact between susceptible persons and asymptomatic EBV shedders. It is associated with the development of the post-transplant lymphoproliferative disorder (PTLD) in the majority of cases [44,45]. PTLD is a heterogeneous lymphoid cell proliferation commonly seen after solid organ transplantation and hematopoietic stem cell transplant. The spectrum of PTLD ranges from an indolent polyclonal proliferation of lymphocytes to aggressive lymphomas. The incidence of PTLD is 50-120% higher in SOT recipients compared to general population and varies according to the type of transplant, the degree of immunosuppression, the age of the recipient, Epstein-Barr virus (EBV) seropositivity of donor and recipient [46,47]. World Health Organization has classified PTLD into four categories based on morphologic, immunophenotypic and molecular criteria. The four categories of PTLD include early lesion, polymorphic PTLD, monomorphic PTLD, Hodgkin lymphoma type PTLD [48]. Reduction in the degree of immunosuppression remains the mainstay of treatment, although response occurs only in half of the patients and durable remissions are not common. Other treatment options include sequential rituximab followed by CHOP chemotherapy, surgery and/or radiotherapy for select cases [49]. Additionally, novel therapeutic approaches including adoptive immunotherapy, cytokine treatment, and anti-EBV-based therapy are currently under evaluation.

Pneumocystis infection

PCP usually manifests within the first 6 months after transplantation and typically presents with dry cough, breathlessness and/or hypoxemia. It is caused by is an opportunistic fungal pathogen known as *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*). Universal antimicrobial prophylaxis with TMP-SMX has led to significant reduction in the incidence of post-transplant PCP. PCP is diagnosed based on clinical history, radiographic findings, sputum or Bronchoalveolar lavage (BAL) staining. Typical chest x-ray findings in PCP include diffuse, bilateral interstitial infiltrates, but other patterns may be seen **(Figure 4)**. Detection of the organism in respiratory specimens either induced sputum or BAL fluid is done by specific staining. Staining is essential for diagnosis as pneumocystis cannot be cultured. Direct fluorescent antibody staining using a fluorescein-conjugated monoclonal antibody can visualize both trophic forms and cysts. Other staining used for detection of trophic forms includes Gram-Weigert, Wright-Giemsa or modified Papanicolaou stains. Cysts can be stained with calcofluor white, cresylecht violet, Grocott-Gomorimethenamine silver or toluidine blue. In rare cases, lung biopsy with tissue stain and PCR is used for diagnosis. There are different types of PCR assays available for the detection of Pneumocystis in induced sputum or BAL fluid, blood or nasopharyngeal aspirate. These techniques increase the rate of detection of Pneumocystis by 7% over BAL staining [50]. Another test used in diagnosis of PCP include beta D-glucan assay. Beta D-glucan is a cell wall component of most fungi including PCP. Serum beta D-glucan assay has a high negative predictive value with sensitivity of 92% and specificity of 86% in detecting PCP [51,52].

Urinary tract infection (UTI)

UTI is one of the common infections after solid organ transplantation and is associated with acute rejection, and impaired allograft function [53,54]. UTI can manifest as asymptomatic bacteriuria, uncomplicated UTI (no systemic symptoms or allograft pain), complicated UTI or recurrent UTI (3 or more episodes of UTI in one year). It is likely that TMP-SMX prophylaxis reduces the incidence of post-transplant bacterial UTI. Patients presenting with features of UTI should undergo urine analysis and urine culture. A selected group of patients may require imaging to rule out structural or functional abnormalities of the urinary tract. Asymptomatic bacteriuria in early post-transplant setting (less than 2 months) should be treated with antibiotics [55]. There is no consensus for treatment in late post-transplant

setting. For patients with uncomplicated UTI, empirical treatment with an oral antibiotic is recommended.

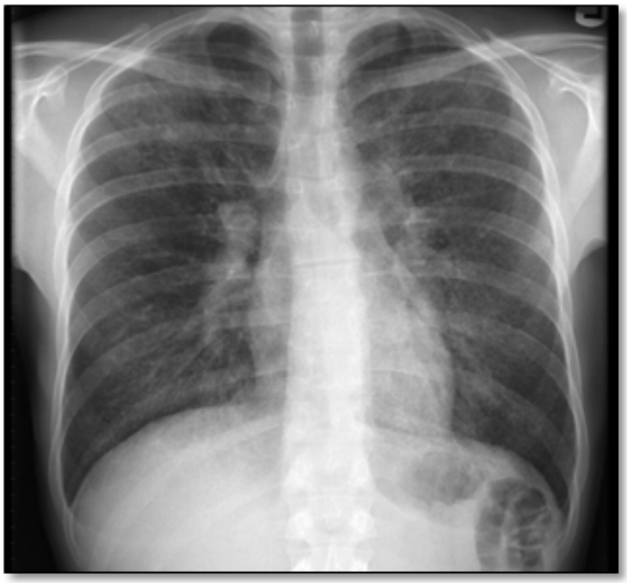

Figure 4. Chest X-ray showing bilateral perihilar interstitial infiltrates characteristic of Pneumocystis infection.
Case courtesy of Prof. Gaillard F, Radiopaedia.org, rID: 9171

Selection of antibiotic is based on local antibiotic resistance pattern, patients past causative organism and antibiotic experience. Complicated UTI requires intravenous antibiotic treatment to cover both gram-positive and gram-negative organism. Duration of treatment is generally 2 to 3 weeks. Recurrent UTIs require further evaluation to look for reflux, inadequate bladder emptying and/or structural abnormalities of the native kidneys becoming the source of infection (e.g. polycystic kidney disease). In this case, nephrectomy of the native kidneys may be a feasible option. Prophylactic rotating antibiotics may be an option in cases of recurrent UTIs.

UTI in kidney transplantation may be associated with urinary leak or urinomas, and few centers use ureteric stenting to prevent this complication. Early urinary leak presents in the first 1 to 4 days of transplantation with excessive drain and is almost always related to a technical problem with implantation. In such a scenario the ureter has usually pulled out of tunnel caused by excessive tension on anastomosis and is more common with extra-vesicle ureteroneocystostomies [56]. Few centers recommend using a ureteral stent to lessen this complication [57]. However, data regarding the routine use of a ureteral stent to prevent urinary leak are equivocal. In a randomized control trial by Benoit et al. [58] which included 194 participants concluded that the incidence of urinary leak was significantly lower in the stented group (1% vs. 6%). However, subsequently, another large randomized trial showed there is no benefit of urinary stenting in the prevention of urinary leak [59]. A Cochrane review [60] which looked at prophylactic ureteric stenting showed lower urologic complication in the stented group compared to the control group. However, the stented group had a higher incidence of urinary tract infection which became comparable with the control group after the addition of prophylactic antibiotic. There are no trials to answer whether selective ureteral stenting is better than universal stenting regarding the quality of life and cost.

Tuberculosis

The incidence of tuberculosis after solid organ transplantation varies according to the geographical region [61]. Indeed, patients transplanted in endemic countries are at increased risk of developing tuberculosis infection [62]. Screening for latent tuberculosis is performed by tuberculin skin test (TST) and interferon-gamma release assays (IGRA). Tuberculosis prophylaxis should be considered in solid organ transplant recipients with a TST>5 mm, positive IGRA, history of untreated latent TB, history of contact with an individual with active TB and/or recipient of an organ from a patient with untreated latent tuberculosis. One has to keep in mind that false positive TST can occur in patients who received the BCG vaccine and IGRA are not very reliable in the end-stage kidney disease population [63]. Latent tuberculosis is usually treated with Isoniazid (5 mg/kg) for 6 to 9 months. The definite diagnosis of active tuberculosis requires staining and culture for acid-fast bacilli (AFB) on sputum, bronchoalveolar lavage fluid, abscess fluid or histopathology on biopsy specimens. Disseminated disease and extrapulmonary tuberculosis is commoner in the transplant recipients compared to the general population. One should keep a high index of suspicion in all patients presenting with typical pulmonary or cutaneous lesions.

In patients with active pulmonary tuberculosis without evidence of isoniazid resistance, rifampicin-containing regimen should be used for a minimum of 6 months (isoniazid, rifampicin, pyrazinamide and ethambutol). In disseminated tuberculosis or isoniazid resistance, anti-tubercular therapy should contain rifampicin for more extended periods. However, rifampicin containing regimes are known to cause significant interactions with the immunosuppression medications [64]. Rifampicin reduces the serum concentration of tacrolimus, cyclosporine and sirolimus by enzyme induction. Periodic therapeutic drug monitoring is therefore recommended when rifampicin is used in transplant recipients. If avoiding the use of rifampicin, a longer than usual duration of treatment is required. Rifabutin is a weaker enzyme inducer and can be used as an alternative agent in the post-transplant scenario, although limited experience is available. All anti-tubercular drugs are associated with specific side effects and therefore regular monitoring of liver function test is recommended [64].

Hepatitis B Infection

The management of chronic Hepatitis B virus (HBV) infection depends upon multiple factors such as the extent of liver involvement, patient's immune status and virological factors. The decision to initiate treatment is based upon the presence or absence of cirrhosis, alanine aminotransferase (ALT) level and the HBV DNA level. All HBV infected transplant recipients who have HBV DNA with or without elevated Alt should be treated with antiviral agents [65-67]. All transplant recipients who have received Rituximab as a part of desensitization protocol should receive antiviral treatment irrespective of HBsAg status due to the high rate of reactivation post-transplantation [68]. The goal of antiviral therapy is suppression of HBV DNA, loss of HBeAg and loss of HBsAg. For treatment naïve patients, nucleoside or nucleotide analogues are preferred. Tenofovir or entecavir are the first-choice nucleotide analogues due to high potency, low rate of resistance with long-term treatment. The decision to choose one drug over the other is based on the patient's previous exposure to the drug. Patients who have never received prior antivirals, entecavir is better suited compared to lamivudine [69-71]. Interferon Alfa and adefovir is not preferred after transplantation due to the risk of rejection and weak antiviral activity respectively [72,73]. Although these drugs have minimal interaction with immunosuppression, therapeutic drug monitoring of calcineurin inhibitor is recommended. Patients on antiviral treatment who develop elevated ALT should be evaluated for noncompliance, drug resistance or etiologies other than HBV infection.

Hepatitis C Infection

Hepatitis c infection after transplantation is associated with liver disease, recurrence or new onset of HCV related kidney disease, PTLD, NODAT [74]. Rarely few patients have developed fibrosing cholestatic hepatitis characterized by cholestasis and progressive liver failure [75]. HCV associated kidney disease after transplant include recurrent glomerular disease or de novo Membranoproliferative glomerulonephritis (MPGN) or Membranous nephropathy (MN), renal thrombotic microangiopathy (TMA) [76]. HCV associated glomerular disease usually presents with progressive proteinuria [77]. The evaluation of patients with chronic hepatitis c virus (HCV) infection involves the assessment of liver disease and viral factors. These patients should be advised for measures to decrease the risk of transmission of diseases and correcting factors associated with accelerated disease including alcohol use, obesity, insulin resistance and substance abuse. All patients with virologic evidence of chronic HCV infection should be considered for antiviral treatment. The goal of treatment is to eradicate HCV RNA and prevent complications such as hepatocellular carcinoma. Directly acting antiviral (DAA) drugs are very effective in the treatment of HCV and combination of drugs depends upon genotype. Few combinations DAA used in post-transplant settings include glecaprevir-pibrentasvir, sofosbuvir-ledipasvir, sofosbuvir-simeprevir, sofosbuvir-daclatasvir and paritaprevir-dasabuvir [77-79]. However, few DAA such as simeprevir and dasabuvir are associated with significant drug interaction with immunosuppressants. Close monitoring of the therapeutic drug level of calcineurin inhibitor is required with use of DAA in solid organ transplantation.

Parasitic Infections

Parasitic infections are a part of differential diagnosis in patients presenting with febrile illness after transplantation, although their incidence is much lower than bacterial and viral diseases. Transplant recipients acquire parasitic infection through grafts, *de novo* infection or reactivation of dormant infection due to immunosuppression. Parasitic infection after solid organ transplantation can present with two types of clinical profiles. It can present with acute systemic illness with anemia, constitutional symptoms and variable organ involvement. This type of presentation is common for malaria, leishmaniasis, trypanosomiasis and toxoplasmosis. The second type of presentation includes localized syndrome such as lower gastrointestinal manifestation seen with protozoa (*Cryptosporidium, microsporidia*) or nematodes (strongyloidiasis, ascariasis).

Diagnosis requires a high index of clinical suspicion, specific sampling technique with special stains, nucleic acid-based test, imaging and serological diagnosis in some cases. Prognosis depends upon the extent of organ involvement and specific treatment.

One of the commonest parasitic infections is malaria which has been reported after kidney, bone marrow and multi-organ transplantation [80-82]. Strict adherence to antimalarial prophylaxis is indicated for patients travelling to malaria endemic area [83]. Antimalarial drugs such as quinine, chloroquine can interact with cyclosporine [84]. There are case reports of recurrence of schistosomal glomerulopathy after kidney transplant and it's recommended to prophylactically treat such patients before transplant as adult worms often live in infected host for decades [85].

Leishmaniasis is also seen after organ transplantation due to recrudescence of dormant infection which usually presents in 4^{th} to 6^{th} week post-transplantation with fever, splenomegaly and pancytopenia [86]. It's usually treated with pentavalent antimonial compound which can interact with cyclosporine [87]. Toxoplasmosis can be transmitted by blood or by transplanted organ and is most frequently reported after heart transplantation [88]. It usually presents with fever, generalized lymphadenopathy, anemia, haemophagocytic syndrome and is treated with pyrimethamine [89].

Trypanosomiasis is also reported after organ transplant with one study from endemic area showing 28% recurrence rate

after heart transplantation [90]. Post-transplant strongyloidiasis can present with fever and gastrointestinal disturbance although its incidence is declining due to use of cyclosporine which has parasiticidal effect [91].

Infection after Liver Transplantation

Infections are a major concern after liver transplantation with observed infection rate of 1 to 2.5 episodes per patient [92]. They are the most frequent cause of death after transplantation in some centers [93]. Identifying risk factors for infection permits the optimal use of preventive strategies. These include vaccination, prophylactic antimicrobials, pre-emptive treatment and educative avoidance. TMP-SMX prophylaxis is administered for 6 to 12 months after liver transplantation [94]. CMV remains the most important viral infection after liver transplantation [95]. Ganciclovir or valganciclovir prophylaxis is recommended for donor seropositive/recipient seronegative (D+/R-) group. In patients who do not receive CMV prophylaxis, it is recommended that an antiviral with activity against HSV and VZV (Acyclovir, valacyclovir, famciclovir) be given during first 3 to 6 months after transplantation and during periods of intensified immunosuppression [38].

Candida is the most common fungal infection after liver transplantation, especially non-albicans group [96]. Antifungal prophylaxis is recommended after liver transplantation, although the exact dose of the drug and duration of treatment is unclear.

Opportunistic infections are uncommon after 6 months post-transplantation in patients who have good graft function. Hepatitis E virus can cause chronic hepatitis in the post-transplantation period and should be considered in patients with unexplained elevation in liver enzymes [97].

Infection after Heart Transplantation

Infections are the most common cause of death after 6 months to one year after heart transplantation [98]. The type of infection is diverse including community-acquired bacterial and viral infections to opportunistic infections. The risk factors for infection depend upon the net state of immunosuppression and epidemiological exposure. Common opportunistic infection after heart transplantation includes CMV disease, Pneumocystis pneumonia and candidiasis. Antimicrobial prophylaxis is recommended for 6 to 12 months as in other solid organ transplantation [99].

Infection after Lung Transplantation

Infections after lung transplantation contribute to over 25 % of all post-transplant deaths [100]. Lung transplant recipients are at increased risk of infections due to the high level of immunosuppression, adverse effect of transplantation on local pulmonary host defences and constant environmental contact. Pneumonia is the most common type of infection after lung transplantation, although bloodstream, pleural space and wound infections are also common [101]. Patients with cystic fibrosis are often colonized with *Pseudomonas aeruginosa* and *Burkholderia cepacia*, both of which are frequently multidrug resistant [102]. It's recommended to start perioperative antibacterial prophylaxis for all lung transplant recipients. TMP-SMX prophylaxis has to be continued indefinitely for prevention of Pneumocystis, Listeria, Nocardia and toxoplasmosis. Clinically important viruses in lung transplant recipients include the community respiratory viruses (influenza, adenovirus, parainfluenza virus) CMV, HSV and VZV. Community respiratory infection may be associated with rejection, particularly chronic allograft dysfunction.

CONCLUSION

Solid organ transplantation has evolved with invent of newer immunosuppressive drugs and test for immune compatibility. Risk of infection after a transplant is determined by the degree of immunosuppression and epidemiological exposure to infection. Use of antimicrobial prophylaxis has altered the nature of infection resulting in delayed and atypical presentation. Signs and symptoms of infection could be nonspecific or even absent, and the diagnosis requires a proactive approach. Infection in transplant recipients can affect graft and patient survival. Novel methods to precisely quantify the net state of immunosuppression are likely to help in individualizing immunosuppressive medication. Close liaison with other specialties is of crucial importance.

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