

Infections in organ transplant recipients

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Abstract: Infections still remain a bugbear for the recipients of organ transplantation due to the need for lifelong immunosuppression. Improvements with newer immunosuppressive agents, and more specific diagnostic and therapeutic agents to prevent and treat infections have led to considerable reduction in fatal infections and have improved survivals. Infections can be community-acquired, nosocomial and often opportunistic. Often the clinical manifestations are atypical and altered or masked by the immunocompromised state. Infections are often disseminated and with mixed and multiple organisms, e.g. tuberculosis and *Nocardia* in the same patient and at the same time. In the absence of typical clinical features, a high degree of clinical suspicion and an aggressive diagnostic approach is required for the early diagnosis and appropriate, specific management of infections.

Introduction

Transplants have become widely accepted as a successful modality for treating end-stage organ diseases. However, the success of organ transplantation depends on a compromise between achieving sufficient immunosuppression to avoid rejection of the graft and maintaining a sufficient level of immune competence to protect the recipient from infections. Improved methods of immunosuppression, development of prophylactic strategies for bacterial, fungal, viral and protozoan infections, and progress in the diagnosis and treatment have led to a consistent decline in the incidence of fatal infections.

Factors determining the state of immunosuppression

- A Pre-operative condition of the patient
 - Presence of end-stage organ disease (cirrhosis, renal failure, etc.)
 - Nutritional status
 - Splenic function
 - Autoimmune diseases
 - Neutropenia
 - Lymphopenia
- B Nature of immunosuppressive therapy
 - Type of drug used
 - Dosage
 - Duration
 - Sequencing of immunosuppressive agents
- C Infection profile
 - Presence or absence of infection in the recipient
 - Type of infection (e.g. immunomodulatory viruses implicated, i.e. Cytomegalo Virus [CMV], Epstein-Barr Virus [EBV], Hepatitis B Virus [HBV], Hepatitis C Virus [HCV] and Human Immunodeficiency Virus [HIV])

D Surgical techniques used

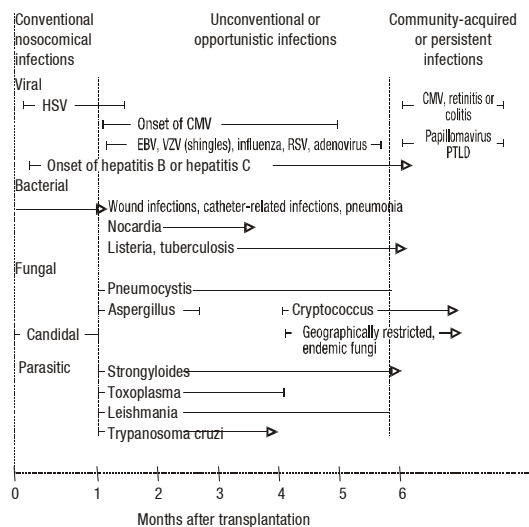
- Presence of devitalized tissues
- Tissue complicated injuries
- Undrained fluid collection
- Presence of indwelling devices

Other risk factors include age,¹ diabetes, neutropenia,² hepatitis, poor graft function and splenectomy.³

The time graph of infection after transplantation

Due to the unique nature of solid organ transplant programmes, the similarity of anti-rejection regimes is depicted in the consistency with which a time graph can be drawn of infections occurring after transplantation (Table 1).^{4,5} However, it should be remembered that there are geographical variations beyond the scope of the graph.

Table 1. Temporal sequence of infections after organ transplantation



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BACTERIAL INFECTIONS

These infections, occurring especially in the first month post transplantation, can be urinary tract infections (UTIs) and upper and lower respiratory tract infections including pneumonias. Among the late-occurring infections, tuberculosis has an incidence of 11%–17% in tropical countries.

Urinary tract Infection (UTI)

Urinary tract infection occurs in 50% or more patients in the first 3 months following transplantation. However, with prophylaxis using low dose-trimethoprim sulphamethoxazole (TMP -SMZ), the incidence has reduced.⁶ UTI's in renal transplant is commonly associated with pyelonephritis, bacteraemia and frequent relapses after standard antibiotic therapy for 10-14 days, even in the absence of urological abnormalities.⁷ Asymptomatic bacteriuria requires treatment for at least 10 days and acute pyelonephritis and/or positive bacteraemia for 4-6 weeks. Since Gram-negative organisms are most commonly implicated, the initial treatment may be with cephalosporins in case of extended spectrum beta-lactamase prevalence carbapenems (meropenem) or with aminoglycosides in severe cases. Candidial infections may require fluconazole. However, careful pre-transplantation screening of recipients and donors can prevent UTI.

Wound infections

Wound infections are now rare in most centres. This may be attributed to improved surgical techniques and newer antibiotics. Important predisposing factors are wound haematomas, urine leaks and lymphocele. Treatment is mainly surgical drainage, antibiotic therapy and aseptic daily dressing.

PULMONARY INFECTIONS

Pulmonary infections remain the most serious in renal allograft recipients (Table 2). Since there is diverse aetiology and a lack of specificity of clinical and radiological findings (Table 3), an aggressive diagnostic approach is often indicated.

Diagnosing pulmonary infections

Along with sputum examination, Gram-stained smear

Table 2. Main aetiological agents of pulmonary infections

Bacteria	<i>Pneumococcus</i> , <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i> , <i>Legionella</i> spp., <i>Mycobacterium</i> spp. <i>Nocardia</i> spp.; <i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella pneumoniae</i> and <i>Chlamydia</i> spp.
Viruses	<i>Cytomegalovirus</i> , <i>Varicella zoster</i>
Fungi	<i>Aspergillus</i> spp., <i>Cryptococcus</i> spp., <i>Candida</i> spp., mucormycosis
Parasites	<i>Pneumocystis carinii</i> , <i>Strongyloides stercoralis</i> , etc.

Table 3. Radiological and clinical characteristics of pulmonary infections

Radiographical abnormality	Acute development	Chronic development
Nodular infiltrate	Bacteria	Fungi, <i>nocardia asteroides</i> , tuberculosis, <i>Pneumocystis carinii</i>
Cavitations	Bacteria (<i>Legionella</i>), fungi	Tuberculosis
Consolidation	Bacteria (<i>Legionella</i>)	Fungi, <i>Nocardia asteroides</i> , tuberculosis, viruses, <i>Pneumocystis carinii</i>
Diffuse interstitial infiltrations		CMV, <i>Pneumocystis carinii</i> , fungi (rare)
Peribronchovascular abnormality	Bacteria, viruses (influenza)	CMV, <i>Pneumocystis carinii</i> , fungi, tuberculosis, <i>nocardia asteroides</i>

examination, specific cultures and radiological tests including computed tomography (CT) scan, fiberoptic bronchoscopy with tomography, biopsy and bronchoalveolar lavage (BAL) are the most frequently used techniques for the diagnosis of specific aetiological agents. BAL cytology has a diagnostic yield of 75%. Lung biopsy is appropriate when a patient with pneumonitis is worsening. Open lung biopsy is traumatic and may require assisted ventilation. Thoracoscopic biopsy, if available, is less invasive and is appropriate for diffuse or peripheral lung lesions. An aggressive approach for early diagnosis is more rewarding and leads to specific therapy.

Bacterial pneumonia

Normally occurring in first month after transplantation are pneumonias caused by Gram-negative bacilli (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) and *Staphylococcus aureus*. While awaiting the culture results, a third-generation cephalosporin with or without an aminoglycoside can be administered. In resistant cases, meropenem, ciprofloxacin or vancomycin may be administered.

Legionella pneumonia

This can cause nosocomial pneumonia. In this case, a chest X-ray shows irregular, nodular shadows that progress to a lobar or diffuse consolidation, cavitation can also occur. Identification may be done by direct immunofluorescent staining of sputum or biopsy samples, or by urine antigen assay. Macrolides are the drugs of choice, however, they interfere with cyclosporin and tacrolimus pharmacokinetics. Rifampicin has also been found to be effective, besides doxycycline and the fluoroquinolones.

Nocardiosis

The diagnosis must be suspected in any case of chronic pneumonitis not responding to antibiotics. The associated presence of cerebral focal abscess and cutaneous manifestations is highly suggestive of the diagnosis. The diagnosis must be confirmed with aspiration, microscopy and culture. Treatment with TMP-SMZ is usually successful.

Alternative drugs are ciprofloxacin, cephalosporins, imipenem and aminoglycosides.

***Pneumocystis carinii* pneumonia (PCP)**

This is a complication in transplant patients, treated either with cyclosporin or with rapamycin. However, the incidence of PCP has become rare with the prophylactic use of TMP-SMZ for the first 3 months post-transplantation. Patients with PCP usually present with fever and dyspnoea, while physical signs are absent. Radiographic abnormalities are variable and non-specific; interstitial pneumonia is frequent. Severe hypoxaemia is usually present. High-dose TMP-SMZ is the treatment of choice. In patients allergic to sulphonamides, slow intravenous infusion of pentamidine (3-4 mg/kg/day) may be indicated. Alternative treatment includes the use of clindamycin.

TUBERCULOSIS

The incidence of tuberculosis is more common in transplant recipients than in the general population and may be as high as 11%-17% in India.^{8,9} INH prophylaxis has been advised in western countries to prevent reactivation but this poses the problem of creating resistance in countries such as India where the incidence of the disease is very high. The mean time interval for the development of tuberculosis post-transplant is around 18.1+17.4 months.¹⁰ Treatment consists of four-drug therapy for a duration, 12-18 months.¹⁰ Rifampicin, being an enzyme inducer; is avoided; as it reduces the blood levels of cyclosporin and tacrolimus.

VIRAL INFECTIONS

Viral infections affect transplant recipients mostly in a period ranging from 3 months to 1 year after transplantation. They account for significant mortality, morbidity and allograft dysfunction. Important viral infections are discussed below.

Cytomegalovirus infection (human herpesvirus 5)

In the western world, approximately 50% of patients awaiting transplantation have been infected with CMV in the past and have tested positive for antibodies. In the Indian subcontinent, the IgG CMV positivity is nearly 100%.

There are three forms of CMV infection in transplant patients:

1. **Primary infection:** This is the most severe variety of infection and is associated with approximately 60% morbidity. The virus can reside in the allograft and this can infect a previously seronegative recipient. These patients have more than 50% risk of symptomatic disease.¹¹
2. **Secondary infection:** This occurs in previously seropositive patients because of reactivation of the patient's own latent virus or reinfection. Systemic inflammation can reactivate CMV from latency. Use of

antilymphocyte globulin, OKT3 and mycophenolate have been shown to increase the incidence of CMV.

3. **Superinfection:** This occurs when the donor and recipient are both seropositive and the virus of donor origin reactivates in the recipient.

Clinical features

Typical CMV disease manifests itself with spiking, constant fever associated with weakness and malaise 4-10 weeks post transplantation. It may also be associated with anaemia, leucopenia, thrombocytopenia, mild lymphocytosis and mild hepatitis (elevated aspartate aminotransferase). Less common features are arthralgias, overt hepatitis, splenomegaly, gastrointestinal ulceration, encephalitis, myocarditis and pneumonitis. Deterioration in the renal function may also occur in some cases. CMV infection may render the patient susceptible to opportunistic infections such as *Pneumocystis carinii* or invasive aspergillosis. It may also expose the patient to increased risk of EBV infection or to lymphoproliferative disorders. Chorioretinitis with a permanent reduction in vision may occur in at least half of the patients. CMV infection may precipitate acute rejection due to upregulation of major histocompatibility complex (MHC) antigens.

Diagnosis

- Serology is helpful for detecting previous CMV infections; however, it cannot be used for early diagnosis and does not provide relevant clinical information.^{12,13}
- Viral cultures of peripheral blood leucocytes (PBL) provide a direct demonstration of the presence of CMV. However, this takes 5-28 days to produce a cytopathic effect and the delay is inevitable.
- Shell vial modification of the buffy coat culture technique shortens the time of viral culture, but is still not useful for an early diagnosis^{14,15} and does not correlate with the clinical course of the infection.¹³
- CMV antigen test is an immunocytochemical method that, by using a monoclonal antibody specific for the pp 65 CMV matrix protein, allows detection and quantification of positive PBL.
- Polymerase chain reaction (PCR) can also be used to detect the DNA of CMV in the plasma or leucocytes of the patient.¹⁶ This test has a good sensitivity and specificity,¹⁷ and can detect the presence of viraemia even before the onset of symptoms.
- In the diagnosis of CMV, it is important to distinguish between latency, active infection and disease. Nucleic acid amplification-based assay (NASBA) is the sure-shot method of diagnosing active disease and, therefore is the most popular method of detecting CMV.

In fatal infections, CMV has been cultured from many sites, including the bone marrow, kidney, liver, lung, pancreas, large bowel and brain.

Management

CMV-negative recipients, CMV-negative donors-recipients have the lowest incidence of CMV infection.^{18,19} When infection does occur, it is most probably due to transfused blood. Leuco-reduction of transfused blood lowers this incidence.¹⁸

70%-90% of recipients CMV-negative recipients, CMV-positive donors-develop primary CMV infection and 50%–80% have CMV disease. None of the available therapeutic regimens reliably prevent this incidence; however, prophylactic and reserve therapies with ganciclovir have, to a large extent, reduced the incidence of CMV disease. CMV hyperimmune globulin has been used as rescue therapy.

CMV-positive recipients, CMV-negative donors the transplant recipients may have reactivation of a latent CMV infection. Antiviral therapy is recommended for patients who receive antilymphocyte globulin as induction therapy.

CMV-positive recipients, CMV-positive donors the recipients, are at a higher risk for both reactivation and superinfection. USRDS and UNOS reveal the worst graft and patient survival at years post transplantation in this group. Antiviral therapy is recommended for those who receive antilymphocyte globulin.

Treatment

Clinical CMV disease requires intravenous administration of ganciclovir, a guanine analogue, at 5 mg/kg every 12 hours, with dose adjustment in case of renal dysfunction. This is continued for 2 weeks followed by oral ganciclovir for up to 3-6 months. To prevent relapse or resistance, treatment should be continued until clearance of viraemia. In case of overt CMV infection, a decrease in immunosuppression and administration of TMP-SMZ for prevention of *P. carinii* infection has been recommended. For patients who develop ganciclovir resistance, foscarnet given intravenously at 60 mg/kg every 8 hours initially followed by 120 mg/kg/day maintenance dose can be useful. However, it is nephrotoxic, causing a reversible nephropathy. Recently a new anti-CMV molecule, cidofovir, has been licensed, which is also nephrotoxic.

Prevention of infection and disease

Primary CMV infection in seronegative recipients can be avoided if the transfused blood and especially the transplanted kidney come from seronegative donors. Live-attenuated CMV vaccine has been administered in the pre-transplant period to immunize seronegative recipients.

Passive immunization with immunoglobulin over the first 4 months after transplantation reduces CMV-related illness in CMV-seronegative recipients from CMV-seropositive donor organs. Oral acyclovir (800-3200 mg depending on the renal function) has been advocated for use as prophylaxis for the first 12 weeks following renal transplantation. However, its efficacy has not been established.

Other antiviral agents

Valganciclovir: This is a valyl-ester prodrug of oral ganciclovir. It has a bioavailability of nearly 70% at doses of 450-900 mg. It produces ganciclovir levels that are similar to intravenous administration of 2.5–5.0 mg/kg of ganciclovir.²⁰

Leflunomide: This is a pyrimidine synthesis inhibitor and immunosuppressive agent that has been utilized to prevent CMV and herpes simplex virus (HSV-I) replication by interfering with virion assembly.²¹ Experimental trials are still continuing regarding its role in the control of CMV infection.

Pre-emptive antiviral treatment has to be based on laboratory tests that indicate CMV activity. In CMV seronegative recipients of a seropositive organ, a programme of weekly testing for the first 2-3 months has a positive predictive value of 80%.

Epstein-Barr virus (EBV)

This virus is endemic in all human populations and after infection is carried lifelong, as a latent infection of the lymphoid cells with only occasional viral replication. The effect of immunosuppression of the cytotoxic T cell population results in its failure to check the proliferation of EBV-infected B lymphocytes. Chemoprophylaxis with acyclovir in EBV-negative transplant recipients has been carried out to prevent lymphoproliferative disorders, but the results are not convincing. The role of a very early and prolonged intravenous administration of ganciclovir is under investigation.²² Rituximab (anti-CD20 monoclonal antibody) has been shown to remit EBV-induced post-transplant lymphoproliferative disorder.

Varicella zoster virus (VZV)

Chickenpox is rare in graft recipients but zoster occurs annually in approximately 3% of renal transplant patients (10 times more than in non-immunocompromised patients). One of the clinical features is rash, which may become confluent, bullous, haemorrhagic or gangrenous. Pneumonitis, encephalitis or meningitis may be fatal. Oral acyclovir (800 mg, four times a day for 7 days) or intravenous acyclovir in the most severe cases (250–500 mg/m² every 8 hours for 7 days) may halt the progression of herpes zoster but it may precipitate renal dysfunction. Valacyclovir at dosage of 1 g three times a day for 7-14 days can also be used. If a patient without antibodies to VZV is exposed to chickenpox, then immunoglobulin is a dose of 125 µl/10kg of body weight should be given within 72 hours of exposure.

Herpes simplex virus (HSV)

Primary infection with HSV is rare in transplant patients. Reactivation, 40% of which is asymptomatic, is more common. Infection usually involves the orolabial region and less commonly the anogenital area, conjunctiva or cornea. Most

patients respond well to oral acyclovir (200-400 mg five times per day for 7-14 days). In the case of encephalitis or other visceral localization, high dose intravenous acyclovir (100 mg/kg every day for 10-14 days) is the treatment of choice.

Human herpesvirus 6 (HHV-6)

Such infections occur in 31%-55% of organ transplant recipients, usually 2-4 weeks after transplant as a result of reactivation caused by intense immunosuppression. In many cases there is a co-infection of HHV-6 and CMV or a reactivation together.²³ Two strains have been identified. HHV-6A and HHV-6B. Renal transplant recipients are exclusively infected with HHV-6B. Clinical sequelae may range from a self-limiting febrile illness to disseminated disease. Bone marrow suppression, meningoencephalitis, interstitial pneumonitis and a mononucleosis like syndrome are the most commonly reported types of clinical disease. HHV-6 responds to ganciclovir and foscarnet, but is resistant to acyclovir.

Human herpesvirus 8 (Kaposi sarcoma)

It may develop in transplant recipients either as a consequence of reactivation or as a primary infection which may be transmitted through the graft.²⁴ A response to treatment with cidofovir has been reported in post-transplant Kaposi sarcoma. Cancer therapy may be required.

Polyomavirus

Serological studies have shown that up to 90% of the population have been exposed to the polyomavirus by adulthood. Three species-BK virus (BKV), JC virus (JCV) and Simian virus (SV 40)-infect humans. In fact, BKV was first discovered in 1971 from renal transplant patients who developed ureteric stenosis.²⁵ Initial infections are usually occult and occur via the respiratory tract or through blood transfusion. Serological activation and shedding of the virus in the urine has been reported in 60% of kidney transplant recipients with graft dysfunction.²⁵ BK viraemia has been seen in 11%, and viruses in 27% of paediatric renal transplant patients.²⁵ JC viraemia was also discovered in about 13.5% of cases. Polyomavirus nephropathy (PVAN) is characterized by mononuclear cell interstitial infiltrates and tubulitis, which can be confused histopathologically with acute cellular rejection. Recognition is critical as the therapeutic choices are diametrically opposite, requiring reduction of immunosuppression. Early cessation of corticosteroid therapy from immunosuppressive protocols has been associated with a decline in the incidence of PVAN.²⁵ Male sex and donor seropositivity coupled with recipient seronegativity are further risk factors for the development of PVAN.

Hepatitis B and hepatitis C viruses

These viruses remain a cause for concern in patients who have

been on *long-term* haemodialysis prior to transplantation. They also carry a significant mortality and morbidity. However, a discussion about them is beyond the scope of this article.

FUNGAL INFECTIONS

The major fungal infections include those caused by *Aspergillus* species, *Histoplasma capsulatum*, *Coccidioides immitis* and *Cryptococcus neoformans*.

Aspergillosis species

This can be found as saprophytes but the repeated demonstration of hyphae on direct microscopy and growth in culture in a patient with unexplained pneumonia is highly diagnostic. It can cause a patchy infiltration followed by consolidation and abscess formation, usually around 1-5 months post transplantation. Mortality is extremely high, especially when dissemination in the form of rhinosinusitis, cerebritis or abscess takes place. Successful treatment depends on three factors: early diagnosis, aggressive antifungal therapy and ability to reduce immunosuppression.²⁶ Amphotericin B is the drug of choice; its lipid formulation is less nephrotoxic and can be used at higher dosages. Itraconazole (200 mg three times a day for 3 days) followed by 200-400 mg/day may be used. New antifungal agents are voriconazole and echinocandins.

Histoplasmosis

This is relatively frequent in endemic areas (America, Africa). It usually presents with fever, malaise, myalgias, non-productive cough, arthralgias and erythematous skin lesions. Hilar adenopathy and small, irregular disseminated infiltration may be seen on the chest X-ray. Recovery of the fungus from the lung biopsy is highly diagnostic. Treatment with amphotericin B is the first-line of therapy. Alternative agents are itraconazole or ketoconazole for at least 6-8 months.

Cryptococcosis

It presents with cough, chest pain, mucopurulent expectoration, haemoptysis and dyspnoea. Fever may be absent. A single nodule or focal or disseminated infiltrates may be the only findings on the chest X-ray. Central nervous system disease may present as subacute meningitis. Amphotericin B with flucytosine is the treatment of choice. India ink staining and latex agglutination tests of the cerebrospinal fluid are highly diagnostic and require early initiation of therapy.

Central nervous system infections

These usually occur within 1-12 months post transplantation. Presentation may be different than in normal patients. The onset may be subacute, and systemic signs may be lacking.

The most reliable symptoms are headache and unexplained fever. Patients should be subjected to CT scan examination and a lumbar puncture to clinch the diagnosis (Table 4).

Table 4. Central nervous system infections in transplant recipient

Syndrome	Most frequent aetiological agent	Clinical characteristic
Acute meningitis	L. monocytogenes	<ul style="list-style-type: none"> Fever, altered sensorium and headache 40 % may have no signs CSF: increased TLC and proteins may be lacking 33% focal radiological findings, 25% - seizures Ampicillin 14-21 days + aminoglycosides 7-10 days
Subacute/chronic meningitis	C. neoformans H. capsulatum N. asteroides S. stercoralis M. tuberculosis	<ul style="list-style-type: none"> Fever or headache over several days or weeks Non-specific presentation Concomitant lung or skin infection in some cases
Focal brain abscess	A. fumigatus	<ul style="list-style-type: none"> Seizures, focal neurological abnormalities. Not found in CSF Concomitant skin, lung and kidney involvement in some cases
Multifocal leucoencephalopathy	Papovavirus HSV CMV EBV	Progressive dementia

HSV : herpes simplex virus; CMV: cytomegalovirus; EBV: epstein-Barr virus; TLC: total leucocyte count

PREVENTION OF INFECTION IN ORGAN TRANSPLANT RECIPIENTS

This is one of the primary goals in the management of organ transplant recipients. Theoretically, the best chance of prevention is represented by the use of low immunosuppression. Availability of more specific immunosuppressive agents have reduced the incidence of severe and fatal infections.

Before transplantation

Patients accepted into a transplant programme should be screened for the presence of active infection. Thorough screening should be done by taking nasal swabs for *Staphylococcus*, as well as dental examination and assessment of the chest and urinary tract.²⁷

During hospitalization

The risk of postoperative infection can be reduced by minimizing the presence and duration of drainage catheters, stents, vein catheters and other foreign bodies.²⁷

Since infections in transplant patients may often have devastating effects, their early diagnosis and treatment forms the crux of the management. Because of the non-specific symptomatology as a consequence of immunosuppression, it

is imperative to have a high index of suspicion.

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