

# NEWER INFECTIONS IN KIDNEY TRANSPLANT RECIPIENTS

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## INTRODUCTION

With the discovery of newer and more potent immunosuppressive agents, there has been a marked decrease in rates of acute rejection and improvement in short term graft survival<sup>1</sup>. However, long term graft and patient survival has not improved significantly. Cardiovascular disease, infections, death with functioning graft, and malignancy are common causes of patient loss<sup>1,2</sup>. Newer infections (eg polyoma virus, adenovirus) have been identified and similarly newer diagnostic modalities have emerged to recognise these infections early. Infections continue to be a bugbear though the pattern of infections has changed over the years<sup>2,7</sup>. This review is an attempt to highlight recent advances in the diagnosis and treatment of opportunistic infections, especially viral infections focussing on cytomegalovirus and polyomavirus (PV) with broad overview of other infections. The general characteristics of infections in transplant recipients are:

1. The etiology of infections is diverse. These include common community acquired bacterial and viral infections and uncommon but often fatal opportunistic infections, e.g. infections due to *Pneumocystis carinii/jiroveci*, *Nocardia* asteroids, *Cryptococcus neoformans*, CMV, VZV, BKV, Influenza, *Legionella* species<sup>2,3</sup>.
2. Inflammatory responses due to infection are impaired by immunosuppressive therapy, which results in diminished/delayed symptoms and signs. As a result, infections are often in advanced stage at the time of presentation to physician.
3. Serologic testing is not generally helpful for the diagnosis of acute infection in immunocompromised host since seroconversion is often delayed. So antigen based tests (e.g. enzyme linked immunosorbent assays (ELISA) or nucleic acid based molecular assays (e.g. polymerase chain reaction (PCR) are needed for diagnosis<sup>2,4</sup>.
4. Better modalities are required to diagnose infections e.g. computerised tomographic (CT) scans or magnetic resonance imaging (MRI). Tissue biopsies with histopathology and microbiology are often needed to make specific diagnosis. These should be done early in the course of disease to fetch early diagnosis, treatment and better outcomes.
5. Surgical intervention is often necessary to cure localized infections; antimicrobial alone are frequently inadequate.

### **Risk of infection following transplantation**

The risk of infection following transplantation depends on two factors: the epidemiologic exposure of the individual and the net state of immunosuppression.

### **Net state of immunosuppression**

This refers to all the factors that contribute to patient's risk of infection. The main factors are the dose, duration and

sequence of immunosuppressive therapies. Presently the drug levels are used to guide these therapies, which is often inaccurate resulting in drug toxicity, infection or graft rejection. In future advanced assays based on gene or protein expression may be available resulting in optimization of therapies with better prevention against infections or rejection<sup>2,3</sup>.

### **Epidemiologic exposures**

The epidemiologic exposure of importance to an individual will vary based upon the nature of the immune deficits. Most transplant patients have multiple deficits. Thus, bacterial and fungal pathogens are more important in the setting of neutropenia while viral and intracellular (e.g. tuberculosis) are more common with T cell immune deficits. Epidemiologic exposures can be divided into four overlapping categories: donor-derived infections, recipient-derived infections, nosocomial infections, and community infections<sup>2,3</sup>.

## CHANGING PATTERN OF INFECTION

Early in the evolution of solid-organ transplantation, there were limited number of available immunosuppressive agents, and antirejection protocols were relatively standardized. As a result, the timeline for the development of common post-transplantation infections was relatively predictable<sup>3,7</sup>. Changes in immunosuppressive regimens, routine prophylaxis, and improved graft survival have altered the original pattern (figure 1). Corticosteroid-sparing regimens and antipneumocystis prophylaxis have made pneumocystis pneumonia less common. Newer immunosuppressive approaches, including the use of sirolimus, mycophenolate mofetil (MMF), T-cell and B-cell depletion, and costimulatory blockade, have largely replaced high-dose corticosteroids and azathioprine<sup>1</sup>.

T-lymphocyte-depleting antibodies commonly used for induction therapy are associated with increased viral activation-notably, activation of cytomegalovirus, EBV, and HIV<sup>5</sup>. Cellular depletion after induction therapy often persists beyond the period of antimicrobial prophylaxis, resulting in late infections with viruses such as cytomegalovirus and BK polyomavirus as well as fungal infections and malignant conditions after transplantation<sup>5</sup>. The timeline for a given patient is reset with each episode of rejection or intensification of immunosuppression (e.g., with bolus corticosteroids), with an increased risk of opportunistic infections.

### **Early Post-Transplantation Period (0-4 weeks after transplantation)**

Three types of infection occur in this period<sup>2,5</sup>

1. **Recipient derived infections:** present in recipient before transplantation, which after inadequate treatment emerges in post transplant period. e.g pretransplant pneumonia and

vascular access infections.

2. **Donor derived infections:** may be nosocomially derived (resistant gram negative bacilli and *S. aureus* or candida), secondary to systemic infection in the donor or contamination during organ procurement.
3. **Infections related to surgery:** include surgical wound infections, pneumonia, urinary tract infections, infections in fluid collections etc. These are nosocomial infections and are due to same antimicrobial resistant bacteria and candida infections observed in immunosuppressed patients. This is responsible for more than 90% infections during this period.

Opportunistic infections are usually not seen in this period. Limited perioperative antibiotic prophylaxis (from a single dose to 24 hours of an antibiotic such as cefazolin) is usually adequate.

### **Intermediate Post-Transplantation Period (1 to 6 months post transplantation)**

Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis generally prevents most urinary tract infections and opportunistic infections such as pneumocystis pneumonia, *L. monocytogenes* infection, *T. gondii* infection, and infection with sulfa-susceptible nocardia species<sup>5</sup>. Infection due to endemic fungi, aspergillus, cryptococcus, *T. cruzi*, or strongyloides may occur. Herpesvirus infections are uncommon with antiviral prophylaxis. However, other viral pathogens, including polyomavirus BK, adenovirus, and recurrent HCV, have emerged. Viral pathogens and allograft rejection are responsible for the majority of febrile episodes that occur during the period from 1 to 6 months after transplantation<sup>2,5</sup>.

### **Late Post-Transplantation Period (>6 months after transplantation)**

The risk of infection diminishes 6 months after transplantation, since immunosuppressive therapy is usually tapered in about 80% of recipients who have satisfactory allograft function. However, transplant recipients have a persistently increased risk of infection due to community-acquired pathogens<sup>5</sup>. A second group of patients have chronic viral infections leading to organ damage (e.g. BK Polyomavirus leading to nephropathy, HCV leading to liver failure, CMV- chronic graft dysfunction, and EBV leading to post transplant lymphoproliferative disorders (PTLD). About 5-10% of patients do not have good graft function and require more intense immunosuppression. These patients are at increased risk for opportunistic infection with listeria or nocardia species, invasive fungal pathogens such as zygomycetes and diatomaceous molds. These patients may benefit from lifetime trimethoprim-sulfamethoxazole or antifungal prophylaxis<sup>2,3,5</sup>.

## **1. VIRAL INFECTIONS**

### **Cytomegalovirus infection after kidney transplantation**

Cytomegalovirus (CMV) is one of the most important infections in renal transplant recipients<sup>8,9</sup>. Exposure to virus, as indicated by the presence of detectable IgG anti-CMV antibodies in the plasma, increases with age in general population and is present in most of the donors and recipients prior to transplantation. Moreover, CMV is cell associated, primarily residing in T lymphocytes, although also found in polymorphonuclear cells, endothelial vascular tissue and renal epithelial cells<sup>8</sup>.

CMV may have substantial impact on host immune responses. It causes up regulation of IL-2 and can prevent the inhibition of IL-2 gene production by cyclosporine. CMV also down regulates MHC-1 molecules on the surface of infected cells to evade host immune

recognition<sup>8,9</sup>.

CMV can be transmitted from the donor either by blood transfusion or by the transplanted kidney<sup>7</sup>. The risk of CMV infection is particularly increased with the use of induction with antithymocytic or antilymphocytic antibody<sup>5</sup>. Thus both the recipient and the donor are screened for anti CMV antibodies prior to transplantation. CMV is also an important cause of morbidity and mortality in the renal transplant setting. CMV disease was associated with relative risk of mortality of 2.5<sup>11</sup>.

### **CMV infection versus disease**

Detection of virus by any method eg- seroconversion, antigen detection, isolation via culture or by molecular techniques is called CMV infection. CMV disease in comparison requires clinical signs and symptoms. The most common presentation of CMV disease is mononucleosis like syndrome with fever, malaise, myalgias and arthralgias, usually associated with leucopenia and mild atypical lymphocytosis. A mild elevation in serum aminotransferase concentrations also may be seen. Some patients have other organ involvement (including hepatitis, pneumonitis, pancreatitis, colitis, meningoencephalitis and rarely myocarditis)<sup>8,9</sup>. CMV chorioretinitis, which is common in AIDS patients, is relatively rare in kidney transplant recipients. CMV disease typically occurs one to four months after transplantation if prophylaxis is not used, or one to four months after discontinuation of prophylaxis, although cases may develop later. Thus the onset of disease usually follows the period of maximal immunosuppression eg for prevention and treatment of acute rejection<sup>8,10</sup>. With the use of MMF, however, invasive CMV disease can occur in the absence of fever and leucopenia. CMV infection is associated with an overall increase in the risk of additional infections, including EBV associated PTL<sup>11</sup>.

Effect of CMV on graft survival- patients with CMV appear to have reduced graft survival. Whether this is a direct effect on the allograft or an indirect consequence of infection leading to acute tubular necrosis and cellular rejection has been disputed<sup>8,11</sup>. CMV disease has been linked to chronic rejection with arterial myointimal thickening, similar to atherosclerotic coronary disease.

**Diagnosis:** techniques for detecting CMV have improved dramatically. Several diagnostic modalities are available<sup>8,10</sup>.

**Serology** – a fourfold increase in the CMV-IgG titer or a markedly positive CMV-IgM titer may be used to suggest recent infection. But this approach has been largely abandoned after advent of polymerase chain reaction (PCR) and antigen detection techniques.

**Culture**- isolation of CMV by culture of urine, buffy coat, and throat or, in patients with pneumonitis, bronchoalveolar lavage fluid (BALF), is the preferred method to diagnose active infection. The culture is done with shell vial, which can be processed in 24- 48 hours.

**CMV antigenemia**- it is a semiquantitative assay in which circulating lymphocytes are stained for CMV early antigen (pp65).

**Molecular assays**- PCR and other amplification assays is mainstay of diagnosis now a day. The total burden of CMV viral particles in the host may correlate with clinical evidence of disease and disease severity or response to therapy. In a study all patients with CMV DNA levels of > 500 copies/μg of total DNA in peripheral blood had clinical evidence of disease. The quantitative CMV levels are lower in plasma compared to blood, so different labs give different results. Invasive tests- such as biopsy, lumbar puncture and colonoscopy are sometimes required to clinch the diagnosis.

### **Prevention of CMV disease**

The incidence of CMV disease has considerably decreased after introduction of preventive strategies eg- prophylaxis and pre-emptive

treatment (From 20-60% to 5%). But only the prophylactic approach resulted in decreased bacterial and fungal infections and mortality<sup>12</sup>. There is no difference in risk of disease with oral or intravenous pre-emptive therapy.

**Agents used for prophylactic therapy:** Meta-analysis of 19 trials in 2005 comparing the prophylaxis versus no prophylaxis showed that prophylaxis resulted in significant decrease in the incidence of CMV infection, CMV disease and mortality. Ganciclovir was superior to acyclovir, while oral ganciclovir was similarly effective as valganciclovir and intravenous ganciclovir<sup>13</sup>.

Valganciclovir- a valyl- ester prodrug of oral ganciclovir, has a bioavailability of nearly 70 percent (compared to 7% of oral ganciclovir) and at doses of 450 to 900 mg produces serum ganciclovir levels that are similar to that measured with intravenous ganciclovir dose of 2.5 to 5 mg/kg.

In PV 16000 international, double dummy, double blinded trial of oral valganciclovir versus oral ganciclovir for the prevention of CMV in solid organ transplant recipients, 364 CMV negative (D+/R-) recipients (120 renal transplant recipients), were randomly assigned at a 2:1 ratio to receive either oral valganciclovir 900 mg per day or oral ganciclovir 1000 mg TID with dose adjustment for renal insufficiency. Treatment was administered for 100 days and the study medication was started within 10 days of transplant surgery. During treatment, only 0.8% and 1.6% of patients in valganciclovir and ganciclovir group developed CMV disease, respectively. This study therefore demonstrated that valganciclovir and ganciclovir has similar efficacy. At six months, CMV disease occurred in 12 and 15 percent in the valganciclovir and oral ganciclovir group respectively<sup>14</sup>. Other antiviral agents in use are CMV hyperimmune globulin, Valacyclovir, Leflunamide.

#### CMV status and prophylactic therapy

The risk of disease depends on recipient and donor seropositive status<sup>13,15</sup>. Accordingly the prophylaxis is prescribed. The use of leukocyte poor blood transfusion substantially decreases the risk of viral transmission.

*CMV positive donor, CMV negative recipient (D+R-)*- this group has highest risk of CMV infection and disease. The risk of disease was as high as 50-70% without prophylaxis, but now with the advent of effective prophylaxis, this risk has decreased substantially (1%) during prophylaxis with ganciclovir or valganciclovir.

*CMV negative donor, CMV positive recipient (D-R+)* - CMV infection/or disease develop in upto 20% of cases.

*CMV positive donor, CMV positive recipient (D+R+)*- these patients are at risk of both reactivation of latent virus and super infection with a new viral strain. Prophylaxis is recommended in these patients.

*CMV negative donor, CMV negative recipient (D-R-)*- low prevalence of disease, so no prophylaxis is recommended.

**Duration of prophylaxis-** the optimal duration of prophylaxis is unknown. Most institutions use approximately three months of prophylaxis except when both donor and recipient are seronegative. In some centers prophylaxis is extended to 180 days for D+R- and D+R+ cases.

#### Treatment of CMV disease

Invasive disease is treated with intravenous ganciclovir 5 mg/kg every 12 hours in patients with normal renal function. Secondary prophylaxis for additional three months is recommended after initial treatment<sup>15</sup>. The most frequent side effect of ganciclovir is leucopenia, which is usually reversible after dose reduction.

Asymptomatic or mild disease is treated with valganciclovir in a dose of 900 mg twice daily, adjusted for kidney function, for a minimum of 21 days or longer. The effectiveness of valganciclovir was best

studied in VICTOR study, in which valganciclovir was compared with iv ganciclovir. Both drugs were similarly effective in suppressing viremia at day 21 and day 49<sup>16</sup>.

In all cases of quantifiable CMV viremia, the antimetabolite (azathioprine or Mycophenolate) should be discontinued, at least until viremia clears. Weekly quantitative PCRs should be obtained during treatment to determine an adequate response. If the quantitative PCR level does not decrease by 50% in two weeks, viral resistance or recipient immunocompetence should be suspected. In this setting, the dose of valganciclovir can be increased or the patient switched to intravenous ganciclovir to overcome relative resistance. Patient can be given CMV hyperimmune globulin in this situation. The treatment should be continued for one week beyond the finding of a negative quantitative CMV PCR<sup>4,15</sup>.

#### Ganciclovir resistance

has been reported with HIV patients, but rare in transplant recipients. Ganciclovir resistance was more common among those who received more intense immunosuppression and/or were administered prolonged ganciclovir prophylactic therapy. In PV 16000 trial, 3 cases (2%) on ganciclovir developed resistance compared to none in valganciclovir group<sup>14</sup>. Most commonly resistance emerges due to mutation in the UL 97 gene, and less commonly due to mutation in UL 54 gene. Ganciclovir resistance should be suspected when patients have persistent unchanged viremia, and or symptoms at 2 weeks into therapy and in such cases, genotypic assays for the detection of mutations should be performed. Treatment of resistant isolates may include foscarnet with or without ganciclovir, or cidofovir<sup>8, 15</sup>.

#### Polyomavirus infections

Human polyomaviruses comprise a genus of DNA viruses in the Papovaviridae family, which cause clinical disease primarily in immunocompromised hosts. JC and BK viruses, named for the patients from whom they were isolated, are the major clinically significant human polyomaviruses. Simian virus (SV40) has been a model experimental system for the study of cell transformation and tumorigenesis for many years<sup>17</sup>.

#### Epidemiology of Polyomavirus Associated Nephropathy (PVAN)

In various reports, it ranges from 1%-10%. The majority of PVA cases occur within the first year posttransplantation. Renal allograft loss due to PVAN ranges from 10% to 80% in various studies<sup>17,20</sup>. Most cases are caused by BK virus.

#### Clinical manifestation

Serologic evidence of past infection with JC and BK viruses is widespread, but significant sequelae of infection are uncommon in the immunocompetent host.

JC virus infection in the immunosuppressed host can lead to progressive multifocal leukoencephalopathy, a devastating demyelinating disease. Patients with PML typically present with rapidly progressive focal neurologic deficits without signs of increased intracranial pressure<sup>9,17</sup>.

Due to its tropism for genitourinary epithelium, BK virus mainly causes disease of the genitourinary tract in transplant recipients. Clinical manifestations include asymptomatic hematuria, hemorrhagic cystitis, ureteral stenosis, and interstitial nephritis (or nephropathy)<sup>9,19</sup>. Risk factors for PVAN<sup>17,20</sup>

- Intense immunosuppressive therapy.
- Immunosuppressive drugs and combinations- The use of combination of MMF with tacrolimus has been seen in more than 50% of all cases reported.
- Antilymphocyte preparations- The use of antilymphocytic

preparations for treatment of rejection was associated with polyomavirus replication in patients who received triple therapy containing tacrolimus or MMF.

- Steroids- The use of intravenous steroid boluses to treat rejection may increase the risk of PVAN.
- Other factors- older age, male gender, white ethnicity, diabetes mellitus and negative BKV serostatus.

#### Screening for polyomavirus replication

Screening is useful in early detection and intervention. Following tests may be performed<sup>19,21</sup>

- Urine cytology (decoy cells)
- Quantification of urinary BKV DNA
- VPI mRNA load.

BKV replication in urine precedes BKV viremia by a median of 4 weeks and histologically documented BKV nephropathy by a median of 12 weeks. It is recommended that renal transplant recipients be screened at least every three months during the first two years posttransplantation. Furthermore screening assays should be performed whenever a workup for allograft dysfunction is indicated and an allograft biopsy is performed.

It is recommended that positive screening tests should be confirmed within four weeks, and or followed by adjunct quantitative diagnostic assays of higher predictive value such as quantification of BKV DNA load in plasma (value >10,000 copies/ml). Persistent polyomavirus load above this value is highly suggestive of PVAN and evaluation with allograft biopsy is required.

#### Diagnosis

**Virus culture:** Virus culture is rarely used outside a research setting. Isolation of these viruses from clinical specimens require weeks to months.

**Urine cytology:** can be used to detect urinary shedding of polyomaviruses. The most characteristic abnormality of polyomavirus-infected cells is an enlarged nucleus with a single large basophilic intranuclear inclusion (decoy cells). There are several limitations of cytology:

- The cytopathologic changes can be confused at times with those due to malignancy or to other viruses, such as adenovirus.
- Cytology does not distinguish JC from BK virus infections.

**PCR:** Positive results of plasma PCR assays correlate with the presence of BK virus-associated nephropathy in renal transplant recipients and have also predicted the risk of disease.

In contrast to other modalities, PCR is positive for JC and/or BK virus sequences in the urine of a significant proportion of HIV-infected patients, apparently normal control populations, and elderly patients without evidence of overt immunosuppression. Thus it is difficult to assess the clinical significance of a positive PCR test of the urine<sup>19</sup>.

**Histopathology:** the definitive diagnosis of PVAN requires a histological workup to identify intranuclear polyomavirus inclusion bodies in tubular epithelial and/or glomerular parietal cells, often associated with epithelial cell necrosis and acute tubular injury. PVAN may be focal and can be associated with varying degrees of inflammatory cell infiltrates, tubular atrophy and fibrosis. The inflammatory cell infiltrate in PVAN may be rich in polymorphonuclear leucocytes and/or lymphocytes and plasma cells. The light microscopic findings are not pathognomic for PVAN, and adjunct diagnostic studies are required. Most centres use immunohistochemistry with antibodies that are specific for polyomavirus proteins such as large T antigen, some centres use in

situ hybridization to identify polyomavirus genomes or electron microscopy to demonstrate virion of compatible morphology<sup>18</sup>.

At least two biopsy cores which contain medullary parenchyma should be examined. A negative biopsy result cannot rule out PVAN because of focal nature of disease.

**PVAN and concurrent rejection:** in the presence of PVAN, the diagnosis of acute rejection may be difficult. There is consensus that endarteritis, fibrinoid vascular necrosis and glomerulitis as well as C4d deposits along peritubular capillaries should be regarded as evidence of concurrent rejection<sup>18,20</sup>.

**Other diagnostic tests:** Electron microscopy can be used to detect polyomavirus particles in urinary sediment or in oligodendrocyte nuclei of brain biopsy specimens. Viral nucleic acids can be detected in urinary sediment or brain biopsy specimens by hybridization methods and viral antigens can be detected with either immunofluorescence or ELISA assays<sup>19</sup>.

#### Treatment of PVAN

- Modification of immunosuppression: reducing the intensity of maintenance immunosuppression currently represents the primary mode of intervention. Patient can be switched from tacrolimus to cyclosporine or sirolimus or from mycophenolate to azathioprine<sup>19,21</sup>.
- Antiviral approaches: cidofovir and leflunamide have some invitro activity against polyomavirus. There is consensus that cidofovir could be used off-label as an investigational drug for the treatment of cases not amenable to decreased maintenance immunosuppression<sup>21</sup>.
- Following reduction of immunosuppression biopsy proven acute rejection may be seen in approximately a quarter of patients. These episodes of rejections may be steroid responsive without recurrence of PVAN. Later on after two weeks immunosuppression can be tapered.

Retransplantation after renal allograft loss due to PVAN- so far incidence has been reported around 15% as compared to 5% in primary transplant<sup>21</sup>.

## HERPES SIMPLEX VIRUS AND VARICELLA ZOSTER VIRUS

Seroprevalence for HSV-1 in the adult population is as high as 60 percent, while VZV rates can be as high as 90 percent<sup>4,10</sup>. Infection in the renal transplant patient is usually caused by reactivation of latent virus. HSV usually presents with oral or genital lesions, but in some instances can cause esophagitis, hepatitis, encephalitis or pneumonitis<sup>9,10</sup>. VZV reactivation usually presents as dermatomal but can disseminate sometimes causing similar problems<sup>22</sup>. In the absence of prophylaxis the HSV may be seen within first month of transplant and VZV can be seen between first to six month post transplant. In patients with disseminated varicella, there was a high rate of disseminated intravascular coagulation and hepatitis (50%), pneumonitis (29%) and mortality in one third of patients<sup>9,22</sup>.

Pretransplant screening for VZV should be performed and naïve patient should be vaccinated with live attenuated varicella vaccine before transplant to prevent primary infection after transplant, an often severe disease with high mortality rate. If VZV naïve patient is exposed to patient infected with VZV, he should be given VZ Immunglobulin within 96 h of exposure<sup>4,22</sup>.

Diagnosis may be made with the aid of direct fluorescence antibody or Tzanck smear for HSV and VZV from vesicular lesions or PCR from CSF or visceral tissue samples. Treatment of disseminated

infections involves intravenous acyclovir, while less severe infection can be treated with oral acyclovir, valacyclovir or famciclovir<sup>4, 22</sup>.

## HUMAN IMMUNODEFICIENCY VIRUS

With the advent of highly active antiretroviral therapy (HAART), HIV infected patients now have improved overall survival rates<sup>24</sup>. Initially HIV infected patients were not considered for renal transplantation as early studies demonstrated an increased risk of mortality following transplantation<sup>23</sup>. However more recent studies have suggested that HIV patients receiving HAART have improved survival compared with historic controls on dialysis<sup>24</sup>.

There are significant drug interactions of immunosuppressive drugs with HAART. The protease inhibitors in HAART regimen inhibit cytochrome p 450, increasing levels of calcineurin inhibitors, requiring dose reduction of these drugs, whereas non nucleoside reverse transcriptase inhibitors can promote activity of cytochrome p450<sup>24</sup>.

Standard triple immunosuppressive regimen consisting of steroids, calcineurin inhibitors and antimetabolite can be used in patients with HIV. But induction with antibody or use of antithymocyte globulin is not recommended for rejection<sup>23, 24</sup>.

## RESPIRATORY VIRUSES

Various viruses can cause respiratory disease in the renal transplant population, including adenovirus, respiratory syncytial virus, influenza, parainfluenza, human metapneumovirus, rhinovirus and coronavirus<sup>4, 9</sup>. They are transmitted by respiratory droplets and aerosols. These viruses can lead to upper respiratory tract disease, as well as bronchitis, pneumonitis and pneumonia.

Adenovirus can cause gastroenteritis, cystitis, hepatitis and also nephritis in renal transplant recipients<sup>9</sup>. Infection with respiratory viruses may be associated with rejection.

The diagnosis is done by examination of virus laden respiratory cells (eg nasopharyngeal washing, bronchoalveolar fluid) by virus specific fluorescent labelled antibody probes.

Influenza vaccine should be administered pretransplant and every year after transplant<sup>4</sup>. Treatment of respiratory viral infections involves supportive care and, in some cases, the use of antiviral medications. Influenza can be treated with oseltamivir or zanamivir. Ribavirin has been approved to treat lower respiratory tract infection with respiratory syncytial virus. Adenovirus infections are usually treated with reduction of immunosuppression<sup>4</sup>.

## EPSTEIN BARR VIRUS AND POST

### TRANSPLANTATION

## LYMPHOPROLIFERATIVE DISORDER

EBV remains latent in lymphocytes following primary infection. A competent immune system, especially T cell response, prevents these cells from propagating. When T cell function is impaired, as in the case of renal transplant patients, this surveillance can fail and PTLD can develop<sup>10, 25</sup>. The risk is increased with use of cytolytic therapies, including antithymocyte globulin and OKT3<sup>5</sup>.

In immunosuppressed transplant recipients, primary EBV infection causes infectious mononucleosis – type syndrome, generally manifesting as lymphocytosis with or without lymphadenopathy or pharyngitis. Meningitis, hepatitis and pancreatitis are also observed<sup>4, 10</sup>. The majority of symptomatic infections in renal transplant recipients are primary infection, related to activation of donor virus. More than 90% of adults have antibodies by the age of 40 years. Renal transplant

recipients have the lowest risk of acquired PTLD in comparison with other transplant population (1-3%). PTLD most commonly occurs in first year post transplant. Compared with general population, PTLD has increased extranodal involvement, poor response to conventional therapies and poor outcomes<sup>25</sup>. The spectrum of disease is broad and ranges from benign polyclonal B cell, infectious mononucleosis type syndrome to malignant monoclonal B cell lymphoma. Most disease is of B cell origin. EBV negative PTLD has been described. Late PTLD (>1-2 years) after transplantation is more often EBV negative in adults<sup>10, 26</sup>.

Serology for EBV should be obtained before transplant for both donor and recipient. Allograft recipients who are EBV negative before transplant and receive an organ from a seropositive donor are at greatest risk of PTLD; consequently it is most commonly seen in pediatric and young adult populations<sup>25, 26</sup>. Currently there is no single standard strategy to prevent PTLD.

Effective prevention of CMV may also prevent EBV infections, primarily by limiting the impact of CMV on immune regulation. Serologic testing is not useful for the diagnosis of acute EBV infection or PTLD in transplantation. Quantitative viral load testing is required for the diagnosis. Definitive diagnosis of PTLD requires histopathological confirmation<sup>9, 25</sup>.

The treatment of PTLD consists of substantial reduction of immunosuppression which can lead to remission in 23 to 86% of patients<sup>25</sup>. Surgical resection may be an option in the renal transplant patient with isolated graft PTLD, where the graft can be removed and all immunosuppression discontinued. Rituximab, a monoclonal antibody to CD20 is also commonly used for the treatment of PTLD. If patients fail these strategies, IFN and IVIG have been used with varying success. Cytotoxic chemotherapy has been used as salvage therapy. The substantial reduction in immunosuppression may lead to graft loss; however patients who experience a complete remission, retransplantation has been successful<sup>25, 26</sup>.

The outcome of PTLD is variable. Patients with isolated allograft involvement have a five year survival of approximately 68% compared with extensive involvement, whose five year survival varies between 36 and 38 percent<sup>10</sup>.

## HEPATITIS B AND C

Patients of Chronic kidney disease (CKD) on dialysis have increased risk for hepatitis B and C. Currently it is estimated that the prevalence of HBV infection in haemodialysis population ranges from 0.1 to 0.4 percent<sup>4</sup>. All patients with CKD should be vaccinated for Hepatitis B before transplantation and their antibody titers should be checked<sup>27</sup>. Only 50-60% dialysis patients develop adequate titres of anti-HBs antibodies.

Patients with HBsAg positivity can be considered for transplantation. However, transplantation in cirrhosis is contraindicated. Liver biopsy should be done before transplant to evaluate the extent of damage<sup>28</sup>. Because there are chances of worsening of liver disease after transplantation in patients infected with HBV, it is prudent to start antiviral therapy before renal transplantation for patients with evidence of active viral replication. Post transplant, the long term graft and patient survival of HBsAg positive patients is inferior to HBsAg negative patients. A much higher risk of mortality from liver disease is seen in recipients who are HBV DNA or HBeAg positive as compared to those who are only HBsAg positive but HBV DNA negative<sup>28, 29</sup>.

The HBsAg positive patients are not considered for donation except for HBsAg positive patients, however donors who are HBeAg positive may be considered for donation, as risk of transmission is very small<sup>9, 28</sup>.

The therapy of Hepatitis B includes one of the antiviral drugs. The optimal duration of therapy is yet to be determined. Cessation of antiviral therapy in immunocompromised host is associated with an increased risk of flare of liver disease<sup>4,28</sup>. Lamivudine is most commonly used and response rates are also good but there is problem of resistance. Alternative drugs are adefovir, entecavir and telbivudine. However these are no long term studies with these drugs in renal transplant recipients<sup>4, 29</sup>.

The prevalence of HCV infection remains high in dialysis population and varies from 2.6% to 22.9% in various units<sup>9</sup>. There is a problem of sensitivity of antibody testing in patients with CKD, so nucleic acid based test should be done in dialysis patients before transplantation<sup>4, 27</sup>. Because of the increased risk of progressive liver disease following transplantation, patients with Hepatitis C should undergo liver biopsy to exclude advanced liver disease. Hepatitis C positive patients have a marked rise in viral load with initiation of immunosuppression immediately post transplant. Since there is large demand for organs, so Hepatitis C positive donors may be considered for donation, although these recipients have diminished graft and patient survival as compared to Hepatitis C negative recipients, but survival may be improved when compared with survival on dialysis<sup>30</sup>. The initial studies with short term follow up did not show any impact of hepatitis C positive status on graft and patient outcomes. But later studies with long term follow up demonstrated worse graft and patient survival in Hepatitis C patients as compared to hepatitis C negative recipients<sup>29</sup>.

Treatment for hepatitis C in general population usually consists of a combination of IFN and ribavirin. Ribavirin is metabolised in the kidney and should not be used in patients with creatinine clearance less than 50, as it can cause haemolytic anemia. Therefore hepatitis C should be treated before transplant with IFN which has shown to decrease viral and mortality due to liver disease in hemodialysis patients. The response is better in genotype 2 and 3, and remission rates upto 70-80% is seen with peg IFN. The response is not so good in genotype 1. Post transplant IFN treatment may lead to acute graft rejection, so it is not recommended except in exceptional situations<sup>30,31</sup>. Similarly ribavirin has been used in some studies with improvement in transaminase levels but no improvement in histology or viral load.

## OTHER IMPORTANT VIRAL INFECTIONS<sup>9, 10, 32</sup>

Infection	Common risk factors	Clinical presentation	Diagnosis	Treatment
Parvovirus B19	Bone marrow, lungs, Heart, kidney	Refractory anemia, pancytopenia, glomerulopathy	Giant proerythroblasts in bone marrow PCR	Intravenous immunoglobulin
Hepatitis E virus	Liver	Jaundice, portal HTN	Biochemistry HEV PCR	Conservative
West Nile virus	CNS, Organ transplantation	Fever, encephalitis	Csf exam., nucleic acid tests	Reduction immunosuppression
Lymphocytic choriomeningitis viral infection (LCMV)	CNS Infected donor (fatal infection)	Fever, encephalopathy	PCR of blood, csf, kidney	No specific
Human herpes virus 6 and 7 (HHV 6,7)	Hematology, liver, CNS	Fever, leucopenia, hepatitis, encephalopathy	Nucleic acid testing, tissue biopsy	Reduction of immunosuppression, ganciclovir, cidofovir
Human herpes virus 8 (HHV8)	Skin, lymph nodes, graft	Kaposi's sarcoma, primary lymphoma	Morphology Nucleic acid test	Reduction of immunosuppression, cytotoxic chemotherapy

## FUNGAL INFECTIONS

The transplant recipients are at increased risk for opportunistic fungal infections, apart from endemic mycoses (coccidioidomycosis, histoplasmosis, blastomycosis and paracoccidioidomycosis), the most important of these are *Pneumocystis carinii* (jiroveci), *Candida*, *Aspergillus Zycomycosis* (*Mucor*, *Rhizopus*) and *Cryptococcus neoformans*. The mortality from fungal infections remains high<sup>33</sup>. Opportunistic fungal infections are most common between one to six months post transplant. Predisposing factors includes the following:

- Use of corticosteroids, particularly the large doses to treat rejection
- Administration of broad spectrum antibiotics
- Overall state of immunosuppression
- Use of indwelling catheters
- Duration and number of surgical procedures
- Disruption of intestinal or bladder mucosa, vascular complications and hyperglycemia.

The incidence of pneumocystis carinii pneumonia has significantly reduced with prophylaxis of TMP/SMX for six months.

## IMPORTANT FUNGAL INFECTIONS POST RENAL TRANSPLANT<sup>2,3,33</sup>

Organism	Common sites	Clinical presentation	Diagnosis	Treatment
<i>Candida</i>	Mucocutaneous, fungal ball at Ureteropelvic junction, pyelonephritis, sometimes systemic involvement	Oral thrush, esophagitis, vaginitis, pneumonitis, peritonitis, endocarditis, cns infection	Positive fungal cultures from multiple sites are diagnostic. CT, MRI lesion	Mucocutaneous- Topical nystatin or Clotrimazole, fluconazole, itraconazole Tissue invasive- iv amphotericin B
<i>Pneumocystis carinii</i> (jiroveci)	lungs	Cough, dyspnea, hypoxemia	Interstitial infiltrates in X ray chest, CT chest, BAL with biopsy	High dose TMP/ SMX for 14-21 days IV Pentamidine, atovaquone etc.
<i>Aspergillus</i>	Lungs and sinus >90%, skin, cns, Rhinocerebral,	Fever, cough, bronchopneumonia with cavity sometimes disseminated infection	Culture of respiratory secretion or tissue histology,	Voriconazole, liposomal amphotericin, surgical debridement
<i>Cryptococcus</i>	Lung, central nervous system	Flu like symptom, Headache, fever, altered sensorium	Serum and csf cryptococcal antigen, tissue biopsy	Initial Liposomal amphotericin B and flucytocine later fluconazole
<i>Mucoraceae</i>	sinus, cns, lung	Rhinocerebral disease, hemorrhagic pneumonia	Culture	Aggressive surgery and Amphotericin

## BACTERIAL INFECTIONS

About 80% of infections in kidney transplant recipients are bacterial. The infections are comparable to those occurring after nontransplant patients. Common infections are urinary tract infections (UTIs), pneumonia with or without bacteremia, deep wound infections, vascular catheter and site infections, fluid collections or devitalized tissues<sup>2,3</sup>.

Historically, UTIs were most common infectious complication of renal transplantation. However with routine prophylaxis with TMP/SMX, frequency of UTIs has reduced to less than 10%. TMP/SMX can also reduce the incidence of *Nocardia asteroides* infection and sepsis related to *Listeria monocytogenes*<sup>(4)</sup>.

Pulmonary bacterial infections constitute most of the life threatening infections in kidney transplant recipients. Common bacterias are- enterobacteriaceae, *Pseudomonas aeruginosa*, *Staph aureus* and *Streptococcus pneumoniae*.

**IMPORTANT BACTERIAL INFECTIONS**

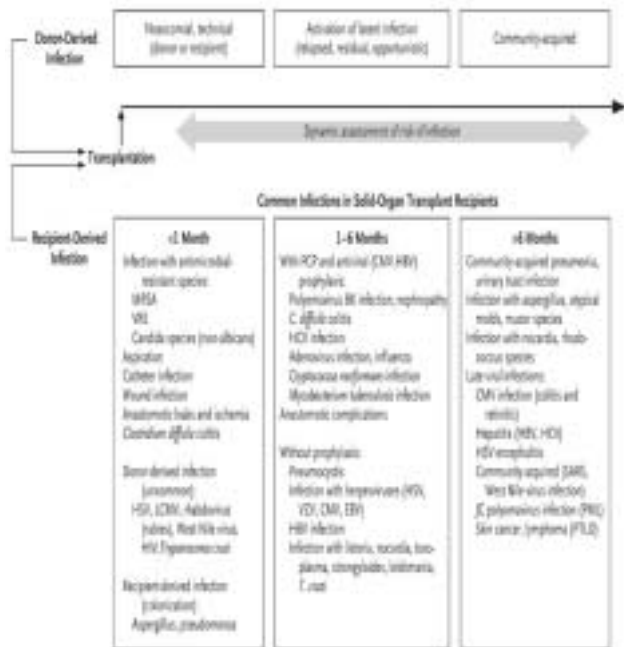
2,3,33,34,35

Infection	Common sites, risk factors	Clinical presentation	Diagnosis	Treatment
Mycobacterium TB	Lungs, disseminated disease, Old TB, exposure	Cough, expectoration, fever	Sputum, Xray, cultures, BAL, biopsies	4 Antitubercular drugs, Avoid Rifampicin with contraindication Duration 12-18 months
Listeria	CNS, GIT Processed meat	Meningoencephalitis, septicemia, gastroenteritis, Focal brain abscess, Ataxia, cranial nerve palsies	Csf exam-pleocytosis, increased protein, culture of blood and csf	Intravenous ampicillin in high doses, gentamicin added for meningitis
Clostridium	GIT, antibiotic use, immunosuppressive drugs, pediatric age gp	Diarrhea, intestinal obstruction, pelvic abscess, pseudomembranous colitis	Stool examination, culture	Oral vancomycin, oral metronidazole
Nocardiosis	Lung, brain, skin, subcutaneous tissues, bone and eyes Early rejection, immunosuppression, neutropenia	Pneumonia – most common	Imaging, BAL, biopsy	TMP/SMX at high doses (2.5-10 mg/kg) Imepenam, amikacin, cephalosporin, quinolones
Legionella	Lungs, Hospital water, ventilator use, corticosteroid boluses	Pneumonia	Imaging and BAL	Intravenous erythropoietin and rifampicin

**CONCLUSIONS**

Post transplant infections remain important cause of morbidity and mortality after kidney transplantation. There is a very fine balance between underimmunosuppression and over immunosuppression. The drug levels do not correlate exactly with the degree of immunosuppression, this results in various complications and remains a major hurdle in improvement of long term graft survival. Sometimes these infections are not identified because of lack of good diagnostic techniques. Techniques currently under development, such as more sensitive microbiologic assays, immunoassays, and genomic and proteomic markers, may provide the potential for individualized immunosuppression and prophylactic strategies and reducing deaths from infection and malignant conditions<sup>2</sup>.

Fig 1. Changing timeline of infections in organ transplant recipients



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