1

Infectious Complications in Kidney Transplantation

Amr El-Husseini[1] and Rashad Hassan[2]
[1]*University of South Florida*
[2]*Mansoura Urology and Nephrology Center*
[1]*USA*
[2]*Egypt*

1. Introduction

Kidney transplantation is associated with lower risk for infection than other solid organ transplantations, reflecting the elective nature of kidney transplantation and clinical and nutritional status of recipients. Infection, however, remains a significant cause of morbidity and mortality in renal transplant recipients. Infections related to transplant surgical complications, acquisition of health care-associated pathogens, and reactivation of latent disease can affect graft function and transplant outcome. Graft dysfunction or chronic rejection leads to augmented immunosuppression, increasing the risk for infection with immunomodulating viruses. Although rare, donor-derived infections can arise by delayed donor seroconversion of unidentified pathogens in the organ donor at the time of organ procurement.

Despite prophylactic therapy against common pathogens; infections are the second most common cause of death after cardiovascular disease in renal transplant recipients. According to the U.S. Renal Data System (USRDS), infections occurred at a rate of 45 per 100 patient-years during the first 3 years after transplantation (Snyder et al., 2009).

2. Viral infections

2.1 Introduction

Viral infections are a major problem in allograft recipients, most commonly 1 to 6 months after transplantation. Clinical disease can occur later, especially after intensification of immunosuppression or physiologic insults that increase the net state of immunosuppression.

Notably, cytomegalovirus (CMV) and herpes simplex virus (HSV) infection rates have decreased since the mid-1990s as a result of effective antiviral prophylaxis; hepatitis B virus (HBV) and hepatitis C virus (HCV) infection rates increased during the same period for unclear reasons.

2.2 Cytomegalovirus (CMV)

2.2.1 Background and clinical presentation

CMV is the most important pathogen in transplant recipients.

CMV infection occurs primarily after the first month of transplantation with an estimated incidence of 30% to 78% if antiviral prophylaxis is not administered, depending on the serologic status of the donor and recipient.

- CMV disease is an important cause of morbidity and mortality and is defined by the presence of clinical signs and symptoms attributable to CMV infection, and the presence of CMV in plasma by Nucleic Acid Testing (NAT) or pp65 antigenemia (KDIGO, 2009).

It has a variety of direct and indirect effects (Fishman & Rubin, 1998; Reinke et al., 1994) which include the following:

1. non-specific febrile syndrome:
   - Fever and neutropenia syndrome with features of infectious mononucleosis, including hepatitis, nephritis, leukopenia, or thrombocytopenia
2. Tissue-invasive CMV disease (defined as CMV disease and CMV detected in tissue with histology, NAT or culture) presented with:
   - Pneumonitis: is the most serious manifestation of CMV disease and is characterized by dyspnea, hypoxemia, interstitial infiltrates, and the detection of CMV antigens, nucleic acids, or inclusion bodies on Broncho-Alveolar Lavage (BAL).
   - Gastrointestinal invasion with colitis, gastritis, ulcers, bleeding, or perforation: Diagnostic endoscopy can reveal solitary or multiple mucosal ulcerations with hemorrhage. Tissue specimens should be stained for CMV using immunofluorescent anti-CMV antibody and examined for inclusion bodies.
   - Hepatitis, pancreatitis
   - Chorioretinitis
   - Central nervous system CMV disease (e.g., meningitis, encephalitis, myelitis): may be more difficult to diagnose. Neurologic disease caused by other neurotropic opportunistic pathogens, and drug toxicities, should be simultaneously investigated.
   - Multiorgan involvement can be observed in disseminated CMV disease.

With the exception of chorioretinitis, the direct clinical manifestations of CMV infection usually occur 1 to 4 months after transplantation; chorioretinitis usually does not occur until later in the transplant course.

Although CMV is a common cause of clinical infectious disease syndromes, the indirect effects of viral infection are equally important. CMV infection produces a profound suppression of a variety of host defenses, predisposing to secondary invasion by such pathogens as P. carinii (jiroveci), Candida, Aspergillus, and some bacteria. CMV also contributes to the risk for graft rejection (through induction of anti-endothelial cell antibodies that contribute to both acute and chronic rejection), post-transplant lymphoproliferative disease (PTLD), Human Herpes Virus-6 (HHV-6) and HHV-7 infections, and acceleration of Hpatits C Virus (HCV) infection.

2.2.2 Routes of transmission

CMV can be transmitted by the allograft, through blood products, or by sexual contact and establishes lifelong latency after primary infection (Hartmann et al., 2006).

2.2.3 Patterns of transmission

Transmission of CMV in the transplant recipient occurs in one of three patterns: primary infection, reactivation, and superinfection (Fishman & Rubin, 1998).

2.2.3.1 Primary Cytomegalovirus Infection

Primary infection occurs most often when seronegative individuals receive grafts from latently infected, seropositive donors, with subsequent reactivation of the virus and systemic dissemination after transplantation. Forty percent to 50% of these patients experience direct infectious disease manifestations of CMV, whereas most are viremic, often without symptoms. Primary CMV infection also may occur in seronegative individuals after transfusion or exposure in the community. This disease may be severe.

2.2.3.2 Secondary Cytomegalovirus Infection

Secondary Cytomegalovirus Infection represents infection in a previously infected seropositive host caused by either:

a. Reactivation Cytomegalovirus Infection. In reactivation infection, seropositive individuals reactivate endogenous virus after transplantation.
   When conventional immunosuppressive therapy is used, approximately 10% to 15% experience direct infectious disease syndromes, with a higher rate with the use of induction antilymphocyte therapy. Fifty percent of these individuals are viremic, often without symptoms.
b. Cytomegalovirus Superinfection. Virus may be reactivated in the setting of an allograft from a seropositive donor transplanted into a seropositive recipient with superinfection with new virus strain.

2.2.4 Risk factors

- Specific risk factors include CMV donor-recipient mismatching and the use of lymphocyte-depleting preparations induction for rejection therapy.
- Other risk factors include episodes of allograft rejection, comorbid illnesses, neutropenia, and, potentially, coinfection with HHV-6 and -7(Hartmann et al., 2006).
- MMF has also been variably reported to be associated with an increased incidence of CMV viremia and CMV disease with increased risk in patients receiving MMF 3 g/day (Fishman & Davis, 2008).

2.2.5 Diagnosis

Clinical management of CMV, including prevention and treatment, is important for the transplant recipient. It is based on an understanding of the causes of CMV activation and the available diagnostic techniques.

Culture-based methods include conventional tissue culture and shell vial centrifugation and can be performed on blood, buffy coat blood fraction, urine, cerebrospinal fluid (CSF), respiratory secretions, or other tissue specimens. Tissue culture is most commonly employed for antiviral resistance testing; although polymerase chain reaction (PCR)-based methods are available those do not require isolation of virus from culture (Pegues et al., 2010).

Staining conventional cell culture or shell vial culture with monoclonal antibody against early CMV viral antigens at 48 hours can decrease the time to diagnosis but is not as sensitive as traditional viral culture.

Serological tests are useful before transplantation to predict risk but are of little value after transplantation in defining clinical disease (this statement includes measurements of anti-CMV IgM levels). Interpretation of CMV serologies may be confounded by the presence of

passive antibody that may have been acquired from a blood or body-fluid contamination (KDIGO, 2009).
The demonstration of CMV inclusions in tissues in the setting of a compatible clinical presentation is the "gold standard" for diagnosis.
Quantitation of the intensity of CMV infection has been linked to the risk for infection in transplant recipients (Caliendo et al., 2000; Humar et al., 2002).
Two types of quantitative assays have been developed: molecular and antigen detection assays.
1-The antigenemia assay is a semiquantitative fluorescent assay in which circulating neutrophils are stained for CMV early antigen (pp65) that is taken up nonspecifically as a measure of the total viral burden in the body.
2-The molecular assays (direct DNA polymerase chain reaction, hybrid capture, amplification assays) are highly specific and sensitive for the diagnosis of CMV disease associated with viremia and to monitor response to antiviral therapy.
The most commonly used assays include plasma-based polymerase chain reaction testing and the whole-blood hybrid capture assay. Whole-blood and plasma-based PCR assays cannot be directly compared. The highest viral loads often are associated with tissue-invasive disease, with the lowest in asymptomatic CMV infection. Either assay can be used in management.
The advent of quantitative assays for the diagnosis and management of CMV infection has allowed noninvasive diagnosis in many patients with two important exceptions:

- Neurological disease, including chorioretinitis
- Gastrointestinal disease, including invasive colitis and gastritis

In these syndromes, the CMV assays are often negative, and tissue diagnosis may be required.
Qualitative CMV DNA detection by PCR is extremely sensitive but cannot differentiate active disease or latent infection (Humar et al., 2002).

2.2.6 Prevention of CMV infection

In the absence of antiviral prophylaxis, symptomatic CMV disease can be seen in approximately 8% of kidney transplant recipients (Paya & Razonable, 2003), although older estimates placed it at 10–60% (Hibberd et al., 1992a). Accordingly, strategies that can prevent CMV infection and disease should lead to improved outcomes following kidney transplantation.
Prevention of CMV infection must be individualized for immunosuppressive regimens and the patient.
Two strategies are commonly used for CMV prevention: **universal prophylaxis** and **preemptive therapy**. Randomized controlled trials have demonstrated that the incidence of CMV disease can be reduced by prophylaxis and preemptive therapies in solid-organ transplant recipients (Hodson et al., 2007; Strippoli et al., 2006).
Universal prophylaxis involves giving antiviral therapy to all at-risk patients beginning at or immediately after transplantation for a defined period.
There is high-quality evidence from a large systematic review that CMV prophylaxis in solid-organ transplant recipients significantly reduces all-cause mortality, CMV disease mortality, CMV disease, but not acute rejection or graft loss. (Hodson et al., 2007)
In **preemptive therapy**, quantitative assays are used to monitor patients at predefined intervals to detect early disease with administration of therapy in case of positive assay.

Preemptive therapy incurs extra costs for monitoring and coordination of outpatient care, while reducing the cost of drugs and the inherent toxicities.
At the present time, the use of viral load monitoring to prompt preemptive therapy is not recommended for high-risk kidney transplant recipients.
The basis for this concern is both a lack of data in CMV D+/R− kidney transplant recipients, the implications of a failure to comply with the preemptive monitoring approach and the relative safety and efficacy of universal chemoprophylaxis in high-risk organ transplant recipients (Hodson et al., 2007).
The approach of universal prophylaxis may be more useful for patients at high risk for CMV disease, whereas preemptive therapy may be more useful for patients at low or intermediate risk for CMV disease.
Prophylaxis has the possible advantage of preventing not only CMV infection during the period of greatest risk but also diminishing infections secondary to HHV-6, HHV-7, and Epstein-Barr Virus (EBV). The indirect effects of CMV (i.e. graft rejection, opportunistic infection) also may be reduced by routine prophylaxis.
In practice, neither universal prophylaxis nor preemptive therapy is perfect. Infrequently, breakthrough disease and ganciclovir resistance have been observed with both approaches (Kalil et al., 2005).
Given the risk for invasive infection, patients at risk for primary infection are generally given prophylaxis for 3 to 6 months after transplantation (especially in patients receiving depleting anti–T lymphocyte antibodies). There is strong evidence linking the use of antibody treatment of rejection with increased risk of CMV infection and disease. The use of these agents results in activation of CMV from latency to active infection and studies in this high-risk population have shown that antiviral chemoprophylaxis reduces the incidence of CMV disease by about 60% (Hodson et al., 2005). Other groups are candidates for preemptive therapy if an appropriate monitoring system is in place, and patient compliance is good. Current data support the use of universal prophylaxis (not preemptive therapy), however, in the prevention of indirect effects of CMV infection, including PTLD, opportunistic infections, allograft rejection, and mortality (Kalil et al., 2005).
The currently used antiviral agents for universal prophylaxis include intravenous or oral ganciclovir, oral valganciclovir, valacyclovir, CMV immunoglobulin (CMVIG), and a combination of antiviral therapy and CMVIG.
Although oral ganciclovir is more convenient to administer than its intravenous formulation, it is substantially less bioavailable (4% to 6%) and achieves significantly lower serum levels.
Valganciclovir, the L-valine ester of ganciclovir, is administered in a dose of 450 to 900 mg per day by mouth for CMV prophylaxis and produces similar area under the curve values to intravenous ganciclovir (5 mg/kg per day) and much higher values than oral ganciclovir (3 g per day) and is more effective than ganciclovir in preventing CMV disease at 6 months among kidney transplant recipients. (Asberg et al., 2007).
Some recent studies failed to demonstrate a benefit of CMVIG administered prophylactically (Hodson et al., 2007) although in nonblinded, nonrandomized trials, CMVIG reduced the incidence of virologically confirmed CMV-associated syndromes and secondary opportunistic infections in D+/R- renal transplants.
Ganciclovir, valganciclovir, and valacyclovir require dosage adjustment for decreased creatinine clearance.

2.2.7 Treatment of CMV infection

Effective antiviral agents for CMV prophylaxis and treatment have substantially decreased the morbidity and mortality associated with CMV disease.

Oral valganciclovir (900 mg twice daily) has been demonstrated to have comparable safety and efficacy to intravenous ganciclovir for clearing CMV viremia and resolving clinical disease in solid organ transplant patients with mild to moderate CMV disease(Paya et al., 2004).

Patients with high CMV viral loads or severe tissue invasive disease, and those who fail to achieve a reduction in viral load after 7 or more days of oral valganciclovir treatment should be treated with intravenous ganciclovir (5 mg/kg twice daily, with dosage adjustments for renal dysfunction) for at least 2 to 3 weeks with a reduction in the immunosuppression if the disease is severe until a quantitative assay for CMV is negative (Sia & Patel, 2000).

Experience in treating refractory CMV disease suggests that the addition of CMV hyperimmune globulin (150 mg/kg/dose intravenously given every 3 to 4 weeks) or intravenous pooled gammaglobulin (IVIG) to ganciclovir may improve the clinical response.

Patients with CMV disease should receive at least weekly monitoring of blood viral load and the presence of CMV in plasma, detected by NAT or pp65 antigenemia, at the end of treatment is a major predictor of recurrent CMV disease (1).

The use of completely oral regimens for treatment appears to be effective with the exception of invasive gastrointestinal disease.

It is worth noting that similar data are not available for pediatric kidney transplant recipients or other children undergoing solid-organ transplantation.

Accordingly, while the use of oral valganciclovir may be appropriate for some adult kidney transplant recipients experiencing mild to moderate CMV disease, all pediatric kidney transplant recipients should receive intravenous ganciclovir for the treatment of CMV disease (KIDGO, 2009).

Further, concern also exists with regards to the use of oral valganciclovir in patients in whom there are questions regarding adequate absorption of this medication.

Adverse effects of ganciclovir include reversible, dose-related granulocytopenia and thrombocytopenia, fever, rash, seizures, nausea, myalgias, abnormalities in liver enzyme determinations, and, rarely, pancreatitis (Paya et al., 2004).

Drug interactions include an increased seizure risk when used in combination with acyclovir and imipenem, and additive marrow suppression with azathioprine, mycophenolate, and TMP-SMX (Paya et al., 2004).

Renal transplant recipients with ongoing risk factors for CMV should receive long-term maintenance therapy with oral ganciclovir (1000 mg 3 times daily), valganciclovir (450 to 900 mg once daily) or valacyclovir (2 g, 4 times daily) (Paya et al., 2004). Relapses occur, primarily in patients not treated beyond the achievement of a negative quantitative assay.

Some relapses occur in gastrointestinal disease because the assays used to follow disease are unreliable in this setting. Repeat endoscopy should be considered to ensure the clearance of infection (Kalil et al., 2005).

Alternative therapies are available in intravenous form only, including foscarnet and cidofovir which can be used to treat disease associated with ganciclovir-resistant CMV strains (Mylonakis et al., 2002).

Although it is active against most ganciclovir-resistant strains of CMV, combination therapy (ganciclovir and foscarnet) for organ transplant recipients is preferred given the toxicities of high-dose, single-agent therapy, and given the antiviral synergy that has been reported (Mylonakis et al., 2002).

Cidofovir has been used in renal transplant recipients, often with nephrotoxicity.
Foscarnet and cidofovir may exhibit synergistic nephrotoxicity with calcineurin inhibitors.
leflunamide also seems to have useful activity against both CMV and BK polyomavirus (Fishman & Davis, 2008).
The anti-CMV activity and safety of maribavir in CMV-seropositive patients were evaluated in a randomized RCT in allogeneic stem-cell transplant recipients but not in KTRs. The results showed that maribavir can reduce the incidence of CMV infection and, unlike ganciclovir, does not cause myelosuppression (Winston et al., 2008).

2.2.8 Chemoprophylaxis

Chemoprophylaxis is defined as the use of an antimicrobial agent in the absence of evidence of active infection, to prevent the acquisition of infection and the development of disease.
A variety of potential antiviral agents have been evaluated.
Ganciclovir, valganciclovir, acyclovir and valacyclovir were demonstrated to be effective in the preventing CMV infection and disease (Hodson et al., 2007). However, head-to-head comparisons demonstrated that ganciclovir was more effective than acyclovir in preventing both CMV infection and CMV disease. Oral valganciclovir was as effective as intravenous ganciclovir in the prevention of both CMV infection and disease. Oral and intravenous ganciclovir yielded similar results. The use of acyclovir and valacyclovir should be restricted to situations where ganciclovir/valganciclovir cannot be used (Hodson et al., 2007).
Randomized controlled trials (RCTs) evaluated oral antiviral agents for the prevention of CMV disease have treated patients for 3 months after transplantation (Hodson et al., 2007). A recent meta-analysis did not find a difference in treatment efficacy for patients receiving less or more than 6 weeks of therapy (KDIGO, 2009). So, Chemoprophylaxis with ganciclovir or valganciclovir for at least 3 months after transplantation reduces CMV infection and disease in high-risk patients.
The impetus behind prolonged treatment is an increasing recognition of late CMV disease. Two studies evaluated ganciclovir in patients who received antilymphocyte antibody therapy demonstrated a reduction in CMV disease (Hibberd et al., 1995; KDIGO, 2009).
Accordingly, the use of intravenous ganciclovir or oral valganciclovir has been recommended for CMV prophylaxis during antilymphocyte antibody therapy (1). The use of oral ganciclovir should be avoided for patients with high level CMV viremia (1). The use of acyclovir or famciclovir is not recommended, given the absence of data supporting the efficacy of these agents. It is also suggested that CMV serologies be repeated for patients CMV-seronegative prior to transplant, who require antibody therapy as treatment for rejection to decide their current risk status.
Lastly, chemoprophylaxis is associated with improved graft survival compared to preemptive antiviral therapy initiated in response to increased CMV load (KDIGO, 2009).

2.2.9 CMV viral load testing

While resolution of clinical signs and symptoms are critical in the management of CMV disease, measurement of the CMV viral load provides additional useful information.
The use of viral load monitoring identifies both virologic response (guiding duration of therapy) as well as the possible presence of antiviral resistance. The presence of detectable CMV load at the end of therapy is associated with an increased rate of recurrent disease (Humar et al., 2002). The time to clearance of CMV in plasma as measured by NAT may be

prolonged compared to pp65, and may be associated with an increase risk of recurrent CMV disease (Weinberg et al., 2000).

2.2.10 Immunosuppression and graft function monitoring during CMV disease

The reduction of immunosuppression used as part of the treatment of CMV disease places patients at some risk for the development of rejection. The presence of CMV infection and disease has been associated with the development of rejection independent of reduction of immunosuppression.

Accordingly, careful monitoring of kidney allograft function is warranted during treatment of CMV disease to guide the use of immunosuppression (KDIGO, 2009).

2.3 Epstein-Barr virus (EBV)

2.3.1 Introduction

EBV is associated with an array of disorders ranging from infectious mononucleosis to nasopharyngeal carcinoma, Burkitt lymphoma, and B-cell lymphomas in immunocompromised patients.

EBV disease is defined by signs and symptoms of active viral infection and increased EBV load.

The EBV viral load is defined as the amount of viral genome that is detectable in the peripheral blood by NAT.

Primary EBV (human herpes virus 4) infection is associated with an increased incidence of post-transplant lymphoproliferative disease (PTLD) in kidney transplant recipients (KTRs). An EBV-negative KTR from an EBV-positive donor is at increased risk for developing PTLD (Cockfield et al., 1993; McDonald et al., 2008). A newly detectable or rising EBV load often precedes EBV disease and PTLD (Rowe et al., 2001). Identification of seronegative patients with a rising EBV load offers the opportunity to preemptively intervene and potentially prevent progression to EBV disease including PTLD (Paya et al., 1999).

Primary EBV infection in EBV-seronegative organ transplant recipients occurs most frequently in the first 3–6 months following organ transplantation (Breinig et al., 1987). This is most likely due to the fact that the source of the EBV infection is attributable to either the donor organ or blood products received by the patient at or near the time of transplant. Serial measurement of EBV loads in previously seronegative patients allows the identification of onset of infection (Rowe et al., 2001).

Continued observation of EBV loads in newly infected patients identifies those patients with rapidly rising viral loads who are likely to be at greatest risk of progressing to EBV disease. Because the most likely sources of EBV infection in KTRs are either passenger leukocytes from the donor allograft or blood products exposure (which are more likely at or near the time of transplantation), the likelihood that they will develop primary EBV infection is reduced with time after transplantation. Accordingly, EBV load monitoring should be performed most frequently during the first 3–6 months after transplant. Because the risk of developing EBV infection after this time period is diminished, but not eliminated, continued surveillance of EBV load is recommended, albeit at less frequent intervals (KDIGO, 2009).

2.3.2 EBV disease diagnosis

EBV virus disease can present with varied manifestations, including nonspecific febrile illness, gastroenteritis, hepatitis and other manifestations that may be attributable to CMV

or other pathogens. Although biopsy to detect the presence of EBV infection within affected tissue is the most definitive way to confirm the diagnosis of EBV disease, histological confirmation may not be feasible for patients with some nonspecific clinical syndromes that may not localize to specific tissue (e.g. febrile syndromes) (2).
Because the EBV viral load is detectable and elevated in the vast majority of KTRs with EBV disease, including PTLD, the combination of the presence of a compatible clinical syndrome in association with a high EBV load provides a sensitive and specific approach to the diagnosis of EBV disease (Green et al., 2006). However, it is still necessary to be cautious in considering this diagnosis, as many patients may have asymptomatic elevations of EBV load. Accordingly, such patients may be misdiagnosed as having EBV disease, if they develop intercurrent infections due to an alternative pathogen at a time that they are having an asymptomatic elevation in their EBV load. In such patients, a tissue diagnosis may be the only method of confirming the presence or absence of EBV disease (KDIGO, 2009).

2.3.3 EBV-associated PTLD

EBV plays a central role in the pathogenesis of PTLD (Nalesnik, 2001; Preiksaitis & Keay, 2001).
The most clearly defined risk factor for PTLD is primary EBV infection, which increases the risk for PTLD by 10-fold to 76-fold.
PTLD are clinical syndromes associated with EBV and lymphoproliferation, which range from self-limited, polyclonal proliferation to malignancies containing clonal chromosomal abnormalities (2).
The approach to the management of PTLD can vary according to the PTLD disease classification.
Furthermore, EBV-negative PTLD lesions have been reported and these lesions may behave differently then EBV-positive lesions and may warrant alternative therapeutic options. In addition, lesions with a characteristic clinical appearance on physical examination or imaging studies may be due to alternative pathogens (e.g. pulmonary nodules attributable to fungal pathogens). Because of all these concerns, it is imperative that suspected PTLD lesions be biopsied and undergoes histolopathologic evaluation by a pathologist experienced with the diagnosis of PTLD (2).
Observational studies have suggested KTRs with EBV disease are at high risk of developing PTLD (Dharnidharka et al., 2001b). Observational studies have also shown that mortality from EBV-associated PTLD is over 50% (Caillard et al, 2006; Opelz & Dohler, 2004). The presence of immunosuppression is major risk factor for the development of EBV disease, including PTLD, in KTRs (Dharnidharka & Harmon, 2001a; McDonald et al., 2008).
High EBV loads have been found at the time of diagnosis of PTLD. Because the EBV load becomes positive 4–16 weeks prior to development of PTLD, the presence of a rising EBV load identifies patients in whom intervention may prevent PTLD (Rowe et al., 2001).
The clinical presentations of EBV-associated PTLD vary and include the following (Paya et al., 1999):

- Unexplained fever (fever of unknown origin)
- A mononucleosis-type syndrome, with fever and malaise, with or without pharyngitis or tonsillitis (often diagnosed incidentally in tonsillectomy specimens).
- Most are non-Hodgkin lymphomas (Hodgkin disease is the most common lymphoma in age-matched controls), are of B-cell origin, and are $CD20^+$.
- Gastrointestinal bleeding, obstruction, or perforation

- Abdominal mass lesions
- Infiltrative disease of the allograft with dysfunction of the transplanted organ that may be confused histologically with severe rejection.
- Hepatocellular or pancreatic dysfunction
- Central nervous system disease

The prolonged or repeated administration of lymphocytic-depleting antibody preparations is a significant risk factor for the development of PTLD. Predictors of poor survival from PTLD include increased age, elevated lactic acid dehydrogenase values, severe organ dysfunction, multiorgan involvement, and constitutional symptoms (fever, night sweats, weight loss) (Fishman, 2007).

2.3.4 Management

Clinical management depends on the stage of disease. In the initial stages, particularly in children, re-establishment of immune function may be sufficient to cause PTLD to regress. At this stage, it is possible that antiviral therapy might have some utility given the viremia and role of EBV as an immunosuppressive agent. With the progression of disease to extranodal and monoclonal malignant forms, reduction in immunosuppression may be useful, but alternative therapies are often required. In kidney transplantation, the failure to regress with significant reductions in immunosuppression may suggest the need to sacrifice the allograft for patient survival. Combinations of anti–B cell therapy (anti-CD20, rituximab), chemotherapy (CHOP: cyclophosphamide, hydroxydaunomycin, vincristine [Oncovin], prednisone), or adoptive immunotherapy with stimulated T cells have been used (Haque et al., 2002; Straathof et al., 2002).

2.4 Hepatitis C Virus (HCV)

2.4.1 Introduction

KTRs infected with HCV have worse patient- and allograft-survival rates and are at increased risk for several complications, including worsening liver disease, new-onset diabetes after transplantation (NODAT) and glomerulonephritis than KTRs without HCV infection.

2.4.2 Patient and graft survival

Controversy exists regarding the impact of pre-transplant HCV infection on the outcome of renal transplantation.

Initially, studies of short follow-up periods suggested that neither patient nor graft survival was altered after transplantation despite an increase in HCV RNA levels (Lau et al., 1993; Lee et al., 2001; Orloff et al., 1995).

In contrast, studies with lengthier follow-up after transplantation have found decreased patient and graft survival in HCV-positive renal transplant recipients (Legendre et al., 1998; Mahmoud et al., 2004; Sezer et al., 2004).

Post-transplantation HCV-related liver disease is often progressive in renal transplant recipients. Factors implicated in more rapid progression of HCV include alcohol abuse and HBV co-infection (Martin & Fabrizi, 2008).

HCC and liver cirrhosis were more frequent causes of mortality in HCV-positive than HCV-negative recipients (Hanafusa et al., 1998).

The Transplant Guideline Work Group determined that liver enzymes should be checked every month for the first 6 months of the post-transplant period, and every 3 months

thereafter. The detection of clinically worsening liver enzymes should prompt referral for hepatologic evaluation. Annual liver ultrasound and alpha-fetoprotein level to screen for hepatocellular carcinoma should be considered in patients with cirrhosis on liver biopsy (KDIGO, 2009).

Most studies regarding post-transplant HCV outcomes comprise chronically infected recipients, usually those who acquired HCV during hemodialysis. However, the subsets of solid organ transplant recipients who become infected with HCV in the peri-operative period have a markedly different course with some studies suggest that HCV acquired at the time of transplantation may have a particularly aggressive course (Delladetsima et al., 2006; Sypsa et al, 2004) most probably because they develope an acute hepatitis at a time of maximum immunosuppression.

2.4.3 Hepatitis C virus and post-transplant diabetes in kidney transplant recipients

The association of diabetes mellitus and HCV has become increasingly apparent more recently in the immunocompetent HCV population and particularly after solid organ transplantation in HCV-infected patients. The overall incidence of post-transplant diabetes mellitus has been reported to vary from 10% to 54% (Fabrizi et al., 2005).

Tacrolimus increases the risk for NODAT, and might be expected to impart at least an additive risk for NODAT to HCV-infected KTRs (KDIGO, 2009; van Duijnhoven et al., 2002). This association also was observed by Bloom and colleagues, who found that among the HCV-positive patients, there was an eight times increased incidence of post-transplant diabetes mellitus in patients treated with tacrolimus (58%) compared with cyclosporine (7.7%) (Bloom et al., 2002).

2.4.4 Hepatitis C virus and post-transplant nephropathy

Hepatitis C virus infection has been implicated in the pathogenesis of glomerulonephritis and mixed cryoglobulinemia in both native and transplanted kidneys and can lead to graft loss. Therefore, the Hepatitis C and Transplant Guideline Work Groups concluded that HCV-infected KTRs should be tested for proteinuria every 3–6 months (KDIGO, 2009).

Membranoproliferative glomerulonephritis (MPGN) is the most common pathological finding likely to arise in patients infected with HCV, followed by membranous nephropathy, minimal change disease, and renal thrombotic microangiopathy. These may be recurrent or manifest as de novo disease (Meyers et al., 2003).

MPGN has been reported in 45% of HCV-positive renal transplant recipients who underwent renal biopsy for worsened renal function. In the HCV-negative group, the incidence was only 5.9% (Meyers et al., 2003). De novo disease was found in 18% of the MPGN patients, and chronic renal allograft nephropathy was similar in HCV-positive and HCV-negative recipients (Cruzado et al., 2001). Initially, MPGN and chronic allograft nephropathy may have similar presentation with proteinuria and can be a diagnostic dilemma requiring electron microscopy to differentiate the two.

As recommended for all KTRs, patients who develop new-onset proteinuria (either urine protein/creatinine ratio >1 or 24-hour urine protein greater than 1 g on two or more occasions) should have an allograft biopsy with immunofluorescence and electron microscopy.

Interferon-based therapies may be effective in treating HCV-related glomerulopathy in native kidney disease. However, interferon use in KTRs is associated with an increased risk

of rejection. Ribavirin can reduce proteinuria in HCV-associated glomerulopathy, although its impact on kidney function is unknown and it does not lead to viral clearance (KDIGO, 2009).

2.4.5 Immunosuppressive protocols in HCV infected renal transplant recipients

No randomized prospective study has been done to determine optimal immunosuppressive regimens in renal transplant recipients infected with HCV. As mentioned earlier, studies have shown tacrolimus as an additive risk in HCV patients for the development of NODAT. Azathioprine and antilymphocyte agents to treat rejection have been implicated in more severe liver disease in HCV-infected recipients. Administration of high-dose steroids and antilymphocyte antibodies should be avoided and only used after a critical evaluation of potential risk and benefit, especially the risk for accelerating the course of liver disease (Pegues et al., 2010).

A liver biopsy should be performed to assess underlying activity and stage of HCV-related liver disease. This information can help guide expected response rates and aggressiveness of therapy. Patients with advanced fibrosis or cirrhosis or both need to be considered for combined liver-kidney transplantion.

2.4.6 Anti-HCVviral therapy

2.4.6.1 Pretransplant antiviral therapy

As mentioned above, HCV is associated with worse patient and graft survivals, increased risk of post-transplant diabetes mellitus and de novo glomerulopathy. So, eradication of HCV before transplantation might mitigate some of these adverse outcomes (Cruzado et al., 2003; Huraib et al., 2001; Kamar et al., 2003b).

Interferon is effective for viral eradication in HCV-infected patients, especially when combined with ribavirin. However, the administration of interferon after kidney transplantation can be deleterious to the allograft and should generally be avoided in KTRs, unless there is indication of worsening hepatic injury (Rostaing et al., 1995).

It would be best if treatment could be undertaken before proceeding to the solid organ transplant.

Results of treatment of HCV in dialysis patients varies, with sustained virological rates ranging from 16% to 68% (Fabrizi et al., 2004b).

Post-transplantation improvements in hepatic activity index were seen to persist in patients treated with interferon while on the waiting list compared with patients who were not given interferon before renal transplantation (Huraib et al., 2001). Post-transplant glomerulopathy also is reduced by pretransplant interferon therapy.

Most studies report treatment regimens including interferon monotherapy administered for 6 to 12 months.

Ribavirin is renally excreted and its metabolites are not cleared by dialysis, and it needs to be used very cautiously if at all in dialysis patients because of the fear of hemolytic anemia that may occur despite low doses of 200 mg three times a week in dialysis patients and can be severe enough to mandate discontinuation of the drug (Tan et al., 2001).

Some pilot studies have reported ribavirin use in addition to interferon in patients on dialysis (Bruchfeld et al., 2001) but there was no evidence that adding ribavirin in dialysis patients provided any added therapeutic benefit.

There is considerable clinical experience, although few studies, using pegylated interferon monotherapy in dialysis patients with chronic HCV (Russo et al., 2006) with an increase in side effects in this population and response rates that are not better than with standard interferon because the half-life of regular interferon is increased in patients on dialysis.

2.4.6.2 Antiviral therapy for HCV after transplantation

Post-transplantation interferon therapy generally is contraindicated in organ transplant recipients other than recipients of liver allografts; this is due to multiple reports of precipitation of renal failure and organ rejection owing to interferon therapy (Said et al., 2008).
Interferon alfa therapy should be limited to patients with severe recurrence of HCV, such as advanced fibrosis/cirrhosis or fibrosing cholestatic HCV.
Ribavirin monotherapy has been associated with reduction in aminotransferases and necroinflammation in renal transplant recipients (may be due to decreased lymphocytic proliferation, decreased synthesis of proinflammatory cytokines, and a decrease of T helper type 2 cytokine production favoring a T helper type 1 profile) but no virological response (Said et al., 2008). On the contrary, Karmer and colleagues found biochemical improvement without histological or virological improvement in these patients (Kamar et al., 2003a).

2.5 Hepatitis B Virus (HBV)

2.5.1 Introduction

The incidence and prevalence of HBV infection among patients awaiting renal transplantation have declined in recent years largely as a result of vaccination of patients on dialysis and improved infection control measures during dialysis. With these measures, the incidence of HBV infection in dialysis patients has decreased considerably in recent years to approximately 1%.
Hepatitis B virus infected patients are at risk of exacerbation of the infection, progressive liver disease, development of hepatocellular carcinoma and decreased survival after kidney transplantation (Aroldi et al., 2005).
Immunosuppression following kidney transplantation leads to increased replication of HBV and results in progressive liver disease.

2.5.2 Liver Biopsy: its role before transplantation

It is difficult; on clinical grounds alone, to estimate the severity of liver disease in chronic kidney disease (CKD) patients. For this reason, liver biopsy should be incorporated in the evaluation of renal transplant candidates with HBsAg and both liver histology and evaluation of HBV replication by serum markers (i.e., HBeAg and HBV DNA) should be concerned before deciding transplant candidacy in HBsAg-positive patients.
In patients with histologically mild liver disease, renal transplantation is not contraindicated. If the initial liver biopsy shows extensive fibrosis and there is active HBV replication, repeat liver biopsy should be considered after a year or more of antiviral therapy to determine whether regression of liver fibrosis has occurred (Pegues et al., 2010).

2.5.3 Disease progression after kidney transplantation

HBV infection in transplant recipients may be associated with only minor elevations of aminotransferase levels despite histologic progression. Known risk factors for progression of HBV-related liver disease include alcohol use; longer duration of infection; high serum

levels of HBV DNA; genotype C; coinfection with hepatitis C and D; HIV infection; and immunosuppression (Pegues et al., 2010).
The patient survival in renal transplant recipients is a well established adverse effect of HBsAg positivity while the effect of HBsAg status on graft survival is less clear, although it might be enhanced in HBV-infected recipients as a result of a diminished immune response resulting from chronic viral infection (Pegues et al., 2010).

2.5.4 Pretransplant management of hepatitis B virus–positive dialysis patients

Lamivudine monotherapy is associated with viral suppression in most patients with end-stage renal disease (Lapinski et al., 2005).
The problems with lamivudine include development of resistance with prolonged antiviral therapy, which can result in virological and clinical breakthrough.

2.5.5 Antiviral Therapy of Chronic Hepatitis B Virus in Renal Transplant Recipients

2.5.5.1 Timing of initiation

Data on optimal timing of initiation of antiviral therapy are scarce.
However, renal transplant recipients with active HBV (HBsAg positive) should be started on antiviral therapy at the time of transplantation irrespective of HBV DNA levels (Han et al., 2001; Filik et al., 2006) or even during dialysis to prevent worsening of liver disease after transplantation.
The primary goals of management are maximal suppression of viral replication, while minimizing development of resistance and prevention of hepatic fibrosis.
Cessation of antiviral therapy in the immunocompromised host is associated with an increased risk of flare of liver disease and rarely decompensated liver disease in transplant recipients (Chan et al., 2002; Liaw et al., 1999).
Indefinite therapy carries its own risks, including that of antiviral toxicity (rare) and of drug resistance.
Although interferon (IFN) and pegylated IFN are efficacious in the treatment of chronic HBV, their use is contraindicated in renal transplant recipients because the immunomodulatory actions of IFN may lead to the precipitation of severe and often irreversible graft dysfunction.
The introduction of lamivudine was a major advance in the management of post-transplantation HBV-related liver disease. A dose of 100 mg/day orally has been shown to be highly effective in suppression of HBV replication and normalization of aminotransferases in greater than 80% of patients (Fabrizi et al., 2004a;, Kletzmayr et al., 2000; Rostaing et al., 1997).
Because lamivudine is metabolized by the kidney, the dose should be reduced in patients with impaired renal function to 50 mg daily for a creatinine clearance of 30 to 49 mL per minute.
Lamivudine is well tolerated, and has no adverse immunomodulatory activity.

2.5.5.2 Duration of therapy

The optimal duration of therapy that ensures long-term remission of viremia and maintenance of normal liver function and minimizes the development of resistance is not known and in an immunocompromised host may need to be indefinite.
At least 24 months of prophylactic treatment has been recommended (Wirth, 2006).

Withdrawal of antiviral therapy may be associated with a relapse and increased viral replication, even resulting in liver failure (Rostaing et al., 1997).
The risk of resistance increases with duration of lamivudine therapy. This is usually reflected by a secondary increase in the HBV DNA titers. A commonly used definition is demonstration of >5 log10 copies/mL rebound of HBV DNA.
The clinical presentation varies. While some patients show no significant biochemical changes or clinical symptoms, others develop deterioration in liver function (Gane & Pilmore, 2002).

2.5.6 Newer agents

Other nucleotide and nucleoside analogues are now available for use in HBV-infected individuals, including adefover, entecavir, telbivudine and tenofovir (Chang et al., 2006; Marcellin et al., 2008; van Bommel et al., 2006). Advantages include potency, low rates of resistance allowing prolonged therapy without breakthrough, and efficacy in lamivudine-resistant patients. No data exist in renal transplant recipients; however, dose reductions may be necessary if renal insufficiency is present.

2.6 Human Immunodeficiency Virus (HIV)

2.6.1 HIV and kidney transplantation

- Patients with HIV require specialized care in centers with appropriate expertise.
- Screening for HIV infection should be carried out on all kidney transplant recipients (ideally before transplantation) in order to identify those kidney transplant recipients that will require specialized care.
- Antiretroviral therapy is necessary to maintain virologic suppression and normal immunologic function in HIV patients undergoing kidney transplantation.
- The concomitant use of antiretroviral agents and immunosuppressive medications creates the potential for drug–drug interactions that may substantially alter blood levels of drugs and require appropriate monitoring and adjustments in dosing (Frassetto et al., 2007).
- Some of the antiretroviral agents, particularly protease inhibitors, are potent inhibitors of P-450 (e.g., ritonavir is the most potent inhibitor of P-450 that is clinically available, and when used alone or in combination [kaletra-retonavir/lopinavir], very small doses of calcineurin inhibitor [e.g., 1 mg/week of tacrolimus] may maintain adequate drug levels (Abbott et al., 2004)

Tenofovir (a component of Truvada and Atrypla) is nephrotoxic and should be avoided after transplantation.

2.6.2 Outcome of kidney transplantation in recipients with HIV

Case series have documented successful outcomes of kidney transplant recipients with HIV (Gruber et al., 2008). However, these HIV patients had been carefully selected and adequately treated for HIV at the time of transplantation. Although HIV is not an absolute contraindication to kidney transplantation, the presence of HIV has major implications in the management of patients following transplantation (4). A major issue of concern in the management of HIV patients is the need to be aware of potential drug–drug interactions among antiretroviral therapy and other medications, including immunosuppressants (Frassetto et al., 2007).

Care must be taken to identify and select those HIV-infected patients who are most likely to benefit from kidney transplantation without an unacceptably high risk of opportunistic infections.
Evidence from a National Institutes of Health (NIH)-sponsored study of organ transplantation in HIV patients has demonstrated both the effectiveness of transplantation as well as the complexity of management of kidney transplant recipients with HIV (Roland et al., 2008). Data accrued from this study has identified specific drug combinations that are associated with drug–drug interactions in these patients. Accordingly, attention must be paid and caution must be used in these patients to account for the potential impact of these interactions (Roland et al., 2008).
Although the data from the NIH study demonstrate the feasibility of transplantation for HIV-infected kidney transplant recipients, the limited number of HIV patients with CKD stage 5 undergoing kidney transplantation to date suggests the need to continue performing this procedure under research protocols and in selected centers with appropriate expertise.
Between November 2003 and June 2009 a prospective, nonrandomized trial was following a total of 150 HIV patients underwent kidney transplantation; survivors were followed for a median period of 1.7 years. In this cohort of carefully selected HIV-infected patients, both patient- and graft survival rates were high at 1 and 3 years, with no increases in complications associated with HIV infection. But there were unexpectedly high rejection rates which indicate the need for better immunotherapy (Stock et al., 2010).
Finally, it is worth noting that review of experience to date suggests that there may be an increased risk for the development of acute cellular rejection in patients with HIV undergoing organ transplantation (KDIGO, 2009).

2.7 BK virus

2.7.1 Introduction

Polyomaviruses:

Polyomaviruses have been identified in transplant recipients in association with nephropathy and ureteral obstruction (BK virus), and in association with demyelinating disease of the brain (JC virus) similar to that in AIDS (Fishman, 2002; Hirsch et al., 2006). Adult levels of seroprevalence are 65% to 90%. BK virus seems to achieve latency in renal tubular epithelial cells. JC virus also has been isolated from renal tissues but seems to have preferred tropism for neural tissues. Reactivation occurs with immunodeficiency and immunosuppression and tissue injury (e.g., ischemia-reperfusion) (Hirsch et al., 2002).

2.7.2 BK nephropathy

BK virus causes latent infection of the kidney; with reactivation during immune suppression.
BK virus is associated with a range of clinical syndromes in immunocompromised hosts, including viruria and viremia, tubulointerstitial nephritis, ureteral ulceration and stenosis, and hemorrhagic cystitis (Fishman, 2002; Hirsch et al., 2002). Active infection of renal allografts has been associated with progressive loss of graft function ("BK nephropathy") in approximately 4% of renal transplant recipients; this is referred to as polyomavirus-associated nephropathy (PVAN). The clinical presentation of disease is usually as sterile pyuria, reflecting shedding of infected tubular and ureteric epithelial cells. These cells contain sheets of virus and are detected by urine cytology as "decoy cells." In some cases,

the patient presents with diminished renal allograft function or with ureteric stenosis and obstruction (Fishman, 2002).

2.7.3 Incidence

- Fifty percent of patients who develop BK viremia do so by 3 months after kidney transplantation.
- Ninety-five percent of BKV nephropathy occurs in the first 2 years after kidney transplantation (Randhawa & Brennan, 2005).

2.7.4 Risk factors

Studies have implicated donor seropositivity, high-dose immunosuppression (particularly tacrolimus and mycophenolate mofetil), pulse-dose steroids, severe ischemia-reperfusion injury, exposure to antilymphocyte therapy, increased number of HLA mismatches between donor and recipient, deceased donor renal transplants, allograft rejection and presence and degree of viremia in the pathogenesis of disease (Fishman, 2002).
The role of specific immunosuppressive agents has not been confirmed.

2.7.5 Diagnosis

The use of urine cytology to detect the presence of infected decoy cells in the urine has approximately 100% sensitivity for BK virus infection but a low (29%) predictive value (Fishman, 2002; Hirsch et al., 2002).
It is a useful screening tool but cannot establish a firm diagnosis.
Monitoring for BK virus in the plasma by DNA PCR is more specific for diagnosis of BK nephropathy than is detection with urine specimens. However, the detection of BK virus DNA in urine specimens may provide the first evidence of polyomavirus infection in the patient (Ramos et al., 2002, 2003).
Given the presence of viremia in renal allograft recipients, it is crucial to reduce immunosuppression whenever possible.
Definitive diagnosis requires a renal biopsy. Renal biopsy specimens initially show cytopathic changes in renal epithelial cells with the gradual evolution of cellular infiltration consistent with the diagnosis of interstitial nephritis. Fibrosis is often prominent occasionally with calcification. Immunostaining for cross-reacting SV40 virus shows patchy staining of viral particles within tubular cells (Fishman & Davis, 2008).

2.7.6 Screening

Whether to screen KTRs with NAT of plasma or urine has been controversial. A negative urine NAT for BKV has almost a 100% negative predictive value (Hirsch et al., 2005). By testing urine, one can avoid performing BKV testing of blood on those patients with negative urine studies. Based on this, some experts recommend screening of urine as the definitive site for BKV surveillance (Hirsch et al., 2005). However, the presence of a positive NAT for BKV in urine, in the absence of an elevated BKV load in the plasma, is not associated with an increased risk for BKV disease (Hirsch et al., 2005). Hence, the use of urine screening requires performance of NAT on the blood of those patients whose level of BK viruria exceeds established thresholds. This requires patients to return to the clinic for the additional test. Accordingly, it is suggested that NAT be performed on plasma, and not the urine of KTRs.
When NAT is not available, microscopic evaluation of the urine for the presence of decoy cells is an acceptable, albeit nonspecific, alternative screening method for BKV disease and

the risk for BKV nephropathy. A negative screening test rules out BKV nephropathy in most cases (high negative predictive value). However, a positive screening test has a very low positive predictive value for BKV nephropathy (Hirsch et al., 2005; Randhawa & Brennan, 2005). Thus, many patients with urine decoy cells will not develop BKV nephropathy. It may be inappropriate to change therapy in such patients based on the presence of urine decoy cells alone.

Emerging data suggest that BKV nephropathy can be prevented if immunosuppressive medications are reduced in patients with BKV detected by a high viral load in plasma (determined by NAT) (Brennan et al., 2005).

2.7.7 Treatment of biopsy-proven BKV nephropathy

The treatment of BKV nephropathy is unsatisfactory.

The risk of BKV nephropathy appears to be correlated with the intensity of immunosuppression, and reduction of immunosuppression can result in a decrease in BKV load and a concomitant reduction of risk of development of BKV nephropathy (Almeras et al., 2008).

Although there are some centers that would use antiviral therapy (including cidofovir, leflunomide and/or ciprofloxacin) as treatment, to date there are no definitive data confirming their effectiveness (Hirsch et al., 2005; Randhawa & Brennan, 2005). However, reduction of immunosuppression does appear to have some impact on BKV nephropathy, though variable rates of graft loss attributable to BKV nephropathy have been reported even when reduction of immunosuppression has been employed. A common practice of immunosuppressive dose reduction is withdrawal of antimetabolite (azathioprine or Mycophenolate Mofetil {MMF}) and reduction in calcineurin inhibitors (CNIs) dosage by 50%. Switching from the antimetabolite MMF to leflunomide (an immunosuppressive agent with antiviral activity and lacking nephrotoxicity) in a maintenance dose of 20 to 40 mg daily has been associated with declining BKV load in blood and improving histology (Williams et al., 2005). Some centers advocate the use of cidofovir for BK nephropathy in low doses (0.25 to 1 mg/kg every 2 weeks) (Andrei et al., 1997; Vats et al., 2003). Significant renal toxicity may be observed with this agent, and may add little to reduction in immunosuppression alone.

2.8 JC virus

JC is the agent responsible for progressive multifocal leukoencephalopathy (PML). This infection of the central nervous system by JC polyomavirus has been observed uncommonly in renal allograft recipients. This infection generally manifests with focal neurologic deficits or seizures and may progress to death after extensive demyelination (Baksh et al., 2001).

2.9 Herpes Simplex Virus (HSV)

2.9.1 Superficial HSV infection

Superficial herpes simplex virus (HSV) infection is defined as disease limited to the skin or mucosal surfaces without evidence of dissemination to visceral organs.

Serologic evidence of HSV1 and HSV2 is common in the general population. Although periodic reactivation of HSV1 and HSV2 infection occurs, these episodes tend to be self-limited in immunocompetent individuals. However, episodes of invasive or disseminated HSV may occur in KTRs receiving immunosuppressive medications, and indeed the

incidence of invasive HSV is higher in KTRs than in the general population (Koneru et al., 1988; Wertheim et al., 1985).
The highest incidence of HSV reactivation occurs early after transplantation, with the greatest risk occurring during the first month following transplantation (3). While presentation later after transplant is associated with a lower risk of dissemination, treatment of superficial infection with oral acyclovir, valacyclovir or famciclovir is still recommended, given the safety and efficacy of these medications (3).
To prevent dissemination, it seems prudent to continue treatment until there are no new, active lesions.

2.9.2 Systemic HSV infection

In contrast to superficial HSV infection, systemic HSV infection involving the lungs, liver, central nervous system or other visceral organs represents a potentially life-threatening complication. Because systemic HSV is life-threatening, hospitalization and treatment with intravenous acyclovir is warranted (3). If possible, immunosuppressive medications should be reduced or withdrawn until the infection has resolved.
Intravenous acyclovir should be continued until there is demonstrative evidence of clinical improvement as measured by resolution of fever, hypoxia and signs or symptoms of hepatitis. For treatment of HSV encephalitis, a higher dosage is given by slow infusion to prevent crystallization within the renal tubules.
Once the patient has reached this level of improvement, completion of therapy may be carried out using oral acyclovir or valacyclovir (3).

2.10 Herpes Zoster Virus (HZV)

2.10.1 Uncomplicated herpes zoster

Uncomplicated zoster is a clinical syndrome characterized by cutaneous clustering of vesicular lesions in a dermatomal distribution of one or more adjacent sensory nerves. In immunocompromised hosts, patients are at risk not only of postherpetic neuralgia but also of severe local dermatomal infection (Rubin & Tolkoff-Rubin, 1983). Similarly, immunosuppressed patients are at increased risk for the development of disseminated cutaneous zoster and visceral dissemination. The higher the level of immunosuppression, the greater the risk of dissemination.
Accordingly, prompt initiation of antiviral therapy with close follow-up is warranted for these patients, even if they have only superficial skin infection (3).

2.10.2 Disseminated or invasive herpes zoster

Patients with only skin disease, but who have lesions involving more than three dermatomes, are considered to have disseminated cutaneous zoster. Similarly, patients with visceral involvement (pneumonia, encephalitis, disseminated intravascular coagulation, or graft dysfunction) in addition to skin disease are considered to have disseminated zoster (3).
Treatment with intravenous acyclovir and temporary reduction in the amount of immunosuppressive medication is efficacious (3, Fehr et al., 2002). Although specific evidence is not available to guide which immunosuppressive agent should be reduced, it would seem logical, whenever possible, to reduce the dosage of CNIs as well as steroids. In the absence of any evidence of intercurrent rejection, an effort should be made to maintain

the reduced level of immunosuppression for a minimum of 3–5 days and until there is evidence of clinical improvement (KDIGO, 2009).

2.10.3 Pzevention of primary varicella zoster infection

The use of varicella zoster immunoglobulin has been demonstrated to prevent or modify varicella in immunosuppressed individuals exposed to varicella (3; 12; Boeckh, 2006).
If varicella zoster immunoglobulin is not available, or if >96 h have passed since the exposure, some experts recommend prophylaxis with a 7-day course of oral acyclovir (80 mg/kg/day administered in four divided doses with a maximum of 800 mg per dose) beginning on day 7–10 after varicella exposure (12; Boeckh, 2006).
The use of varicella vaccine is not recommended as a postexposure prophylactic strategy in KTRs.

2.11 Parvovirus

In the transplant population, infection with parvovirus B19 can be presented with refractory severe anemia, pancytopenia, thrombotic microangiopathy, fibrosing cholestatic hepatitis, encephalitis, and graft dysfunction. Parvovirus infection commonly occurs within the first 3 months of transplantation with reported donor transmission and can be diagnosed with bone marrow examination that reveals typical giant proerythroblasts, and the diagnosis should be confirmed by detection of B19 virus DNA in serum by PCR assay. Treatment consists of high-dose IVIG (0.5 mg/kg per day for 5 to 10 days), reduction of immunosuppression, and, if possible, discontinuation of tacrolimus therapy for recurrent or persistent disease (Pegues et al., 2010).

3. Fungal infections

3.1 Introduction

Fungal infections remain a significant cause of morbidity and mortality in renal transplant recipients, despite ongoing refinements in immunosuppressive therapy, graft preservation, and surgical techniques. The mortality from fungal infections remains high, although the incidence of fungal infections in renal transplant recipients is less than that reported for other solid organ transplant recipients, and is related to the pathogenicity of the organisms, site of infection, impaired host inflammatory response, potential for rapid clinical progression, failure to recognize a high-risk patient, and comorbidities, such as renal failure and diabetes mellitus (Pegues et al., 2010).

3.2 Antifungal prophylaxis

3.2.1 Introduction

The incidence of invasive fungal infections following solid organ transplantation ranges from 5 to 42 percent and varies with the organ being transplanted. Candida and Aspergillus species are the leading causative agents, and the majority of these infections occur within the first month after transplantation. These infections are associated with high overall mortality rates (Paya, 1993; Singh, 2000).

3.2.2 Patient selection

Patients who should be considered for antifungal prophylaxis include those with:

- Renal and hepatic dysfunction.

- Large blood transfusion requirements.
- Prolonged ICU stays.
- Additional surgery posttransplant including laparotomy and retransplantation.
- Known fungal colonization pretransplantation.
- Prior (broad-spectrum) antimicrobial use.

None of the currently available antifungal agents is ideal for all of the indications for posttransplant prophylaxis.

3.2.3 Fluconazole

Fluconazole appears to be safe and has not been associated with hepatotoxicity following liver transplantation; it can be used as prophylaxis against susceptible Candida species and reduces invasive infections in such patients (Playford et al., 2004).

Fluconazole does not have activity against filamentous fungi. In addition, some Candida species have relative resistance (high minimum inhibitory concentrations [MICs]) to the drug. Drug interactions with calcineurin inhibitors are variable but will increase these drug levels in most patients. Similarly, serum calcineurin inhibitor levels will fall when prophylaxis is discontinued; dose readjustment is essential to prevent graft rejection.

3.2.4 Itraconazole

Itraconazole capsules have poor oral bioavailability and should not be relied upon in the critically ill patient after transplantation. The itraconazole suspension has better oral bioavailability, but trials to date have failed to demonstrate the efficacy of the oral solution for the prevention of invasive aspergillosis (Menichetti et al., 1999).

Efficacy of the intravenous formulation as prophylaxis waits testing in clinical trials. Significant drug interactions with calcineurin inhibitors result in levels increased two to four fold over baseline.

3.2.5 Voriconazole

Voriconazole was approved by the FDA for the treatment of aspergillosis, scedosporiosis, and fusariosis in 2002. This azole offers broader filamentous mold activity than either fluconazole or itraconazole, but has no activity against the zygomycetes. In addition, it has excellent oral bioavailability. However, no prophylactic trials have been performed to date. In addition, as with the other azoles, voriconazole is a significant inhibitor of the cytochrome P450 enzymes. Of particular note, co-administration of voriconazole and sirolimus is contraindicated due to these interactions (11). Significant drug interactions with calcineurin inhibitors result in levels 3-5 fold over baseline in most patients.

3.2.6 Amphotericin B

Amphotericin B (both regular and lipid formulations) are used in a number of centers for the prevention of fungal infections. Several studies have demonstrated the failure of low-dose regimens as prophylaxis for invasive aspergillosis (Lorf et al., 1999; Perfect et al., 1992), and such therapies should be used with caution.

3.2.7 Echinocandins

There are multiple FDA-approved echinocandins with similar spectra of antifungal activity including caspofungin, micafungin, and anidulafungin. No trials of prophylaxis in solid

organ transplantation have been performed to date. These agents are not inducers or inhibitors of the cytochrome P450 enzymes. However, cyclosporine moderately increases the area under the curve (AUC) of caspofungin and elevations in hepatic transaminases were noted in healthy subjects when the drugs were administered concomitantly. These drugs are available in IV formulations only (Mora-Duarte et al., 2002).

3.3 Candida

The most common fungal pathogen in transplant patients is Candida, with more than 50% being of non-albicans strains.

Candida infections occur most commonly during the first month following transplantation and are usually associated with transplant surgical technical complications, early rejection, and enhanced immunosuppression (Fishman, 2007).

Candida infection is most commonly associated with an endogenous source of colonization, but inadequate health care worker hand hygiene may contribute to acquisition from an exogenous source. C. albicans is the most common species, followed by C. glabrata, C. tropicalis, and C. parapsilosis. Speciation is clinically useful because nonalbicans Candida species vary in in-vitro susceptibility to amphotericin B and azoles (10).

Mucocutaneous candidal infection (e.g., oral thrush, esophageal infection, cutaneous infection at intertriginous sites, candidal vaginitis) is most common in diabetics, with high-dose steroid therapy, and during broad-spectrum antibacterial therapy. These infections are usually treatable through correction of the underlying metabolic abnormality and topical therapy with clotrimazole or nystatin without associated risks that may be present for systemically absorbed antifungal agents. However, a recent report suggested a potential drug–drug interaction between clotrimazole and tacrolimus (Vasquez et al., 2001). It is important to note that there are drug–drug interactions between fluconazole and calcineurin inhibitors.

Although data regarding the appropriate duration of prophylaxis for these agents are not available for kidney transplant recipients, the risk is greatest early after transplantation when patients are receiving their highest levels of immunosuppression, and are more likely to be exposed to antibacterial agents that increase the risk for Candida infections. Accordingly, these agents can likely be discontinued once the patient is on maintenance immunosuppression, particularly when steroid doses are stable and low (10).

Thrush also may complicate viral (HSV, CMV) or toxic (drugs including mycophenolate mofetil) esophagitis.

Other sites of Candida infection include wound infections; cystitis, pyelonephritis, and ureteral obstruction by Candida elements or "fungal ball"; intra-abdominal infections, including infected perigraft fluid collections or peritonitis; and intravascular device-associated fungemia (10).

Optimal management of candidal infection occurring in association with the presence of vascular access catheters, surgical drains, genitourinary tract stents, and bladder catheters requires removal of the foreign body and systemic antifungal therapy with fluconazole or echinocandin.

Renal parenchymal infection most often results from candidemia and hematogenous spread, although ascending infection from the bladder can occur (10).

Candiduria is a special problem in renal transplant recipients, even if the patient is asymptomatic. Particularly in individuals with poor bladder function, obstructing fungal balls can develop at the ureteropelvic junction, resulting in obstructive uropathy, ascending

pyelonephritis, and the possibility of systemic dissemination. A single positive blood culture result for Candida species necessitates systemic antifungal therapy; this finding carries a risk of visceral invasion of greater than 50% in this population (Fishman & Davis, 2008).

3.4 Aspergillus

Patients at risk for aspergillosis include those receiving repeated courses of enhanced immunosuppression for rejection and those with chronic graft dysfunction, diabetes, comorbid medical illnesses, or CMV infection.

The clinical spectra of aspergillosis include: pneumonia and other tissue-invasive forms, including genitourinary, central nervous system, rhinocerebral, gastrointestinal, skin, wound, and musculoskeletal disease (Pegues et al., 2010).

Invasive aspergillosis is a medical emergency in the transplant recipient, with the portal of entry being the lungs and sinuses in more than 90% of patients and the skin in most of those remaining.

The pathological hallmark of invasive aspergillosis is blood vessel invasion, which accounts for the three clinical characteristics of this infection—tissue infarction, hemorrhage, and systemic dissemination with metastatic invasion. Early in the course of transplantation, central nervous system involvement with fungal infection is most often due to Aspergillus; 1 year or later after transplantation, other fungi (Zygomycetes, dematiaceous fungi) become more prominent (Fishman & Davis, 2008).

Diagnosis of aspergillus infection depends on a high clinical suspicion, isolation of Aspergillus species from a sterile body site or repeated isolation from the respiratory tract, and typical radiographic findings.

Radiologic appearances of pulmonary aspergillosis in kidney transplant recipients include nodules, diffuse or wedge-shaped opacities, empyema, or cavitary forms. Serial measurement of aspergillus galactomannan in the serum may aid in the early diagnosis of invasive aspergillosis in the high-risk setting (Pegues et al., 2010).

Voriconazole is the drug of choice for documented Aspergillus infection, despite its significant interactions with calcineurin inhibitors and rapamycin (Herbrecht et al., 2002).

Liposomal amphotericin is an equally effective alternative, and combination therapies are under study. Surgical debridement is usually essential for successful clearance of such invasive infections.

3.5 Pneumocystosis

3.5.1 Introduction

Pneumocystis jirovecii (formally known as Pneumocystis carinii) is an opportunistic fungal pathogen known to cause life-threatening pneumonia in immunocompromised patients, including kidney transplant recipients.

The risk of infection with Pneumocystis is greatest in the first 2-6 months after transplantation and during periods of increased immunosuppression (Fishman & Rubin, 1998; Fishman, 2001).

Most transplant centers report an incidence of Pneumocystis pneumonia of approximately 10% in the first 6 months after transplantation in patients not receiving trimethoprim/sulfamethoxazole (or alternative drugs) as prophylaxis. There is a continued risk of infection in cases of: recipients who require over immunosuppression for prolonged periods because of poor allograft function or chronic rejection, recipients with chronic CMV infection, and recipients undergoing treatments that increase the level of immunodeficiency,

such as cancer chemotherapy or neutropenia secondary to drug toxicity (Fishman & Davis, 2008).

3.5.2 Clinical presentation

P. jirovecii pneumonia (PCP) is defined as the presence of lower respiratory-tract infection due to P. jirovecii.

It typically presents with fever, dyspnea, nonproductive cough, marked hypoxemia with arterial-alveolar mismatching, and diffuse interstitial infiltration or focal air space consolidation on chest radiograph. Unusual presentations are possible in renal transplant recipients, including pulmonary mass lesions.

In the transplant recipient, Pneumocystis pneumonia is generally acute to subacute in development. Atypical Pneumocystis infection (radiographically or clinically) may be seen in patients who have coexisting pulmonary infections or who develop disease while receiving prophylaxis with second-choice agents (e.g., pentamidine or atovaquone).

Significant extrapulmonary disease is uncommon in the transplant recipient (Fishman, 2001).

3.5.3 Diagnosis

The characteristic hypoxemia of Pneumocystis pneumonia produces a broad alveolar-arterial partial pressure of oxygen gradient. The level of serum lactate dehydrogenase is elevated in most patients with Pneumocystis pneumonia (>300 IU/mL).

There is no diagnostic pattern exists for Pneumocystis pneumonia on routine chest radiograph that may be entirely normal or develop the classic pattern of perihilar and interstitial ground-glass infiltrates. Chest CT scans are more sensitive to the diffuse interstitial and nodular pattern than routine radiographs.

The manifestations of P. carinii (jiroveci) pneumonia –both clinically and radiologically- are virtually identical to the manifestations of CMV and it is very difficult to determine whether both pathogens are present (Fishman & Davis, 2008).

A definitive diagnosis of PCP is made by demonstration of organisms in lung tissue or lower respiratory tract secretions. Because no specific diagnostic pattern exists on any given imaging test, it is imperative that the diagnosis of PCP be confirmed by lung biopsy or bronchoalveolar lavage (KDIGO, 2009).

3.5.4 Prophylaxis

The importance of preventing Pneumocystis infection cannot be overemphasized and although PCP is potentially a life-threatening complication of kidney transplant recipients, the use of chemoprophylaxis has been shown to be extremely effective in preventing the development of clinical disease attributable to this pathogen.

Prophylaxis against disease should be reinstituted following augmentation of immunosuppression, such as steroid bolus for acute rejection.

Prophylactic agents, in order of efficacy, include trimethoprim–sulfamethoxazole (TMP-SMX), monthly intravenous or aerosolized pentamidine, daily dapsone, daily atovaquone, and the combination of clindamycin and pyrimethamine.

Indications for the use of alternative preventive agents include the development of allergic reactions and/or drug-induced neutropenia from TMP-SMX (KDIGO, 2009).

Low-dose TMP-SMX is well tolerated and should be used in the absence of concrete data showing true allergy or interstitial nephritis.

TMP-SMX is the most effective agent for prevention of infection caused by P.carinii (jiroveci). The advantages of TMP-SMX include increased efficacy; lower cost; availability of oral preparations; and possible protection against other organisms, including T. gondii, Isospora belli, Cyclospora cayetanensis, Nocardia asteroides, and common urinary, respiratory, and gastrointestinal bacterial pathogens (Fishman & Davis, 2008). None of the alternative regimens is as good as daily TMP-SMX and none provides the antibacterial protection of that agent (Rodriguez & Fishman, 2004). Thus, another agent (daily fluoroquinolone) must be added for antibacterial activity. This may be of greatest importance in renal and lung transplant recipients where the early incidence of postoperative bacterial infections is high.

There was no difference in efficacy for PCP when TMP-SMX was given daily or three times per week (Hughes et al., 1987). However, in kidney transplant recipients, the use of daily TMP-SMX may be associated with a decreased risk of bacterial infection and may be easier for patient adherence (Fox et al., 1990).

Although definitive evidence for the duration of PCP prophylaxis is not available, most experts agree that it should be continued for at least 6 months (and perhaps as long as 1 year) following transplantation (5). Because most kidney transplant recipients will remain on immunosuppression for the rest of their lives, some experts recommend a more prolonged and perhaps even indefinite use of PCP prophylaxis.

3.5.5 Treatment

Prior to the use of TMP-SMX, mortality from PCP in kidney transplant recipients was very high (Hennequin et al., 1995; Sterling et al., 1984).

The treatment of PCP includes both the use of intravenous TMP-SMX as well as corticosteroids for kidney transplant recipients with significant hypoxemia and reduction of immunosuppressive medications (5). RCTs have demonstrated that the use of corticosteroids in the first 72 hours of PCP in HIV patients with moderate to severe PCP resulted in improved outcome, including morbidity, mortality and avoidance of intubation (5). The usual duration of treatment is 2–3 weeks.

First-line treatment is with TMP-SMX 15 mg/kg for 21 days. Treatment of severe disease should include adjunctive steroids as for HIV-infected persons with PCP (60 mg/day initially, then taper).

Second-line agents include intravenous pentamidine isethionate (4 mg/kg per day, used in patients with proven TMP-SMX allergy), dapsone-trimethoprim (100 mg dapsone daily with trimethoprim 100 mg twice daily), or clindamycin plus primaquine (600 mg 4 times daily clindamycin with 30 mg base daily primaquine).

Adverse effects of trimethoprim include nephrotoxicity, pancreatitis, and bone marrow suppression. Dapsone is associated with hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency.

Mild to moderate P. jiroveci pneumonia can be treated with atovaquone (750 mg orally twice daily for 21 days) in patients allergic to TMP-SMX (Pegues et al., 2010).

3.6 Cryptococcus

3.6.1 Clinical presentation after transplantation

Cryptococcal infection is rarely seen in the transplant recipient until more than 6 months after transplantation. The most common presentation of cryptococcal infection in the relatively intact transplant recipient is that of an asymptomatic pulmonary nodule, often

with active organisms present, while in the chronic patient, pneumonia and meningitis are common, with skin involvement at sites of tissue injury (catheters) and in prostate or bone (Fishman & Davis, 2008).

3.6.2 Diagnosis and treatment

Cryptococcosis should be suspected in transplant recipients who present - more than 6 months after transplantation - with unexplained headaches (especially when accompanied by fevers), decreased state of consciousness, failure to thrive, or unexplained focal skin lesion (which requires biopsy for culture and pathological evaluation).
Diagnosis requires detection of serum cryptococcal antigen, but all such patients should have lumbar puncture for cell counts and cryptococcal antigen studies. Liposomal amphotericin and flucytosine (after obtaining serum levels) are probably the best initial treatment followed by high-dose fluconazole until the cryptococcal antigen is cleared from blood and cerebrospinal fluid. Scarring and hydrocephalus may be observed (Fishman & Davis, 2008).

3.7 Treatment of fungal infection

3.7.1 Amphotericin B deoxycholate (AmB)

AmB was used for treatment of invasive candidiasis, cryptococcosis, coccidioidomycosis, histoplasmosis, and aspergillosis but owing to inherent toxicities and intolerance, newer agents have increasingly been used in renal transplant recipients. Its lipid formulations are all associated with lower risks for nephrotoxicity, metabolic derangements, and infusion-associated side effects than is AmB.

3.7.2 Voriconazole

Voriconazole is superior to conventional AmB for the treatment of invasive aspergillosis and also has in vitro activity against a wider range of organisms (Herbrecht et al., 2002).

3.7.3 Itraconazole

Despite its good in vitro activity against Aspergillus species; Itraconazole use is generally reserved for treatment of less-severe aspergillosis (Menichetti et al., 1999) or maintenance therapy following initial response to lipid amphotericin or voriconazole and for treatment of endemic mycoses. All of the azoles impair calcineurin inhibitor metabolism and increase calcineurin blood levels.

3.7.4 Fluconazole

Fluconazole is the first-line agent of the treatment or prevention of reactivation coccidioidomycosis in renal transplant recipients. The development of fungal resistance or tolerance can result from the long-term use of fluconazole that also may increase the risk for fungal superinfection with C. glabrata, C. krusei, or C. tropicalis (Playford et al., 2004). Fluconazole and 5-flucytosine can be used for cryptococcal disease.

3.7.5 Echinocandins

Echinocardins including caspofungin, anidulafungin, and micafungin are fungicidal for Candida species, including fluconazole-resistant species. These agents are effective, well

tolerated, and have few drug-drug interactions. So, they increasingly are being used to treat serious infections associated with nonalbicans Candida species in transplant recipients (Mora-Duarte et al., 2002). Echinocandins are available only as intravenous formulations.
Finally, the development of any serious fungal infection in a transplant recipient mandates a critical evaluation of the immunosuppressive regimen with minimizing the corticosteroid dose, keeping the blood levels of CNIs in the low therapeutic range, and discontinuation of other immunosuppressive agents temporarily. In case of life-threatening fungal infection with clinical treatment failure despite appropriate antifungal therapy, discontinuation of immunosuppression at the cost of graft loss may be warranted.

4. Bacterial infections

4.1 Introduction

In the early post-transplantation period, the bacterial pathogens are similar to those causing health care-associated infections in the non-transplant surgical population with Enterobacteriaceae, and Staphylococcus and Pseudomonas species are the most commonly isolated health care pathogens and increasingly are multidrug resistant (Fishman, 2007).
Aerobic gram-negative bacilli, including Enterobacteriaceae and P. aeruginosa, are the most common organisms causing pneumonia and UTIs in kidney transplant recipients. Klebsiella pneumoniae and E. coli strains with resistance to extended-spectrum cephalosporins are increasingly associated with nosocomial urinary tract infections (Green et al., 2004).

4.2 Urinary Tract Infection (UTI)

A urinary tract infection (UTI) is an infection causing signs and symptoms of cystitis or pyelonephritis (including the presence of signs of systemic inflammation), which is documented to be caused by an infectious agent. Kidney allograft pyelonephritis is an infection of the kidney allograft that is usually accompanied by characteristic signs and symptoms of systemic inflammation and a positive urine and/or blood culture. Occasionally, pyelonephritis is diagnosed by allograft biopsy. Antibiotic prophylaxis is the use of an antimicrobial agent (or agents) to prevent the development of a UTI (KDIGO, 2009).
Observational studies have documented a high incidence of UTI in KTRs (Schmaldienst et al., 2002). Pyelonephritis of the kidney allograft is a common complication in KTRs (Schmaldienst et al., 2002). It may cause graft failure, sepsis and death. The use of antibiotic prophylaxis with trimethoprim–sulfamethoxazole has been demonstrated to decrease the frequency of bacterial infections, including UTI in KTRs (Fox et al., 1990). The use of trimethoprim–sulfamethoxazole for the first 9 months following kidney transplant was associated with statistically significant decreases in number of any bacterial infection, overall number of UTI and number of noncatheter UTI.
Although the use of ciproflaxicin also appeared effective in the prevention of UTI after KTRs, patients treated with this regimen were at risk for, and developed Pneumocystis jirovecii pneumonia (PCP) (Hibberd et al., 1992b). Accordingly, the use of TMP-SMX is preferred over ciprofloxacin at least during the first 6 months after transplantation.
Evidence suggests that late UTIs tend to be benign, without associated bacteremia, metastatic foci or effect on long-term graft function (Munoz, 2001).
For this reason, it is recommended to provide prophylaxis for a minimum of 6 months. For patients who are allergic to TMP-SMX, the recommended alternative agent would be

nitrofurantoin, which is widely recommended as an alternative to TMP-SMX, is chosen over ciprofloxacin (despite demonstrated effectiveness in KTRs) in an effort to limit the likelihood of emergence of antibacterial resistance.
Kidney allograft pyelonephritis may be associated with bacteremia, metastatic spread, impaired graft function and even death. Accordingly, KTRs with clinical and laboratory evidence suggestive of kidney allograft pyelonephritis should be hospitalized and be treated with intravenous antibiotics for at least the initial course of therapy. This is particularly true in early infections (first 4–6 months following kidney transplantation) (KDIGO, 2009). Recognition of the morbidity and mortality associated with allograft pyelonephritis led to recommendations in the 1980s to treat UTIs with as long as a 6-week course of antimicrobials for early UTI following transplantation. More recently, UTI after kidney transplantation has been associated with considerably lower morbidity and mortality (Munoz, 2001). Accordingly, a less-prolonged course may be required, although patients experiencing relapsing infection should be considered for a more prolonged therapeutic course.
Because of the potential for serious complications, KTRs with kidney allograft pyelonephritis should be hospitalized and treated with intravenous antibiotics, at least initially.

4.3 Mycobacterial infection

Tuberculosis (TB) and nontuberculous mycobacteria (NTM) are potential causes of serious infection in renal allograft recipients that may present as early as the first post-transplantation month.

4.3.1 Tuberculosis (TB)

4.3.1.1 Natural course and diagnosis after transplantation

The incidence of active tuberculosis is estimated to be 1% to 4% following renal transplantation and is higher in those who resided in or traveled to a country with a high prevalence of TB infection.
The most frequent source of TB infections in KTRs is reactivation of quiescent foci of Mycobacterium tuberculosis that persist after initial asymptomatic infection (Drobniewski & Ferguson, 1996). Accordingly, screening and identification of individuals with evidence of prior latent infection with TB should allow treatment prior to development of clinical disease, resulting in improved outcome.
Atypical presentations of M. tuberculosis and NTM disease may delay diagnosis and contribute to morbidity in the transplant population. Reactivation tuberculosis warrants special vigilance, especially among transplant recipients with a prior history of mycobacterial infection, with old granulomatous disease on chest radiograph, or from countries with high TB prevalence. Up to 40% of renal transplant recipients with reactivation tuberculosis will present with disseminated infection, with involvement of the skin, skeleton (bone and joint), or central nervous system and disseminated disease should be suggested with finding granuloma in biopsy specimens from extrapulmonary sites (9).
Interferon-gamma release assays such as T-SPOT.TB and QuantiFERON are an alternative to the tuberculin skin test for detecting latent TB infection (Triverio et al., 2009). Their sensitivity and specificity, however, have not been systematically evaluated in KTRs.
The use of BCG vaccine is especially common in regions where the prevalence of TB is high. In these regions, it is therefore difficult to distinguish purified-protein derivative (PPD) skin

tests that are positive due to BCG from those that are positive due to prior infection with M. tuberculosis. Accordingly, it is recommended that the history of BCG vaccination should be ignored and that a 9-month course of prophylactic isoniazid should be used (6).
The use of prophylactic isoniazid in patients with a past or current positive PPD skin test, and/or a history of TB without adequate documented treatment, has been previously recommended by the European Best Practice Guidelines for Renal Transplantation (6) and the American Society of Transplantation Guidelines for the Prevention and Management of Infectious Complications of Solid Organ Transplantation (8).
If, according to these guidelines, vaccination with BCG can give a 'false-positive' PPD skin test, then some patients may be treated unnecessarily. Most believe that the effect of BCG should not persist for more than 10 years (9).

4.3.1.2 Therapy

Because of the increase in multidrug-resistant (MDR) strains, appropriate therapy should include four agents: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) or intramuscular streptomycin (SM) for 2 months or until susceptibility tests results are available followed by up to 10 months of INH and RIF (7).
Both INH and RIF affect the cytochrome P-450 enzyme system. INH increases CNIs and mTOR inhibitors levels, and RIF decreases these drug levels, increasing the risk for rejection. These interactions are usually predictable and may occur within 1 to 3 days of initiating antituberculous therapy. Appropriate dosage adjustments and monitoring are required (8).
One potential alternative is to substitute rifabutin for rifampin. Rifabutin has activity against M. tuberculosis that is similar to rifampin, but rifabutin is not as strong an inducer of CYP3A4 as rifampin (Vachharajani et al., 2002).
However, there is little published experience with rifabutin in KTRs.

4.3.2 Non-Tuberculous Mycobacteria (NTM)

Infection with NTM, including M. kansasii, M. fortuitum, M. chelonei, M. xenopi, M. marinum, and M. abscessus, has been reported in renal transplant recipients. These NTM can be isolated from sputum, lung tissue, skin, bone, and other disseminated sites. Many of the NTM are intrinsically resistant to standard antituberculous agents, and susceptibility testing should be performed against standard antituberculous agents, quinolones, macrolides, cephalosporins, and linezolid. Typical treatment includes combinations of agents for prolonged durations exceeding 12 months (Roy & Weisdorf, 1998).

4.4 Listeriosis

In renal transplant recipients, infection with L. monocytogenes typically occurs 6 or more months after transplantation and presents as meningoencephalitis or septicemia and in some cases, febrile gastroenteritis may occur. Bacteremia should be treated with intravenous ampicillin (2 gm every 4 hours for 2 weeks.), while meningitis should be treated with high-dose ampicillin and gentamicin for 3 weeks with performing repeat lumbar puncture to document cure (Pegues et al., 2010).

4.5 Legionellosis

Legionella species infections have been reported in kidney transplant recipients. Risk factors include repeated corticosteroid boluses, prolonged mechanical ventilation, and exposure to Legionella-contaminated hospital water supplies. L. micdadei and L. pneumophila

commonly cause pneumonia presents with a nonproductive cough, a temperature-pulse dissociation, elevated hepatic enzymes, diarrhea, hyponatremia, myalgias, and altered mental status but extrapulmonary involvement, including culture-negative endocarditis and renal, hepatic, and central nervous system infection, have been reported. Chest x-ray findings include alveolar or interstitial infiltrates, cavities, pleural effusions, or lobar consolidation. Diagnosis can be confirmed by culture on special media or direct-fluorescent antibody testing of sputum, tissue, or bronchoalveolar fluid. In addition, a urinary antigen test should be performed for L. pneumophila serogroup 1. Empiric treatment should be administered immediately in suspected cases as delayed treatment is associated with increased mortality. In organ transplants, optimal treatment should include azithromycin and a quinolone for 14 to 21 days, depending on severity of illness (Pegues et al., 2010).

5. Parasites

5.1 Introduction

Acquisition of infection, clinical severity, and outcome of a parasitic disease depend on innate and acquired host immunity as well as the parasite's own immune response against the host when infection is established. Organ transplant recipients may acquire significant parasitic disease in 3 ways: transmission with the graft, de novo infection, or activation of dormant infection as a consequence of immunosuppression. Malaria, Trypanosoma, Toxoplasma, and Leishmania are the principal parasites that may be transmitted with bone marrow, kidney, or liver homografts, and microsporidia with xenotransplants. De novo infection with malaria and kala-azar may occur in immunocompromised travelers visiting in endemic areas, while immunocompromised natives are subject to superinfection with different strains of endemic parasites, reinfection with schistosomiasis, or rarely, with primary infections such as acanthamoeba. The list of parasites that may be reactivated in the immunocompromised host includes giardiasis, balantidiasis, strongyloidiasis, capillariasis, malaria, Chagas' disease, and kalaazar. The broad clinical syndromes of parasitic infection in transplant recipients include prolonged pyrexia, lower gastrointestinal symptoms, bronchopneumonia, and meningoencephalitis. Specific syndromes include the hematologic manifestations of malaria, myocarditis in Chagas' disease, acute renal failure in malaria and leishmaniasis, and the typical skin lesions of Chagas' and cutaneous leishmaniasis. Many antiparasitic drugs have the potential for gastrointestinal, hepatic, renal, and hematologic toxicity, and may interact with the metabolism of immunosuppressive agents. It is recommended that transplant clinicians have a high index of suspicion of parasitic infections as an important transmission threat, as well as a potential cause of significant posttransplant morbidity (Barsoum, 2004).

5.2 Malaria

Transmission of the disease has been reported with many organ transplants, as kidney (Holzer et al., 1985), bone marrow (Abdelkefi et al., 2004), and multiorgan (Chiche et al., 2003). Malarial antibodies also have been detected in a recipient of a heart transplant who received his graft from an infected donor (Fischer et al., 1999). Transmission of malaria has been traced to infected blood transfused to a kidney transplant recipient (Moran et al., 2004).

Primary or reinfection is a distinct risk in exposed transplant recipients. For this reason, chemoprophylaxis has been strongly advocated for travelers visiting endemic areas (Anteyi et al., 2003; Boggild et al., 2004). Unfortunately, infection can still be acquired in nonendemic locations including European or American airports (Giacomini, 1998) or indigenous malarial foci as those in New York (Iftikhar & Roistacher, 1995) or Georgia (MacArthur et al., 2001) in the United States.

The clinical picture of malaria in transplant recipients is usually severe, owing to the impaired immune response. It is characterized by pyrexia, which may lack the typical periodicity or rigors. Anemia is severe, being typically hemolytic and occasionally hemophagocytic (Abdelkefi et al., 2004). It is often associated with thrombocytopenia (MacArthur et al., 2001). Acute graft dysfunction may occur as a consequence of the hemodynamic consequences of falciparum infection (Barsoum, 2000). Whether the immune response to malarial infection has an impact on subsequent rejection is unknown (Barsoum, 2004).

5.3 Babesiosis

The causative organisms are protozoa closely similar to plasmodia. Babesiosis, attributed to transfusion with contaminated blood, has been reported in KTRs (Perdrizet et al., 2000). Fever, hemolytic anemia, and impaired graft function dominate the clinical picture. A hemophagosytic syndrome has been reported in an asplenic renal transplant recipient (Slovut et al., 1996). Treatment is by a combination of clindamycin and quinine, with therapeutic apheresis in severe cases (Evenson et al., 1998).

5.4 Schistosomiasis

The association between renal transplantation and schistosomiasis is frequently seen in endemic schistosomal regions and among immigrants living in western countries. The recipient, the donor or both may have active schistosomiasis or have a history of schistosomal infection, with permanent changes in the urinary or gastrointestinal tracts (Evenson et al., 1998).

KTRs may be exposed to new or reinfection of Schistosomal infection if they resume their usual habits of exposure to contaminated water. This has been reported in Egypt (Shokeir, 2001), where 23% of recipients at high risk were reinfected. The clinical profile in those cases was not significantly different from natural infection in immunocompetent individuals.

Recrudescence of schistosomal glomerulopathy has been reported in an endemic area in South America, where mesangioproliferative glomerulonephritis with schistosomal antigen deposits developed in a recent kidney transplant recipient who originally had been infected with S. mansoni (Sobh et al., 2001). Accordingly, it has been suggested to prophylactically treat patients with such infection before undergoing transplantation, since adult worms often live silently in an infected host for decades and are able to induce glomerular lesions through immune-complex deposits containing schistosomal gut antigens (Deelder et al., 1980).

5.5 Toxoplasmosis

Posttransplant toxoplasmosis has been reported most frequently with heart transplants (Hermanns et al., 2001). It also has been reported with bone marrow (Ortonne., 2001), stem cell (Lopez-Duarte et al., 2003), liver (Barcan et al., 2002), kidney (Sukthana et al., 2001),

simultaneous liver-pancreas, and liver-kidney-pancreas (Hommann et al., 2002) transplants. Transmission of the disease can occur with either blood transfusion or transplanted organs. A study of 31 patients with posttransplant toxoplasmosis has shown that transmission occurred in 10, recrudescence in 2, and the mode of infection remained unknown in 19 (Renoult et al., 1997). The disease is characterized by pyrexia, lymphadenopathy, and multiorgan involvement. Anemia is common, and a hemophagocytic syndrome has been reported in several cases (Karras et al., 2004). Encephalitis is a serious and frequent complication (Lopez-Duarte et al., 2003). Peripheral neuropathy is common, taking a Guillain-Barré pattern in a recently reported case (Gonzalez et al., 2000). Chorioretinitis, similar to that seen in CMV infection, is frequently seen (Moshfeghi et al., 2004). Pulmonary infiltrates, with pleural involvement may occur (Barcan et al., 2002). Pyrimethamine is the treatment of choice.

5.6 Cryptosporidiosis

Cryptosporidium is an intestinal protozoan, which is often a benign commensal in the human intestine that can cause clinical disease in the immunocompromised patient. It is a notorious infection in intestinal transplants (Moshfeghi et al., 2004) but has also been reported as a recrudescence disease in recipients of liver (Campos et al., 2000), kidney (Minz et al., 2004), and bone marrow (Muller et al., 2004) transplants.

It may cause a diarrheal illness that can lead to significant fluid and electrolyte depletion and may be fatal. It can also persist, leading to chronic diarrhea with hepatobiliary involvement (Ferreira & Borges, 2002). There is no specific treatment, but the most widely used therapy is paromomycin.

5.7 Microsporidiasis

Microsporidia are intracellular spore-forming protozoa that are ubiquitous in the environment and may live in the intestine of insects, birds, and mammals. Human infection has been described most commonly with Enterocytozoon bieneusi in patients with HIV disease and only rarely in those with other forms of immunosuppression. Microsporidiosis have been reported in KTRs (Carlson et al., 2004; Mohindra et al., 2002).

Infection usually begins with diarrhea and cholangitis. Disseminated microsporidiosis is dominated by a febrile systemic inflammatory response, with rapid development of pneumonia and encephalitis, which is often fatal. The treatment of choice is albendazole (Anane & Attouchi, 2010).

6. References

Abbott, KC.; Swanson, SJ.; Agodoa, LY.& Kimmel, PL. (2004). Human immunodeficiency virus infection and kidney transplantation in the era of highly active antiretroviral therapy and modern immunosuppression, *J Am Soc Nephrol,* Vol., 15; pp.1633-1639.

Abdelkefi, A.; Ben Othman, T.; Torjman, L.; Ladeb, S.; Lakhal, A.; Belhadj, S. et al. (2004). Plasmodium falciparum causing hemophagocytic syndrome after allogeneic blood stem cell transplantation. *Hematol J*, Vol., 5; pp. 449-450.

Almeras, C.; Foulongne, V.; Garrigue, V.; Szwarc, I.; Vetromile, F.; Segondy, M., et al. (2008). Does reduction in immunosuppression in viremic patients prevent BK virus

nephropathy in de novo renal transplant recipients? A prospective study. *Transplantation*, Vol., 85; pp. 1099–1104.

Anane, S. & Attouchi, H. (2010). Microsporidiosis: epidemiology, clinical data and therapy. *Gastroenterol Clin Biol*, Vol., 34; pp. 450-464.

Andrei, G.; Snoeck, R.; Vandeputte, M. & De Clercq, E.(1997). Activities of various compounds against murine and primate polyomaviruses. *Antimicrob Agents Chemother*, Vol., 41; pp. 587-593.

Anteyi, EA.; Liman, HM.; & Gbaji, A. (2003). Malaria prophylaxis in post renal transplant recipients in the tropics: is it necessary? *Cent Afr J Med*, Vol., 49; pp. 63-66.

Aroldi, A.; Lampertico, P.; Montagnino, G.; Passerini, P.; Villa, M.; Campise, MR, et al. (2005). Natural history of hepatitis B and C in renal allograft recipients. *Transplantation,* Vol., 79; pp. 1132–1136.

Asberg, A.; Humar, A.; Rollaq, H.; Jardine, AG.; Mouas, H.; Pescovitz, MD, et al. (2007). Oral valganciclovir is non inferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant*, Vol., 7; pp. 2106-2113.

Baksh, FK.; Finkelstein, SD.; Swalsky, PA.; Stoner, GL.; Ryschkewitsch, CF. & Randhawa, P. (2001). Molecular genotyping of BK and JC viruses in human polyomavirus-associated interstitial nephritis after renal transplantation. *Am J Kidney Dis,* Vol., 38; pp. 354-365.

Barcan, LA.; Dallurzo, ML.; Clara, LO.; Valledor, A.; Macias, S.; Zorkin, E., et al. (2002). Toxoplasmagondii pneumonia in liver transplantation: survival after a severe case of reactivation. *Transpl Infect Dis*, Vol., 4; pp. 93-96.

Barsoum, RS. (2000). Malarial acute renal failure. *J Am Soc Nephrol*, Vol., 11; pp. 2147-2154.

Barsoum, RS. (2004). Parasitic infections in organ transplantation. *Exp Clin Transplant*, vol, 2 ; pp. 258-2567.

Bloom, RD.; Rao, V.; Weng, F.; Grossman, RA.; Cohen, D. & Mange, KC. (2002). Association of hepatitis with posttransplant diabetes in renal transplant patients on tacrolimus. *J Am Soc Nephrol,* Vol., 13; pp. 1374-1380.

Boeckh, M. (2006). Prevention of VZV infection in immunosuppressed patients using antiviral agents. *Herpes*, Vol., 13; pp. 60–65.

Boggild, AK.; Sano, M.; Humar, A.; Salit, I.; Gilman, M. & Kain, KC. (2004). Travel patterns and risk behavior in solid organ transplant recipients. *J Travel Med*, Vol., 11; pp. 37-43.

Breinig, MK.; Zitelli, B.; Starzl, TE. & Ho, M. (1987). Epstein-Barr virus, cytomegalovirus, and other viral infections in children after liver transplantation. *J Infect Dis* Vol., 156; pp. 273–279.

Brennan, DC.; Agha, I.; Bohl, DL.; Schnitzler, MA.; Hardinger, KL.; Lockwood, M, et al. (2005). Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction. *Am J Transplant*, Vol., 5; pp. 582–594.

Caillard, S.; Lelong, C.; Pessione, F.; Moulin, B. & French PTLD Working Group. (2006). Post-transplant lymphoproliferative disorders occurring after renal transplantation in adults: Report of 230 cases from the French Registry. *Am J Transplant*, Vol., 6; pp. 2735–2742.

Caliendo, AM.; St George, K.; Kao, SY.; Allega, J.; Tan, BH.; La Fontaine, R., et al. (2000). Comparison of quantitative cytomegalovirus (CMV) PCR in plasma and CMV antigenemia assay: clinical utility of the prototype Amplicor CMV Monitor test in transplant recipients. *J Clin Microbiol*, Vol., 38; pp. 2122-2127.

Campos, M.; Jouzdani, E.; Sempoux, C.; Buts, JP.; Reding, R.; Otte, JB. & Sokal, EM. (2000). Sclerosing cholangitis associated to cryptosporidiosis in liver-transplanted children. *Eur J Pediatr*, Vol., 159; pp. 113-115.

Carlson, JR.; Li, L.; Helton, CL.; Munn, RJ.; Wasson, K.; Perez, RV., et al. (2004). Disseminated microsporidiosis in a pancreas/kidney transplant recipient. *Arch Pathol Lab Med*, Vol., 128; pp. e41-e43.

Chan, TM.; Fang, GX.; Tang, CS.; Cheng, IK.; Lai, KN. & Ho, SK. (2002). Preemptive lamivudine therapy based on HBV DNA level in HBsAg-positive kidney allograft recipients. *Hepatology*, Vol., 36; pp. 1246-1252.

Chang, TT.; Gish, RG.; de Man, R.; Gadano, A.; Sollano, J.; Chao, YC., et al. (2006). A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med*, Vol., 354; pp.1001-1010.

Chiche, L.; Lesage, A.; Duhamel, C.; Salame, E.; Malet, M.; Samba, D, et al. (2003). Posttransplant malaria: first case of transmission of Plasmodium falciparum from a white multiorgan donor to four recipients. *Transplantation*, Vol., 75; pp. 166-168.

Cockfield, SM.; Preiksaitis, JK.; Jewell, LD. & Parfrey, NA. (1993). Post-transplant lymphoproliferative disorder in renal allograft recipients. Clinical experience and risk factor analysis in a single center. *Transplantation*, Vol., 56; pp. 88–96.

Cruzado, JM.; Carrera, M.; Torras, J. & Grinyó, JM. (2001). Hepatitis C virus infection and de novo glomerular lesions in renal allografts. *Am J Transplant*, Vol., 1; pp. 171-178.

Cruzado, JM.; Casanovas-Taltavull, T.; Torras, J.; Baliellas, C.; Gil-Vernet, S. & Grinyó, JM. (2003). Pretransplant interferon prevents hepatitis C virus-associated glomerulonephritis in renal allografts by HCV-RNA clearance. *Am J Transplant*, Vol., 3; pp. 357-360.

Deelder, AM.; Kornelis, D.; Van Marck, EA.; Eveleigh, PC. & Van Egmond, JG. (1980). Schistosoma mansoni: characterization of two circulating polysaccharide antigens and the immunological response to these antigens in mouse, hamster, and human infections. *Exp Parasitol*, Vol., 50; pp. 16-32.

Delladetsima, I.; Psichogiou, M.; Sypsa, V.; Psimenou, E.; Kostakis, A.; Hatzakis, A., et al. (2006). The course of hepatitis C virus infection in pretransplantation anti-hepatitis C virus-negative renal transplant recipients: a retrospective follow-up study. *Am J Kidney Dis*, Vol., 47; pp. 309-316.

Dharnidharka, VR. & Harmon, WE. (2001a). Management of pediatric postrenal transplantation infections. *Semin Nephrol*, Vol., 21; pp. 521–531.

Dharnidharka, VR.; Sullivan, EK.; Stablein, DM.; Tejani, AH.; Harmon, WE & North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). (2001b).Risk factors for posttransplant lymphoproliferative disorder (PTLD) in pediatric kidney transplantation: A report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Transplantation*, Vol., 71; pp. 1065–1068.

Drobniewski, FA. & Ferguson, J. (1996) Tuberculosis in renal transplant units. *Nephrol Dial Transplant*, Vol., 11; pp. 768–770.

Evenson, DA.; Perry, E.; Kloster, B.; Hurley, R. & Stroncek, DF. (1998). Therapeutic apheresis for babesiosis. *J Clin Apheresis*, Vol., 13; pp. 32-36.

Fabrizi, F.; Dulai, G.; Dixit, V.; Bunnapradist, S. & Martin, P. (2004a). Lamivudine for the treatment of hepatitis B virus-related liver disease after renal transplantation: meta-analysis of clinical trials. *Transplantation*, Vol., 77; pp. 859-864.

Fabrizi, F.; Martin, P. & Bunnapradist, S. (2004b). Treatment of chronic viral hepatitis in patients with renal disease. *Gastroenterol Clin North Am*, Vol., 33; pp. 655-670.

Fabrizi, F.; Martin, P.; Dixit, V.; Bunnapradist, S.; Kanwal, F. & Dulai, G. (2005). Post-transplant diabetes mellitus and HCV seropositive status after renal transplantation: meta-analysis of clinical studies. *Am J Transplant*, Vol., 5; pp. 2433-2440.

Fehr, T.; Bossart, W.; Wahl, C. & Binswanger, U. (2002). Disseminated varicella infection in adult renal allograft recipients: Four cases and a review of the literature. *Transplantation*, Vol., 73; pp. 608–611.

Ferreira, MS. & Borges, AS. (2002). Some aspects of protozoan infections in immunocompromised patients- a review. *Mem Inst Oswaldo Cruz*, Vol., 97; pp. 443-457.

Filik, L.; Karakayali, H.; Moray, G.; Dalgiç, A.; Emiroğlu, R.; Ozdemir, N., et al. (2006). Lamivudine therapy in kidney allograft recipients who are seropositive for hepatitis B surface antigen. *Transplant Proc*, Vol., 38; pp. 496–498.

Fischer, L.; Sterneck, M.; Claus, M.; Costard-Jackle, A.; Fleischer, B.; Herbst, H., et al. (1999). Transmission of malaria tertiana by multi-organ donation. *Clin Transplan*, Vol., 13; pp. 491-495.

Fishman, JA. (1995). Pneumocystis carinii and parasitic infections in transplantation. *Infect Dis Clin North Am*, Vol., 9; pp. 1005-1044.

Fishman, JA. & Rubin, RH. (1998). Infection in organ-transplant recipients. *N Engl J Med*, Vol., 338; pp. 1741-1751.

Fishman, JA. (2001). Prevention of infection caused by Pneumocystis carinii in transplant recipients. *Clin Infect Dis*, Vol., 33; pp. 1397-1405.

Fishman, JA. (2002). BK virus nephropathy—polyomavirus adding insult to injury. *N Engl J Med*, Vol., 347; pp. 527-530.

Fishman, JA. (2007). Infections in organ-transplant recipients. *N Engl J Med*, Vol., 357; pp. 2601-2614.

Fishman, JA. & Davis, JA. (2008). Infections in renal transplant recipients. In: Sir Peter J.Morris, Stuart J. Knechtle. (eds). *KIDNEY TRANSPLANTATION: PRINCIPLES AND PRACTICE*, 6th ed. Elsevier, pp. 492-507. ISBN: 978-1-4160-3343-1. Philadelphia.

Fox, BC.; Sollinger, HW.; Belzer, FO. & Maki, DG. (1990). A prospective, randomized, double-blind study of trimethoprim-sulfamethoxazole for prophylaxis of infection in renal transplantation: Clinical efficacy, absorption of trimethoprim-sulfamethoxazole, effects on the microflora, and the cost-benefit of prophylaxis. *Am J Med*, Vol., 89; pp. 255–274.

Frassetto, LA.; Browne, M.; Cheng, A.; Wolfe, AR.; Roland, ME.; Stock, PG., et al. (2007). Immunosuppressant pharmacokinetics and dosing modifications in HIV-1 infected liver and kidney transplant recipients. *Am J Transplant*, Vol., 7; pp. 2816–2820.

Gane, E. & Pilmore, H. (2002). Management of chronic viral hepatitis before and after renal transplantation. *Transplantation*, Vol., 74; pp. 427–437.

Giacomini, T. (1998). Malaria in airports and their neighborhoods. *Rev Prat*, Vol, 48; pp. 264-267.

Gonzalez, MI.; Caballero, D.; Lopez, C.; Alburquerque, T.; Hernandez, R.; de la Loma, A., et al. (2000). Cerebral toxoplasmosis and Guillain-Barré syndrome after allogeneic peripheral stem cell transplantation. *Transpl Infect Dis*, Vol., 2; pp 145-149.

Green, M.; Avery, R. & Preiksaitis, J. (2004). Guidelines for the prevention and management of infectious complications of solid organ transplantation. *Am J Transplant*, Vol., 4 (Suppl 10); pp. 6-165.

Green, M.; Michaels, MG.; Katz, BZ.; Burroughs, M.; Gerber, D.; Shneider, BL., et al. (2006). CMV-IVIG for prevention of Epstein Barr virus disease and posttransplant lymphoproliferative disease in pediatric liver transplant recipients. *Am J Transplant*, Vol., 6; pp. 1906–1912.

Gruber, SA.; Doshi, MD.; Cincotta, E.; Brown, KL.; Singh, A.; Morawski, K., et al. (2008). Preliminary experience with renal transplantation in HIV+recipients: Low acute rejection and infection rates. *Transplantation*, Vol., 86; pp. 269–274.

Han, DJ.; Kim, TH.; Park, SK.; Lee, SK.; Kim, SB.; Yang, WS., et al. (2001). Results on preemptive or prophylactic treatment of lamivudine in HBsAg (+) renal allograft recipients: Comparison with salvage treatment after hepatic dysfunction with HBV recurrence. *Transplantation*, Vol., 71; pp. 387–394.

Hanafusa, T.; Ichikawa, Y.; Kishikawa, H.; Kyo, M.; Fukunishi, T.; Kokado., Y, et al. (1998). Retrospective study on the impact of hepatitis C virus infection on kidney transplant patients over 20 years. *Transplantation*, Vol., 66; pp 471-476.

Haque, T.; Wilkie, GM.; Taylor, C.; Amlot, PL.; Murad, P.; Iley, A., et al. (2002). Treatment of Epstein-Barr-viruspositive post-transplantation lymphoproliferative disease with partly HLA-matched allogeneic cytotoxic T cells. *Lancet*, Vol., 360; pp. 436-442.

Hartmann, A.; Sagedal, S. & Hjelmesaeth, J. (2006). The natural course of cytomegalovirus infection and disease in renal transplant recipients. *Transplantation*, Vol., 82; S15-S17.

Hennequin, C.; Page, B.; Roux, P.; Legendre, C. & Kreis, H. (1995). Outbreak of Pneumocystis carinii pneumonia in a renal transplant unit. *Eur J Clin Microbiol Infect Dis*, Vol., 14; pp. 122–126.

Herbrecht, R.; Denning, DW.; Patterson, TF.; Bennett, JE.; Greene, RE.; Oestmann, JW., et al. (2002). Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*, Vol., 347; pp. 408-415.

Hermanns, B.; Brunn, A.; Schwarz, ER.; Sachweh, JS.; Seipelt, I.; Schroder, JM., et al. (2001). Fulminant toxoplasmosis in a heart transplant recipient. *Pathol Res Pract*, Vol., 197; pp.: 211-215.

Hibberd, PL.; Tolkoff-Rubin, NE.; Cosimi, AB.; Schooley, RT.; Isaacson, D.; Doran, M., et al. (1992a). Symptomatic cytomegalovirus disease in the cytomegalovirus antibody

seropositive renal transplant recipient treated with OKT3. *Transplantation*, Vol., 53; pp. 68–72.

Hibberd, PL.; Tolkoff-Rubin, NE.; Doran, M.; Delvecchio, A.; Cosimi, AB.; Delmonico, FL., et al. (1992b). Trimethoprim-sulfamethoxazole compared with ciprofloxacin for the prevention of urinary tract infection in renal transplant recipients. A double-blind, randomized controlled trial. *Online J Curr Clin Trials*, Doc No 15.

Hibberd, PL.; Tolkoff-Rubin, NE.; Conti, D.; Stuart, F.; Thistlethwaite, JR.; Neylan, JF., et al. (1995). Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients. A randomized controlled trial. *Ann Intern Med*, Vol., 123; pp. 18–26.

Hirsch, HH.; Knowles, W.; Dickenmann, M.; Passweg, J.; Klimkait, T.; Mihatsch, MJ., et al. (2002). Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. *N Engl J Med*, Vol., 347; pp. 488-496.

Hirsch, HH.; Brennan, DC.; Drachenberg, CB.; Ginevri, F.; Gordon, J.; Limaye, AP., et al. (2005). Polyomavirus associated nephropathy in renal transplantation: Interdisciplinary analyses and recommendations. *Transplantation*, Vol., 79; pp. 1277–1286.

Hirsch, HH.; Drachenberg, CB.; Steiger, J. & Ramos, E. (2006). Polyomavirus-associated nephropathy in renal transplantation: critical issues of screening and management. *Adv Exp Med Biol*, Vol., 577; pp. 160-173.

Hodson, EM.; Barclay, PG.; Craig, JC.; Jones, C.; Kable, K.; Strippoli, GF., et al. (2005). Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst Rev*, CD003774.

Hodson, EM.; Jones, CA.; Strippoli, GF.; Webster, AC. & Craig, JC. (2007). Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. *Cochrane Database Syst Rev*, CD005129.

Holzer, BR.; Gluck, Z.; Zambelli, D. & Fey, M. (1985). Transmission of malaria by renal transplantation. *Transplantation*. Vol., 39; pp. 315-316.

Hommann, M.; Schotte, U.; Voigt, R.; Glutig, H.; Grube, T.; Kupper, B., et al. (2002). Cerebral toxoplasmosis after combined liver-pancreas-kidney and liver-pancreas transplantation. *Transplant Proc*, Vol., 34; pp. 2294-2295.

Hughes, WT.; Rivera, GK.; Schell, MJ.; Thornton, D. & Lott, L. (1987). Successful intermittent chemoprophylaxis for Pneumocystis carinii pneumonitis. *N Engl J Med*, Vol., 316; pp. 1627–1632.

Humar, A.; Kumar, D.; Boivin, G. & Caliendo, AM. (2002). Cytomegalovirus (CMV) virus load kinetics to predict recurrent disease in solid-organ transplant patients with CMV disease. *J Infect Dis*, Vol., 186; pp. 829–833.

Huraib, S.; Iqbal, A.; Tanimu, D. & Abdullah, A. (2001). Sustained virological and histological response with pretransplant interferon therapy in renal transplant patients with chronic viral hepatitis C. *Am J Nephrol,* Vol., 21; pp. 435-440. Iftikhar, SA. & Roistacher, K. (1995). Indigenous Plasmodium falciparum malaria in Queens, NY. *Arch Intern Med*, Vol., 155 pp. 1099-1101.

Kalil, AC.; Levitsky, J.; Lyden, E.; Stoner, J. & Freifeld, AG. (2005). Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. *Ann Intern Med*, Vol., 143; pp. 870-880.

Kamar, N.; Sandres-Saune, K.; Selves, J.; Ribes, D.; Cointault, O.; Durand, D., et al. (2003a). Long-term ribavirin therapy in hepatitis C virus-positive renal transplant patients: effects on renal function and liver histology. *Am J Kidney Dis*, Vol., 42; pp. 184-192.

Kamar, N.; Toupance, O.; Buchler, M.; Sandres-Saune, K.; Izopet, J.; Durand, D., et al. (2003b). Evidence that clearance of hepatitis C virus RNA after alpha-interferon therapy in dialysis patients is sustained after renal transplantation. *J Am Soc Nephrol*, Vol., 14; pp. 2092-2098.

Karras, A.; Thervet, E.; Legendre, C. & Groupe Cooperatif de transplantation d'Ile de France. (2004). Hemophagocytic syndrome in renal transplant recipients: report of 17 cases and review of literature. *Transplantation*, Vol., 77; pp. 238-243.

KDIGO: Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. (2009) *Am J Transplant*, Vol., 9(Suppl 3): S1–S157.

Kletzmayr, J.; Watschinger, B.; Müller, C.; Demetriou, D.; Puchhammer-Stöckl, E.; Ferenci, P., et al. (2000). Twelve months of lamivudine treatment for chronic hepatitis B virus infection in renal transplant recipients. *Transplantation*, Vol., 70; pp. 1404-1407.

Koneru, B.; Tzakis, AG.; DePuydt, LE.; Demetris, AJ.; Armstrong, JA.; Dummer, JS., et al. (1988). Transmission of fatal herpes simplex infection through renal transplantation. *Transplantation*, Vol., 45; pp. 653–656.

Lapinski, TW.; Flisiak, R.; Jaroszewicz, J.; Michalewicz, M. & Kowalczuk, O. (2005). Efficiency and safety of lamivudine therapy in patients with chronic HBV infection, dialysis or after kidney transplantation. *World J Gastroenterol*, Vol., 11; pp. 400–402.

Lau, JY.; Davis, GL.; Brunson, ME.; Qian, KP.; Lin, HJ.; Quan, S., et al. (1993). Hepatitis C virus infection in kidney transplant recipients. *Hepatology,* Vol., 18; pp. 1027-1031.

Lee, WC.; Shu, KH.; Cheng, CH.; Wu, MJ.; Chen, CH. & Lian, JC. (2001). Long-term impact of hepatitis B, C virus infection on renal transplantation. *Am J Nephrol*, Vol., 21; pp. 300-306.

Legendre, C.; Garrigue, V.; Le Bihan, C.; Mamzer-Bruneel, MF.; Chaix, ML.; Landais, P., et al. (1998). Harmful long-term impact of hepatitis C virus infection in kidney transplant recipients. *Transplantation*, Vol., 65; pp. 667-670.

Liaw, YF.; Chien, RN.; Yeh, CT.; Tsai, SL. & Chu, CM. (1999). Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy. *Hepatology*, Vol., 30; pp. 567-572.

Lopez-Duarte, M.; Insunza, A.; Conde, E.; Iriondo, A.; Mazorra, F. & Zubizarreta, A. (2003). Cerebral toxoplasmosis after autologous peripheral blood stem cell transplantation. *Eur J Clin Microbiol Infect Dis*, Vol., 22; pp. 548-550.

Lorf, T.; Braun, F.; Rüchel, R.; Müller, A.; Sattler, B. & Ringe, B. (1999). Systemic mycoses during prophylactical use of liposomal amphotericin B (Ambisome) after liver transplantation. *Mycoses*, Vol., 42; pp. 47-53.

MacArthur, JR.; Holtz, TH.; Jenkins, J.; Newell, JP.; Koehler, JE.; Parise, ME. & Kachur, SP. (2001). Probable locally acquired mosquito-transmitted malaria in Georgia, 1999. *Clin Infect Dis*, Vol., 32; pp. E124-E128.

Marcellin, P.; Heathcote, EJ.; Buti, M.; Gane, E.; de Man, RA.; Krastev, Z., et al. (2008). Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med*, Vol., 359; pp. 2442–2455.

Mahmoud, IM.; Elhabashi, AF.; Elsawy, E.; El-Husseini, AA.; Sheha, GE. & Sobh, MA. (2004). The impact of hepatitis C virus viremia on renal graft and patient survival: a 9-year prospective study. *Am J Kidney Dis*, Vol., 43; pp. 131-139.

Martin, P. & Fabrizi, F. (2008). Hepatitis C virus and kidney disease. *J Hepatol,* Vol., 49; pp. 613-624.

McDonald, RA.; Smith, JM.; Ho, M.; Lindblad, R.; Ikle, D.; Grimm, P., et al. (2008). Incidence of PTLD in pediatric renal transplant recipients receiving basiliximab, calcineurin inhibitor, sirolimus and steroids. *Am J Transplant*, Vol., 8; pp. 984–989.

Menichetti, F.; Del Favero, A.; Martino, P.; Bucaneve, G.; Micozzi, A.; Girmenia, C., et al. (1999). Itraconazole oral solution as prophylaxis for fungal infections in neutropenic patients with hematologic malignancies: A randomized, placebo-controlled, double-blind, multicenter trial. GIMEMA Infection Program. Gruppo Italiano Malattie Ematologiche dell' Adulto. *Clin Infect Dis*, Vol., 28; pp. 250-255.

Meyers, CM.; Seeff, LB.; Stehman-Breen, CO. & Hoofnagle, JH. (2003). Hepatitis C and renal disease: an update. *Am J Kidney Dis*, Vol., 42; pp. 631-657.

Minz, M.; Udgiri, NK.; Heer, MK.; Kashyap, R. & Malla, N. (2004). Cryptosporidiasis in live related renal transplant recipients: a single center experience. *Transplantation*, Vol., 77; pp. 1916-1917.

Mohindra, AR.; Lee, MW.; Visvesvara, G.; Moura, H.; Parasuraman, R.; Leitch, GJ., et al. (2002). Disseminated microsporidiosis in a renal transplant recipient. *Transpl Infect Dis*, Vol., 4; pp. 102-107.

Mora-Duarte, J.; Betts, R.; Rotstein, C.; Colombo, AL.; Thompson-Moya, L.; Smietana, J., et al. (2002). Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med*, Vol., 347; pp. 2020-2029.

Moran, E.; Collins, L.; Clayton, S.; Peto, T. & Bowler ,IC. (2004). Case of cryptic malaria. *Common Dis Public Health*, Vol., 7; pp. 142-144.

Moshfeghi, DM.; Dodds, EM.; Couto, CA.; Santos, CI.; Nicholson, DH.; Lowder, CY. & Davis, JL. (2004). Diagnostic approaches to severe, atypical toxoplasmosis mimicking acute retinal necrosis. *Ophthalmology*, Vol., 111; pp. 716-725.

Muller, CI.; Zeiser, R.; Grullich, C.; Finke, J.; Bertz, H.; Schmitt-Graff, A. & Kreisel, W. (2004) Intestinal cryptosporidiosis mimicking acute graft-versus-host disease following matched unrelated hematopoietic stem cell transplantation. *Transplantation*. Vol., 77; pp. 1478-1479.

Munoz, P. (2001). Management of urinary tract infections and lymphocele in renal transplant recipients.*Clin Infect Dis*, Vol., 33 (Suppl 1): S53–57.

Mylonakis, E.; Kallas, WM. & Fishman, JA. (2002). Combination antiviral therapy for ganciclovir-resistant cytomegalovirus infection in solid-organ transplant recipients. *Clin Infect Dis*, Vol., 34; pp. 1337-1341.

Nalesnik, M. (2001). The diverse pathology of posttransplant lymphoproliferative disorders: importance of a standardized approach. *Transpl Infect Dis*, Vol., 3; pp. 88-96.

Opelz, G. & Dohler, B. (2004). Lymphomas after solid organ transplantation: A collaborative transplant study report. *Am J Transplant*, Vol., 4; pp. 222–230.

Orloff ,SL.; Stempel, CA.; Wright, TL.; Tomlanovich, SJ.; Amend, WJ.; Stock, PG., et al. (1995). Long-term outcome in kidney transplant patients with hepatitis C (HCV) infection. *Clin Transplant,* Vol., 9; pp. 119-124.

Ortonne, N.; Ribaud, P.; Meignin, V.; Sarfati, C.; Esperou, H.; Devergie, A., et al. (2001). Toxoplasmic pneumonitis leading to fatal acute respiratory distress syndrome after engraftment in three bone marrow transplant recipients. *Transplantation*, Vol., 72; pp. 1838-1840.

Paya, CV. (1993). Fungal infections in solid-organ transplantation. *Clin Infect Dis*, Vol., 16; pp. 677-688.

Paya, C.; Fung, JJ.; Nalesnik, MA.; Kieff, E.; Green, M.; Gores, G., et al. (1999). Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. *Transplantation*, Vol., 68; pp. 1517-1525.

Paya, C. & Razonable, R. (2003). Cytomegalovirus infection after organ transplantation. In: Bowden R, Ljungman P, Paya C (eds). *Transplant infections*, 2nd ed. Lippincott, Williams and Wilkins, pp 298–325.

Paya, C.; Humar, A.; Dominguez, E.; Washburn, K.; Blumberg, E.; Alexander, B., et al. (2004). Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant*, Vol., 4; pp. 611-620.

Pegues, DA.; Kubak, BM.; Maree, CL. & Gregson, AL. (2010). Infections in Kidney Transplantation. In: Gabriel M. Danovitch (ed). *Handbook of Kidney Transplantation* , 5th Edition. Lippincott, Williams and Wilkins, pp 252–279. ISBN-13: 978-0-7817-9374-2.

Perdrizet, GA.; Olson, NH.; Krause, PJ.; Banever, GT.; Spielman, A. & Cable, RG. (2000). Babesiosis in a renal transplant recipient acquired through blood transfusion. *Transplantation*, Vol., 70; pp. 205-208.

Perfect, JR.; Klotman, ME.; Gilbert, CC.; Crawford, DD.; Rosner, GL.; Wright, KA., et al. (1992). Prophylactic intravenous amphotericin B in neutropenic autologous bone marrow transplant recipients. *J Infect Dis*, Vol., 165; pp. 891-897.

Playford, EG.; Webster, AC.; Sorell, TC. & Craig, JC. (2004). Antifungal agents for preventing fungal infections in solid organ transplant recipients. *Cochrane Database Syst Rev*, CD004291.

Preiksaitis, JK. & Keay, S. (2001). Diagnosis and management of posttransplant lymphoproliferative disorder in solid-organ transplant recipients. *Clin Infect Dis*, Vol., 33(Suppl 1):S38.

Ramos, E.; Drachenberg, CB.; Papadimitriou, JC.; Hamze, O.; Fink, JC.; Klassen, DK., et al. (2002). Clinical course of polyoma virus nephropathy in 67 renal transplant patients. *J Am Soc Nephrol*, Vol., 13; pp. 2145-2151.

Ramos, E.; Drachenberg, CB.; Portocarrero, M.; Wali, R.; Klassen, DK.; Fink, JC., et al. (2003). BK virus nephropathy diagnosis and treatment: experience at the University of

Maryland Renal Transplant Program. In Cecka JM, Terasaki PI (eds): *Clinical Transplants 2002*. Los Angeles, UCLA Immunogenetics Center, pp 143-153.

Randhawa, P. & Brennan, DC. (2006). BK virus infection in transplant recipients: An overview and update. *Am J Transplant*, Vol., 6; pp. 2000–2005.

Reinke, P.; Fietze, E.; Ode-Hakim, S.; Prösch, S.; Lippert, J.; Ewert, R., et al. (1994). Late-acute renal allograft rejection and symptomless cytomegalovirus infection. *Lancet*, Vol., 344; pp. 1737-1738.

Renoult, E.; Georges, E.; Biava, MF.; Hulin, C.; Frimat, L.; Hestin, D. & Kessler, M. (1997). Toxoplasmosis in kidney transplant recipients: report of six cases and review. *Clin Infect Dis*, Vol., 24; pp. 625-634.

Rodriguez, M. & Fishman, JA. (2004). Prevention of infection due to Pneumocystis spp. in human immunodeficiency virus-negative immunocompromised patients. *Clin Microbiol Rev*, Vol., 17; pp. 770-782.

Roland, ME.; Barin, B.; Carlson, L.; Frassetto, LA.; Terrault, NA.; Hirose, R., et al. (2008). HIV-infected liver and kidney transplant recipients: 1- and 3-year outcomes. *Am J Transplant*, Vol., 8; pp. 355–365.

Rostaing, L.; Izopet, J.; Baron, E.; Duffaut, M.; Puel, J. & Durand, D. (1995). Treatment of chronic hepatitis C with recombinant interferon alpha in kidney transplant recipients. *Transplantation*, Vol., 59; pp. 1426-1431.

Rostaing, L.; Henry, S.; Cisterne, JM.; Duffaut, M.; Icart, J. & Durand, D. (1997). Efficacy and safety of lamivudine on replication of recurrent hepatitis B after cadaveric renal transplantation. *Transplantation*, Vol., 64; pp. 1624-1627.

Rowe, DT.; Webber, S.; Schauer, EM.; Reyes, J. & Green, M. (2001). Epstein-Barr virus load monitoring: Its role in the prevention and management of posttransplant lymphoproliferative disease. *Transpl Infect Dis*, Vol., 3; pp. 79–87.

Roy, V. & Weisdorf, D. (1998). Typical and atypical mycobacterium. In Bowden RA, Ljungman P, Paya CV (eds): *Transplant Infections*. Lippincott Raven, Philadelphia.

Rubin, RH. & Tolkoff-Rubin, NE. (1983). Viral infection in the renal transplant patient. *Proc Eur Dial Transplant Assoc*, Vol., 19; pp. 513–526.

Russo, MW.; Ghalib, R.; Sigal, S. & Joshi, V. (2006). Randomized trial of pegylated interferon alpha-2b monotherapy in aemodialysis patients with chronic hepatitis C. *Nephrol Dial Transplant*, Vol., 21; pp. 437-443.

Said, A.; Safdar, N.; Wells, J. & Lucey, MR. (2008). Liver disease in renal transplant recipients. In: Sir Peter J.Morris, Stuart J. Knechtle. (eds). *KIDNEY TRANSPLANTATION: PRINCIPLES AND PRACTICE*, 6th ed. Elsevier, pp. 508-533. ISBN: 978-1-4160-3343-1. Philadelphia.

Schmaldienst, S.; Dittrich, E. & Horl, WH. (2002). Urinary tract infections after renal transplantation. *Curr Opin Urol*, Vol., 12; pp. 125-130.

Sezer, S.; Ozdemir, FN.; Akcay, A.; Arat, Z.; Boyacioglu, S. & Haberal, M. (2004). Renal transplantation offers a better survival in HCV-infected ESRD patients. *Clin Transplant*, Vol., 18; pp. 619-623.

Shokeir, AA. (2001). Renal transplantation: the impact of schistosomiasis. *BJU Int*, Vol., 88; pp. 915-920.

Sia, IG. & Patel, R. (2000). New strategies for prevention and therapy of cytomegalovirus infection and disease in solid-organ transplant recipients. *Clin Microbiol Rev*, Vol., 13; pp. 83-121.

Singh, N. (2000). Antifungal prophylaxis for solid organ transplant recipients: Seeking clarity amidst controversy. *Clin Infect Dis*, Vol., 31; pp. 545-553.

Snyder. JJ.; Israni, AK.; Peng, Y.;Zhang, L.;Simon, TA. & Kasiske BL. (2009). Rates of first infection following kidney transplantation in yhe United States. *Kidney Int*, Vol., 75; pp 317-326.

Slovut, DP.; Benedetti, E. & Matas, AJ. (1996). Babesiosis and hemophagocytic syndrome in an asplenic renal transplant recipient. *Transplantation*, Vol., 62; pp. 537-539.

Sobh, MA.; el-Agroudy, AE.; Moustafa, FE.; Shokeir, AA.; el-Shazly, A. & Ghoneim, MA. (1992). Impact of schistosomiasis on patient and graft outcome after kidney transplantation. *Nephrol Dial Transplant*, Vol., 7; pp. 858-864.

Sterling, RP.; Bradley, BB.; Khalil, KG.; Kerman, RH. & Conklin, RH. (1984). Comparison of biopsy-proven Pneumocystis carinii pneumonia in acquired immune deficiency syndrome patients and renal allograft recipients. *Ann Thorac Surg*, Vol., 38; pp. 494–499.

Stock, PG.; Barin, B.; Murphy, B.; Hanto, D.; Diego, JM.; Light, J., et al. (2010). Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med,* Vol., 363; pp. 2004-2014.

Straathof, KC.; Savoldo, B.; Heslop, H. & Rooney, CM. (2002). Immunotherapy for posttransplant lymphoproliferative disease. Br J *Hematol*, Vol., 118; pp. 728-740.

Strippoli, GF.; Hodson, EM.; Jones, C. & Craig, JC. (2006). Preemptive treatment for cytomegalovirus viremia to prevent cytomegalovirus disease in solid organ transplant recipients. *Transplantation*, Vol., 81; pp. 139–145.

Sukthana, Y.; Chintana, T.; Damrongkitchaiporn, S. & Lekkla, A. (2001). Serological study of Toxoplasma gondii in kidney recipients. *J Med Assoc Thai*, Vol., 84; pp. 1137-1141.

Sypsa, V.; Touloumi, G.; Tassopoulos, NC.; Ketikoglou, I.; Vafiadis, I.; Hatzis, G., et al. (2004). Reconstructing and predicting the hepatitis C virus epidemic in Greece: increasing trends of cirrhosis and hepatocellular carcinoma despite the decline in incidence of HCV infection. *J Viral Hepat*, Vol., 11; pp. 366-374.

Tan, AC.; Brouwer, JT.; Glue, P.; van Leusen, R.; Kauffmann, RH.; Schalm, SW., et al. (2001). Safety of interferon and ribavirin therapy in haemodialysis patients with chronic hepatitis C: results of a pilot study. *Nephrol Dial Transplant*, Vol., 16; pp. 193-195.

Triverio, PA.; Bridevaux, PO.; Roux-Lombard, P.; Niksic, L.; Rochat, T.; Martin, PY., et al. (2009). Interferon-gamma release assays versus tuberculin skin testing for detection of latent tuberculosis in chronic haemodialysis patients. *Nephrol Dial Transplant*, Vol., 24; pp. 1952–1956.

Vachharajani, TJ.; Oza, UG.; Phadke, AG. & Kirpalani, AL. (2002). Tuberculosis in renal transplant recipients: Rifampicin sparing treatment protocol. *Int Urol Nephrol*, Vol., 34; pp. 551–553.

van Bommel, F.; Zollner, B.; Sarrazin, C.; Spengler, U.; Hüppe, D.; Möller, B., et al. (2006). Tenofovir for patients with lamivudine-resistant hepatitis B virus (HBV) infection and high HBV DNA level during adefovir therapy. *Hepatology*, Vol., 44; pp. 318-325.

van Duijnhoven, EM.; Christiaans, MH.; Boots, JM.; Nieman, FH.; Wolffenbuttel, BH. & van Hooff, JP. (2002). Glucose metabolism in the first 3 years after renal transplantation in patients receiving tacrolimus versus cyclosporine-based immunosuppression. *J Am Soc Nephrol*, Vol., 13; pp. 213-220.

Vasquez, E.; Pollak, R. & Benedetti, E. (2001). Clotrimazole increases tacrolimus blood levels: A drug interaction in kidney transplant patients. *Clin Transplant*, Vol., 15; pp. 95–99.

Vats, A.; Shapiro, R.; Singh Randhawa, P.; Scantlebury, V.; Tuzuner, A.; Saxena, M., et al. (2003). Quantitative viral load monitoring and cidofovir therapy for the management of BK virus-associated nephropathy in children and adults. *Transplantation*, Vol., 75; pp. 105-112.

Weinberg, A.; Hodges, TN.; Li, S.; Cai, G. & Zamora, MR. (2000). Comparison of PCR, antigenemia assay, and rapid blood culture for detection and prevention of cytomegalovirus disease after lung transplantation. *J Clin Microbiol*, Vol., 38; pp. 768–772.

Wertheim, P.; Slaterus, KW.; Geelen, JL.; van der Noordaa, J. & Wilmink, JM. (1985). Cytomegalo and herpes simplex virus infections in renal transplant recipients. *Scand J Urol Nephrol Suppl*, Vol., 92; pp. 5–8.

Williams, JW.; Javaid, B.; Kadambi, PV.; Gillen, D.; Harland, R.; Thistlewaite, JR., et al. (2005). Leflunomide for polyomavirus type BK nephropathy. *N Engl J Med*, Vol., 352; pp. 1157–1158.

Winston, DJ.; Young, JA.; Pullarkat, V.; Papanicolaou, GA.; Vij, R.; Vance, E., et al. (2008). Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. *Blood*, Vol., 1; pp. 5403-5410.

Wirth, S. (2006). Antiviral treatment of hepatitis B following solid organ transplantation in children. *Pediatr Transplant*, Vol., 10; pp. 271–275.

[1] Cytomegalovirus. (2004). *Am J Transplant*, Vol., 4(Suppl 10); pp. 51–58.

[2] Epstein-Barr virus and lymphoproliferative disorders after transplantation. (2004). *Am J Transplant*, Vol., 4; pp. 59–65.

[3] Guidelines for the prevention and management of infectious complications of solid organ transplantation: HHV-6, HHV-7, HHV-8, HSV-1 and -2, VZV. (2004). *Am J Transplant*, Vol., 4; pp. 66–71.

[4] Solid organ transplantation in the HIV-infected patient. (2004). *Am J Transplant*, Vol., 4; pp. 83–88.

[5] Pneumocystis jiroveci (formerly Pneumocystis carinii). (2004). *Am J Transplant*, Vol., 4 (Suppl 10); pp. 135–141.

[6] European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient.(2002). IV.7.2. Late infections. Tuberculosis. *Nephrol Dial Transplant*, Vol., 17(Suppl 4); pp. 39–43.

[7]. MMWR: Treatment of tuberculosis.(2003). Centers for Disease Control and Prevention. In (vol 52, RR11), Atlanta, GA, USA, American Thoracic Society, CDC, and Infectious Diseases Society of America, pp 1–77

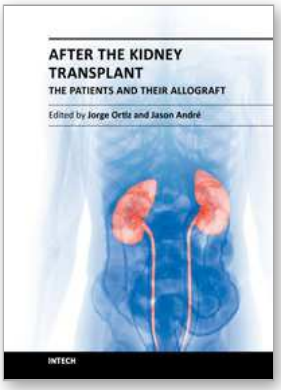
[8] Mycobacterium tuberculosis. (2004). *Am J Transplant*, Vol., 4 (Suppl 10); pp. 37-41.

[9] Screening for tuberculosis and tuberculosis infection in high-risk populations. (1995). Recommendations of the Advisory Council for the Elimination of Tuberculosis.*MMWRRecomm Rep*, Vol., 44; pp. 19–34.

[10] Fungal infections. (2004).*Am J Transplant*, Vol., 4(Suppl 10); pp. 110–134.

[11] VFEND" Package Insert, May 2002 Pfizer Inc, NY, NY 10017.

[12] Varicella-zoster infections. In: Pickering L, Baker C, Long S, McMillan J (eds). Red book: 2006 report of the committee on infectious disease of the American Academy of Pediatrics, 27th edn. American Academy of Pediatrics: Elk Grove Village, IL, 2006, pp 711–725.



After the Kidney Transplant - The Patients and Their Allograft

Edited by Prof. Jorge Ortiz

ISBN 978-953-307-807-6
Hard cover, 386 pages
Publisher InTech
Published online 17, August, 2011
Published in print edition August, 2011

There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipientâ€™s tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Amr El-Husseini and Rashad Hassan (2011). Infectious Complications in Kidney Transplantation, After the Kidney Transplant - The Patients and Their Allograft, Prof. Jorge Ortiz (Ed.), ISBN: 978-953-307-807-6, InTech, Available from: http://www.intechopen.com/books/after-the-kidney-transplant-the-patients-and-their-allograft/infectious-complications-in-kidney-transplantation

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821