



Common viral infections in kidney transplant recipients

Jakapat Vanichanan^{1,*}, Suwasin Udomkarnjananun^{2,3,*}, Yingyos Avihingsanon^{2,3,4}, Kamonwan Jutivorakool¹

¹Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

²Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

³Renal Immunology and Therapeutic Apheresis Research Unit, Chulalongkorn University, Bangkok, Thailand

⁴Excellence Center of Immunology and Immune-mediated Diseases, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

Infectious complications have been considered as a major cause of morbidity and mortality after kidney transplantation, especially in the Asian population. Therefore, prevention, early detection, and prompt treatment of such infections are crucial in kidney transplant recipients. Among all infectious complications, viruses are considered to be the most common agents because of their abundance, infectivity, and latency ability. Herpes simplex virus, varicella zoster virus, Epstein–Barr virus, cytomegalovirus, hepatitis B virus, BK polyomavirus, and adenovirus are well-known etiologic agents of viral infections in kidney transplant patients worldwide because of their wide range of distribution. As DNA viruses, they are able to reactivate after affected patients receive immunosuppressive agents. These DNA viruses can cause systemic diseases or allograft dysfunction, especially in the first six months after transplantation. Pretransplant evaluation and immunization as well as appropriate prophylaxis and preemptive approaches after transplant have been established in the guidelines and are used effectively to reduce the incidence of these viral infections. This review will describe the etiology, diagnosis, prevention, and treatment of viral infections that commonly affect kidney transplant recipients.

Keywords: Asia, Hepatitis, Immunosuppression, Kidney transplantation, Virus diseases

Introduction

Kidney transplantation is the best treatment option for

patients with end-stage kidney diseases. Quality of life and longevity following transplantation are nearly equal to those of healthy individuals. Although kidney transplantation is better than chronic dialysis, immunosuppression remains a major concern. Moreover, there is an increased risk of infection in certain groups such as the elderly or undernourished people with chronic kidney diseases. This risk of infection increases further in patients in developing or tropical countries. In Thailand, the most common causes of kidney recipient death are sepsis and pulmonary infection [1]. In Asian countries, there is an increased use of potent immunosuppressive drugs as well as transplant in high-risk patients, compared to the earlier era of transplantation. For example, blood-group-incompatible kidney transplants require an aggressive preconditioning protocol; this approach nota-

Received June 22, 2018; **Revised** September 22, 2018;

Accepted October 7, 2018

Correspondence: Yingyos Avihingsanon

Division of Nephrology, Department of Medicine, Excellence Center of Immunology and Immune-mediated Diseases, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand. E-mail: yingyos.a@chula.ac.th

ORCID: <https://orcid.org/0000-0002-5718-3843>

*Jakapat Vanichanan and Suwasin Udomkarnjananun contributed equally to this study as co-first authors.

Copyright © 2018 by The Korean Society of Nephrology

© This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

bly may result in cytomegalovirus (CMV) or BK polyomavirus (BKV) infection [2].

CMV and BKV are the most common causes of viral infection after kidney transplantation. However, clinical presentations vary; therefore, well-trained transplant physicians need to be aware of this so that they can take care of the patients accordingly. Patients afflicted with CMV disease commonly present with fever, leucopenia, transaminitis, or enterocolitis. CMV disease is clearly associated with high morbidity and mortality in transplant recipients. Preemptive treatment for CMV infection is recommended in those with CMV viremia, whereas preventive treatment is preferable in donor CMV immunoglobulin (Ig) G-positive and recipient IgG-negative (D+/R-) cases [3,4].

There has been an increased rate of viral infection observed to be ongoing in transplant recipients. These infections are commonly acquired during dialysis or blood transfusion, especially viral hepatitis and human immunodeficiency virus (HIV). Thailand is an endemic area for the hepatitis A virus (HAV) and hepatitis B virus (HBV) [5,6]. As a result, universal screening for these viruses in both potential donors and recipients must be completed prior to transplantation. Donors with HBV or hepatitis C virus (HCV) must be handled with caution. Recipients immunized against HBV are allowed to receive kidneys from HBV-infected donors; however, HB antibody level must be carefully monitored [7]. Direct-acting antiviral (DAA) drugs have been recently developed. Although antiviral drugs against HBV remain an unfulfilled need, anti-HCV drugs are very effective.

HIV is endemic in Thailand, and there are a significant number of HIV-infected individuals with end-stage kidney disease. Due to their status, these people typically live with long-term dialysis and no opportunity for kidney transplantation. Although kidney transplantations in HIV-infected recipients have been widely performed in Western countries, immunosuppressive drugs must be cautiously prescribed [8]. Pretransplant evaluation must be carefully done, and posttransplant care for HIV-infected patients requires different approaches. There is a strong drug–drug interaction between highly active antiretroviral therapy (HAART) and calcineurin inhibitors (CNIs); therefore, these drugs should be carefully used [9].

Posttransplant malignancy has been clearly associated with many viral infections. Disturbing the immune sys-

tem could lead to either allograft rejection or malignancy. Both types of complications are clearly associated with short graft and patient survival. Certain viral infections are associated with rejection of the graft or cause malignancy. Transplant physicians must keep the patient's immune system in balance: too much immunosuppression could increase the risk of infection and malignancy, whereas too little immunosuppression could lead to rejection of the graft. Thus, it is important to monitor the patient's health after transplantation to ensure that these complications do not occur.

General concept of viral infection in transplant recipients

Viruses are small infectious agents that obligatory require living host cells for replication. The viruses penetrate viable cells via attachment of viral proteins to specific receptors on the cell surface [10]. After the viruses have entered the host cells, they undergo viral replication. For RNA viruses, replication of the virus is performed in the cytoplasm of the host cell; for DNA viruses and retroviruses, replication of the virus occurs in the nucleus of the host cell. Releasing viral particles from the cells results in lysis of the cells; therefore, this process is termed the lytic phase [11]. Once this phase occurs, viruses can spread to adjacent or distant uninfected cells via the bloodstream or neuronal route, causing viral illnesses [12]. In immunocompetent individuals, most viral infections are self-limiting because the intact innate (interferon [IFN]- α and β) and adaptive immunities (CD_8^+ cytotoxic T-lymphocyte, CD_4^+ helper T-cell subset) are capable of eliminating the viruses [13,14].

Some types of viruses can establish persistent infections in immunocompetent hosts, which can be divided into chronic and latent infections. Continuous prolonged viral replication and shredding are observed in chronic viral infections (e.g., HBV and HCV), while maintenance of the viral genome without replication is found in latent viral infections (e.g., herpesviruses and polyomaviruses) [15]. Latency is achieved when the genomes of the viruses remain in the nucleus or cytoplasm of the infected cells by subversion of the apoptotic pathways and cannot be cleared by the host immune system [16,17]. On the other hand, constant host immune surveillance especially by CD_8^+ T-cells and the persistent production of IFN- γ

and tumor necrosis factor- α are able to block reactivation of latent infections [18]. Receiving immunosuppressive agents following solid organ transplantation (SOT) can disrupt the immune function and cause viral reactivation, particularly in the first six months after transplant [19].

Several viruses, particularly CMV, can have an indirect effect on the host immune system. Multiple proteins encoded by CMV contain immunomodulating activity, which can either suppress the immune system or increase the inflammatory process. Therefore, reactivation of CMV becomes an important risk factor in allograft rejection, as well as acquisition of other opportunistic infections [20]. CMV prophylaxis has been proven to be beneficial in preventing CMV disease but also in graft survival and overall outcomes [21]. In addition to the direct and indirect effects of viral infection, it has been shown that persistent viral infections can significantly increase the risk of malignancy among transplant recipients. Chronic inflammation and an inability to eradicate the pathogens contribute to viral oncogenesis. The responses from the human immune system are supposed to be beneficial for the host, but these responses can also lead to DNA damage, aberrant cell proliferation, and neoangiogenesis. Most oncogenic viruses have the ability to integrate themselves into a host's genome and express their viral oncogenic protein [22]. Some viruses can escape the host immune system by inducing the regulatory T-cells, which down-regulate the host immune response [23]. In the immunocompetent host, the immune system can control viral infection and prevent the abnormal cell proliferation or neoangiogenesis processes. Unlike in the immunocompetent patient, however, patients on immunosuppressive medications (i.e., transplant recipients) have dysfunctional immune surveillance systems. Immunosuppressed patients cannot eradicate these oncogenic viruses and premalignant cells.

Common viral infections in transplant recipients

Cytomegalovirus

CMV infection is the most important viral infection that can occur following SOT. CMV infection can directly and indirectly affect the kidney allograft. Direct effects include CMV syndrome (e.g., fever, fatigue, myalgia,

and leucopenia) or tissue-invasive CMV diseases (e.g., pneumonitis, gastritis, duodenitis, or colitis). Regarding indirect effects, CMV infection can cause acute or chronic graft injuries, allograft rejection, poor graft survival, and acquisition of other opportunistic infections especially invasive fungal infections [24]. The risk factors for CMV infection are low lymphocyte count [25,26], low complement or natural killer cell count [27–29], IgG hypogammaglobulinemia [27,30,31], donor–recipient CMV serology mismatch, and the use of lymphocyte-depleting agents [32,33]. The incidence of CMV infection depends on the donor and recipient serology profiles. The incidence of CMV infection can reach up to 60% among patients with CMV IgG D+/R– [34]. The incidence of CMV infection varies from 5% to 30% for patients with CMV IgG R+ [35], but the incidence can be as high as 50% in patients who received T-cell depletion therapy [33,36,37].

Preventive strategies for CMV infection after SOTs are either preemptive or prophylaxis treatment. Patients with high risk (i.e., those who have D+/R– CMV IgG or who have received T-cell depletion for induction) should receive universal prophylaxis treatment, whereas patients with low to intermediate risk can undergo preemptive treatment. Kidney transplant recipients with CMV in a D+/R– situation should receive prophylaxis for 200 days; the IMPACT study showed that CMV disease occurred in 21.3% of the patients who received prophylaxis for 200 days and in 36.8% of the patients who received prophylaxis for 100 days [38]. The preemptive strategies require monitoring of CMV viral load at least once a week for three months after transplantation and, when the CMV viral load reaches the threshold, preemptive treatment should be started. However, the guidelines for management of CMV in SOT suggest that the dynamics of CMV viral load over time are more predicative of the disease than the absolute value [32]. These guidelines recommended using the World Health Organization international standard for surveillance and to report CMV viral load as IU/mL. The change of CMV viral load value should be significant if at least 0.5 log₁₀ IU/mL or at least three-fold changes were met. Table 1 compares the advantages and disadvantages between the two treatment approaches. Currently, both preventive measures are acceptable in R+ kidney recipients. However, several studies have demonstrated benefits of oral ganciclovir or valganciclovir prophylaxis over preemptive therapy

Table 1. Comparison between preemptive strategy and prophylaxis for CMV infection

	Preemptive strategy	Prophylactic strategy
Principle approach	Monitor for CMV by PCR Treat when viral replication is detected	Early treatment with antiviral drug Continue for 100–200 days
Advantages	Avoid drug toxicity Fewer people with late CMV disease Enhance host-defense against CMV	Initial suppression of CMV Avoid indirect effects of CMV infection including triggering rejection and acquisition of opportunist infection
Risks	Risk of CMV disease due to rapid CMV replication Indirect CMV effects	Toxicity from anti-viral drug (mainly leucopenia) Late CMV disease Develop ganciclovir-resistant mutants
Cost	Cost for PCR monitoring	Cost for antiviral drug

CMV, cytomegalovirus; PCR, polymerase chain reaction.

in R+ patients including lower rates of CMV disease and impaired graft function [39–41]. Valacyclovir can be selected as an alternative option for CMV prophylaxis in kidney transplant recipients, since it showed comparable efficacy in CMV prevention to the preemptive approach in one study [42]. For preemptive CMV treatment, therapy should stop after the result is less than the lower limit of quantification, and the test should be repeated at one week thereafter [32]. Antiviral prophylaxis and preemptive approach are also preferred in transplant recipients who receive lymphocyte depleting agent for induction or treatment of rejection [24].

The drugs of choice for CMV syndrome and tissue-invasive CMV disease are valganciclovir or intravenous ganciclovir; the two drugs have the same efficacy and similar long-term outcomes [43]. However, intravenous ganciclovir is preferred as the initial treatment for patients with severe or life-threatening CMV disease, such as those with high viral load or those with questionable gastrointestinal absorption. The treatment should be continued for a minimum of two weeks or until the clinical symptoms have resolved and the virus has been eradicated; eradication of CMV is defined as a CMV viral load below the lower limit of quantification on one or two consecutive weekly samples. A secondary prophylaxis is not routinely recommended [32]. Foscarnet and cidofovir are considered as second and third line treatment which should be used only in documented UL97-mutant CMV strain due to their nephrotoxic property [24].

Epstein–Barr virus and posttransplant lymphoproliferative disorder

Epstein–Barr virus (EBV) is a gamma herpesvirus with

a seroprevalence of more than 90% in adults. The clinical manifestation of EBV infection in SOT recipients varies from asymptomatic to uncomplicated infectious mononucleosis, hepatitis, pneumonitis, lung mass, lymphadenopathy, hepatosplenomegaly, central nervous systemic disease, gastrointestinal disease, and posttransplant lymphoproliferative disorder (PTLD). The incidence of PTLD varies by type of organ transplantation. Kidney transplantation has the lowest incidence, followed by pancreatic transplantation, liver transplantation, heart transplantation, lung transplantation, and small bowel transplantation, in that order [44–46]. Risk factors for developing PTLD include type of transplanted organ; EBV mismatch; and type of induction immunosuppressive therapy used such as antithymocyte globulin, muromonab-CD3, and belatacept [44,47].

The incidence of PTLD has a biphasic onset, which means that most cases of EBV-positive transplant recipients develop PTLD within the first year after transplantation, whereas EBV-negative transplant recipients develop PTLD five to 15 years after transplantation [45,48,49]. Intra-graft PTLD occurred mainly in the first two years after transplantation. Cerebral PTLD occurred mainly between the second and seventh year after transplantation. The incidence of gastrointestinal tract PTLD was relatively low in the first five years and then increased dramatically at the sixth and seventh year posttransplantation, spreading to other locations of the body [50].

The diagnosis and categorization of PTLD depend on histopathology according to the World Health Organization 2017 classification. There are still no recommendations as to when EBV should be monitored for and what the cutoff values should be. The high-risk categories for EBV infection and PTLD were not clearly defined. PTLD

can be treated by reducing the use of immunosuppressive drugs, surgical removal, radiotherapy, adoptive immunotherapy, or chemotherapy [51].

BK polyomavirus

BKV is a nonenveloped, double-stranded DNA virus and a member of the *Polyomaviridae* family. BKV infection after transplantation can cause hemorrhagic cystitis, tubulointerstitial nephritis, ureteric stricture, BKV-associated nephropathy (BKVAN), and premature graft failure. The seroprevalence in adults was reported to be 40% to 100%. After BKV infection via the oral or respiratory tract, the BKV remains latent in renal tubular epithelial cells [52].

The risk factors for BKVAN include human leukocyte antigen (HLA)-mismatch, deceased donor, mismatched BKV-specific antibody of donor/recipient (D+/R-), older age of the recipient, retention of the ureteric stent, reception of antirejection treatment, tacrolimus–mycophenolic use, or retransplantation after graft loss due to BKVAN [52,53].

The incidence of BK viremia was reported to be 23% to 73%, that of BK viremia was 8% to 15%, and that of BKVAN was 1% to 7%; the BKVAN rate is highest at three months to six months posttransplantation [53]. In Thailand, the incidence of BK viremia was 20%, that of BK viremia was 3.4% to 4%, and that of BKVAN was 6.4% to 8.4%. The significant risk factors for BKV infection were a mycophenolate dose greater than 1 g/day, receiving a kidney from a deceased donor, and/or CMV infection [54,55]. The median time to diagnosis of BKV infection was 6.8 to 10.9 months after transplantation [54,55], which matches findings from a previous report [52].

The recommendation for screening for BKV is by way of quantitative DNA virus testing of the urine every one month to three months during the first two years after transplantation and then annually until the fifth year posttransplantation. However, BK viremia is sensitive for detecting active BKV infection but not specific for nephropathy and has a positive predictive value of 29% to 67%. Detection of BKV DNA in plasma may represent a better indicator for nephropathy, especially when plasma BKV load is greater than 4 log₁₀ copies/mL or when there is impaired renal allograft function, which has a positive predictive value greater than 90%. The gold standard for

diagnosing BKVAN is kidney histology, including tubulointerstitial nephritis with cytopathic changes and positive immunohistochemistry using antibodies generally targeting cross-reacting SV40 large T-antigen or BKV antigens, or *in-situ* hybridization for BKV nucleic acids [56].

The mainstay of treatment for BKVAN is to reduce immunosuppressive drugs. This can be done by withdrawing mycophenolate mofetil or tacrolimus, replacing tacrolimus with cyclosporine, or withdrawing CNIs. The efficacy of antiviral therapy as an adjuvant therapy to immunosuppression reduction is still controversial. Cidofovir is a nucleotide analogue of cytosine with an antiviral effect. It has been effectively used to treat BKVAN in kidney transplant recipients with a dose of 0.25 to 1.0 mg/kg at one-week to three-week intervals [57,58]. However, there are also studies that have failed to show a benefit of cidofovir in the treatment of BKVAN [52,59]. Moreover, the nephrotoxicity of cidofovir is an important concern that can worsen allograft function. Large randomized clinical trials are required to demonstrate the true efficacy of cidofovir.

Leflunomide is another alternative treatment for BKV nephropathy. It is an anti-inflammatory drug that inhibits pyrimidine synthesis. In one study, leflunomide was administered at a loading dose of 100 mg/day for three days to five days followed by a maintenance dose of 20 mg to 60 mg daily, keeping the trough levels at 50 to 100 µg/mL [52]. An efficacy study of leflunomide in addition to immunosuppression reduction for the treatment of BK viremia and BKVAN showed that 42% to 71% of the patients cleared BKV viremia [60,61]; notably, only 54% of the patients used leflunomide at the therapeutic dose, and 60% of them required leflunomide at least 60 mg/day [60]. Leflunomide in combination with ciprofloxacin has been used in some centers and has shown possible benefits for virus reduction [62]. However, all of the publications of BKVAN treatment with leflunomide have been case series [63]. Without the results of controlled clinical studies to consider, utilization of leflunomide for treatment of BKVAN requires further evaluation.

Ciprofloxacin has antiviral activity against BKV by inhibiting DNA topoisomerase activity. Case reports and case series of successful ciprofloxacin uses for treatment of BKVAN in kidney transplantation have been reported [64,65]. However, levofloxacin, another quinolone, failed to demonstrate efficacy in the treatment of BK viremia

in a multicenter, double-blinded, randomized placebo-controlled trial [66]. To date, the use of quinolones for treatment of BKVAN cannot be generally recommended due to the lack of strong evidence [67]. In Thailand, we observed the successful use of leflunomide with ciprofloxacin, along with decreasing immunosuppressive drug use in two BKVAN kidney transplant recipients. The kidney function of both patients improved, and their serum creatinine level decreased to baseline [68].

Intravenous Ig (IVIG) preparations were administered in doses ranging from 0.2 to 2.0 g/kg in conjunction with reduced immunosuppressive drugs [52]. A study of IVIG treatment was conducted in patients who did not respond to eight weeks of the adjusted immunosuppressive drugs and leflunomide and showed that 90% of the patients cleared viremia, and 96.7% of the patients had graft survival beyond 12 months [69]. A more recent retrospective cohort study of IVIG as an adjuvant therapy to the combination of immunosuppression reduction, leflunomide, ciprofloxacin, and cidofovir resulted in more effectively cleared viremia and BK immunohistochemistry from repeated allograft biopsy in comparison with the IVIG-nonreceiving group [70]. The combination of these treatments is interesting and might enhance the opportunity to improve allograft survival in patients with BKVAN.

Viral hepatitis

Hepatitis A virus

HAV is a nonenveloped RNA virus from the *Picornaviridae* family that is transmitted via the fecal–oral route. This virus is considered to be the most common cause of viral hepatitis and the second most common infectious disease among travelers [71]. The incidence of HAV infection was estimated to be around 1.5 million cases per year, with the condition mostly occurring in developing countries including South Asia and Southeast Asia [72]. Clinical presentations are typical acute hepatitis that can range from mild jaundice to fulminant hepatitis; however, chronic hepatitis is rare [73,74]. Data on seroprevalence of HAV are scarce. In an endemic area, 73% of hemodialysis patients have positive HAV antibodies, and 90% of kidney transplant recipients with HCV coinfection have positive HAV antibodies [75,76]. According to the

current recommendations, kidney transplant candidates and recipients who have chronic liver disease or risk factors for HAV should be tested for HAV IgG, and a vaccine should be offered to those with a negative result [77]. The HAV vaccine should be given in two doses at six months apart; seroconversion was found in only 24% to 27% of kidney transplant recipients [78,79]. Therefore, the HAV vaccine should be given prior to kidney transplantation. Moreover, the HAV can be transmitted through organ transplantation and reactivate after liver transplantation [80,81].

Hepatitis B virus

HBV is a DNA virus from the family *Hepadnaviridae* that primarily targets human hepatocytes, resulting in hepatitis. HBV can be transmitted sexually, mother-to-child, as well as via blood transfusion and organ transplantation [77]. After infection, the virion DNA is harbored in the nucleus of the hepatocyte, which can cause chronic infection and long-term complications such as cirrhosis or hepatocellular carcinoma [82]. Markers to detect HBV infection vary according to geographical area. In the Asia-Pacific region, the prevalence of hepatitis B surface antigen (HBsAg) positivity was between 1.3% and 14.6% in hemodialysis patients [83]. Reactivation of HBV after transplantation is an important concern and is found in up to 94% and 5% in recipients with positive HBsAg and antibody to hepatitis B core antigen (anti-HBc), respectively [84,85]. Therefore, an appropriate pretransplant evaluation for HBV infection is crucial. The HBV vaccine should be offered to patients with negative results for all serological markers for HBV infection. All recipients with chronic HBV infection should be evaluated for treatment prior to transplantation, and those who do not meet the treatment criteria should receive either tenofovir or entecavir after transplantation [86,87]. In recipients with isolated anti-HBc, prophylaxis is still the preferred strategy after transplantation [88].

HBV serology testing in donors is also an important issue because it can assist the physician with making a decision whether to use an organ or not. Organs from donors with isolated anti-HBc are acceptable for transplant; however, after treatment, the seroconversion was reported up to 10% in kidney recipients with antibody to hepatitis B surface antigen (anti-HBs) titer < 100 IU/L

[77,89]. According to the current guidelines, antiviral prophylaxis is not required in recipients with anti-HBs titer above 10 IU/L; however, one-year lamivudine prophylaxis may be considered in recipients with negative anti-HBs [90]. Donors with positive HBsAg are considered to be contraindicated for organ utilization. The current data demonstrated that there is no evidence of donor-derived HBV infection; it has been shown that there is excellent graft survival in recipients with anti-HBs > 100 U/L who received an organ from a HBsAg-positive donor who did not receive any antiviral prophylaxis [7]. However, the consensus guidelines still recommend indefinite entecavir or tenofovir prophylaxis in all recipients regardless of immune status, and hepatitis B immune globulin (HBIG) should be considered in recipients with anti-HBs < 100 U/L [90].

Hepatitis C virus

HCV is an RNA virus from the *Flaviviridae* family. Similar to HBV, HCV can be transmitted via organ transplantation; blood exposure; sexual intercourse; and, more uncommonly, through the transplacenta. HCV can maintain its genome in the cytoplasm of hepatocytes and can cause chronic infection that can result in cirrhosis and hepatocellular carcinoma [91]. The seroprevalence of HCV ranges between 5% and 60% among hemodialysis patients, differing according to geographic location [92]. Data have clearly shown that HCV-positive recipients who undergo kidney transplantation have better survival rates than do patients on the waiting list. However, these populations still have a lower rate of graft survival compared with HCV-negative transplant recipients [93,94]. Initial screening for anti-HCV should be performed in all transplant candidates. If the patient has a positive anti-HCV result, then HCV viral load should be done. Candidates with documented chronic HCV infection should be handled on a case-by-case basis. The HCV genotype and hepatic fibrosis should be assessed to determine whether the patient should undergo the transplantation procedure. Patients with mild to moderate liver disease (F0–F2) do not require treatment before listing, whereas those with bridging fibrosis (F3) and compensated cirrhosis (F4) should be treated and achieve a sustained virological response (SVR) prior to listing [77,95].

In the past, the treatment options for HCV in transplant

recipients were limited because pegylated-interferon-based regimens increased the rate of acute allograft rejection. Currently, DAAs target the NS5B polymerase, NS5A protein, and NS3/4A protease; these drugs have been approved as the standard treatment for chronic HCV infection. DAA-based regimens yield a greater than 90% SVR at 12 weeks, especially in naïve patients [96]. Several reports using DAA-based regimens in kidney transplant recipients demonstrated similar SVR rates; furthermore, there were no significant adverse drug reactions or instances of graft rejection when these drugs were used in kidney transplant recipients [97,98]. However, there are significant drug–drug interactions between simeprevir and cyclosporine as well as the combination of paritaprevir/ritonavir/ombitasvir/dasabuvir and cyclosporine or tacrolimus. Therefore, the doses of immunosuppressive drugs should be adjusted, and their levels should be closely monitored [99]. The utilization of organs from HCV-positive donors is currently an interesting issue because there is a limited donor pool and high mortality rate among those patients on the waiting list. For nonhepatic transplantation, organs from HCV-positive donors should be considered for HCV-positive recipients, while transplantation to HCV-negative recipients remains contraindicated [77]. Nevertheless, there was an open-label pilot study conducted using organs from HCV type 1 viremic donors for HCV-negative recipients followed by DAA therapy after transplantation. After six months of follow-up, all patients achieved SVR with good graft function. This result may suggest efficacy and safety in utilizing HCV-positive organs for HCV-negative recipients, but more data are needed [100].

Hepatitis D virus

Hepatitis D virus (HDV) is a small RNA virus that requires the presence of HBsAg to complete the process to release virion [101]. Along with HBV, HDV can be transmitted via illicit drug use, blood transfusions, and sexual intercourse. HBV–HDV coinfection is common in specific areas such as the Pacific island. Testing for HDV infection is not recommended during routine screening, unless there is a high level of suspicion [77]. Data of HDV after transplantation were mostly sourced from cases of liver transplantation. None of the cases with HBV–HDV coinfection developed recurrent HDV viremia after clear-

ance of HBsAg posttransplantation. Despite the lack of effective medication against HDV, the adequate control of HBV seems to be an appropriate practice in managing HDV infection [102].

Hepatitis E virus

Hepatitis E virus (HEV) is an RNA virus from the family *Hepeviridae* that transmits via the fecal–oral route similarly to HAV. HEV is known to cause self-limiting hepatitis, but severe fulminant disease can occur in individuals with chronic hepatitis or pregnant women. The prevalence of HEV was found to be higher in developing countries. The seroprevalence of anti-HEV IgG was 2.6%, 3.9%, and 10.4% in liver transplant recipients from Japan, the Netherlands, and France, respectively, while positive anti-HEV IgG was found up to 14.5% and 26% among kidney transplant recipients in France and Thailand. Since there is a low prevalence of HEV, routine screening is not recommended in transplant candidates [103–105]. One study from France reported a 6.5% prevalence of acute HEV in organ transplant recipients, with more than half of the recipients progressing to chronic hepatitis; the diagnosis was done by polymerase chain reaction using serum and stool specimens [105]. Chronic HEV infection in both hepatic and nonhepatic transplant recipients can have long-term complications such as liver fibrosis and HEV-associated glomerulonephritis [106–108]. A reduction in immunosuppressive agent use was associated with viral clearance in more than 30% of the patients and should be considered as a main therapy in managing chronic HEV infection [109]. Pegylated IFN- α contains some antiviral activities against HEV but also carries the risk of allograft rejection [110]. A three-month course of ribavirin was used for the treatment of chronic HEV (genotype 3) and yielded 95% viral clearance with 78% SVR at six months in one retrospective, multicentered study [111]. While no antiviral agent is currently recommended in the standard guidelines, treatment with ribavirin seems to be promising; however, additional studies are needed to confirm the efficacy and safety of ribavirin in treating HEV.

Human immunodeficiency virus

HIV-positive patients with end-stage renal disease may

have limited access to kidney transplantation. However, kidney transplantation in HIV-infected patients results in better quality of life than continuous dialysis [112,113]. HIV patients with suppressed viral load and high CD4 cell count are good candidates for transplantation [114] because they do not have opportunistic infections or malignancy. A nationwide study conducted in the United States showed similar patient and graft survival rates in transplant recipients with or without HIV infection [115], despite a high rate of acute rejection [116,117]. It has been proposed that the acute rejection that occurs is due to cross-reactivity between HIV infection and the HLA molecules, which causes the memory T-cells to expand quickly after transplantation [118–120]. However, most evidence indicates that the interaction between a boosted protease inhibitor-based (boosted PI) regimen and immunosuppressive drugs is the cause of acute rejection [121]. Boosted PI is a strong cytochrome P450 3A4 (CYP3A4) inhibitor and thus increases the concentration of CNIs in the blood. Patients who received boosted PI will have to lower their CNI dosage to achieve the targeted recommended trough concentrations. This may decrease the area under the concentration time curve of CNIs and result in acute rejection of the organ [122]. The use of integrase inhibitor or non-nucleoside reverse-transcriptase inhibitors (NNRTIs) to replace boosted PI is an alternative choice [123]. It is worth mentioning that NNRTIs are CYP3A4 inducers and so can decrease the CNI level. However, unlike boosted PI, use of NNRTI along with CNIs did not show any inferior transplantation outcomes. For induction therapy, antithymocyte globulin is the only inductor that can decrease acute rejection rate in HIV-positive recipients [8,124]. Altogether, HIV infection is not a barrier to transplantation in end-stage renal disease patients. With HAART, the knowledge of drug interactions between immunosuppressive drugs and HAART, and monitoring for opportunistic infections, we can expect the transplantation outcomes to be as good in HIV-positive patients as in HIV-negative patients.

Viral infection and rejection in kidney transplantation

Rejection of kidney allograft is also frequently associated with viral infection. Early study in the beginning of the kidney transplantation era showed that 72% of CMV-

infected recipients developed rejection episodes, while only 17% of the recipients without the virus infection experienced rejection [125]. Viral infections can lead to acute or chronic rejection episodes. Mechanisms of CMV-induced allograft rejection have been moderately studied [126–128]. Many mechanisms were reported including (1) activation of HLA class I antigen-specific T-cells from cross-reactivity with CMV antigen; (2) direct damage to endothelial cells; and (3) release of proinflammatory cytokines (i.e., interleukin [IL]-1, IL-6, IL-8, and tumor necrosis factor- α). These complex interplays result in an increase in the expression of HLA class II molecules on the allograft and adhesion molecules on the leukocytes and endothelial cells.

Moreover, physicians usually decrease immunosuppressive drugs in an infection, resulting in a rejection episode [129,130]. During antirejection therapy, the net state of immunosuppression is increased again, which causes the latent virus to become reactivated, especially for CMV and polyomavirus. Furthermore, an antirejection strategy may remove viral-specific antibodies. Therefore, patients are more susceptible to primary or reactivation of viral infection. A balanced immune system and frequent monitoring for common viruses are important posttransplantation [131]. Using mammalian target of rapamycin inhibitor (mTORi) (with or without CNI minimization) as the main immunosuppressive regimen resulted in a lower incidence of CMV and BK polyoma infections com-

pared to the standard dose of CNI, which showed no differences in the rate of acute rejection [132].

Viral infection and malignancy in kidney transplantation

Current maintenance of immunosuppressive regimens in the posttransplantation period leads to better patient and allograft survival. Considering the late posttransplantation period, complications such as malignancy are gaining more interest. It is well-known that viral infection is one of the major causes of malignancy. Common human oncogenic viruses include EBV, human papillomavirus, human T-cell lymphotropic virus-1, Kaposi's sarcoma herpesvirus (also known as human herpesvirus-8), Merkel cell polyomavirus, HBV, and HCV [133,134]. Recently, the BKV has been reported to be associated with urothelial carcinoma in kidney transplantation patients [135,136]. The recommendations for malignancy screening following kidney transplantation are shown in Table 2 [135,137–139]. For treatment, there is increasing evidence that the use of mTORi as an immunosuppressive regimen can inhibit viral replication and cancer proliferation. There is strong evidence that mTORi therapy can inhibit Kaposi's sarcoma [140]. The next promising target for mTORi-based regimen is cutaneous squamous cell carcinoma [141].

Table 2. Recommended malignancy screening protocol after kidney transplantation

Cancer	Protocol
Breast cancer	<ul style="list-style-type: none"> Ages 40 to 54 years: annual mammography Age \geq 55 years: biannual mammography (discontinue when life expectancy is less than 10 years)
Cervical cancer	<ul style="list-style-type: none"> Ages 21 to 29 years: Pap and HPV tests every three years Ages 30 to 64 years: Pap and HPV tests every five years Age \geq 65 years: discontinue if negative Pap and HPV tests for two years or negative Pap tests for three years
Colorectal cancer	<ul style="list-style-type: none"> Age \geq 50 years without family history of colorectal cancer: computed tomography colonoscopy every five years, colonoscopy every 10 years, flexible sigmoidoscopy every three years, and annual fecal occult blood test or multitarget stool DNA test every three years If positive family history, screening should be initiated at an early age
Prostate cancer	<ul style="list-style-type: none"> Age \geq 50 years: PSA with or without digital rectal examination in men with an at least 10-year life expectancy
Lung cancer	<ul style="list-style-type: none"> Current or former smokers who have quit smoking within 15 years; ages 55 to 74 years with at least a 30 pack/year smoking history: annual low-dose computed tomography chest scan
Skin cancer	<ul style="list-style-type: none"> Total body examination by dermatologist every 6 to 12 months
Posttransplant lymphoproliferative disorders	<ul style="list-style-type: none"> EBV viral load during the first year posttransplantation in D+/R– recipients
Urological cancer	<ul style="list-style-type: none"> Ultrasonography every 2 to 5 years

EBV, Epstein–Barr virus; HPV, human papilloma virus; Pap, Papanicolaou; PSA, prostate-specific antigen.

Conclusion

Viral infections, particularly CMV and BKV, remain a major obstacle in long-term kidney graft survival. Like all transplant infectious diseases, increase in the incidence of viral infections can also increase the risk of rejection and malignancy after SOT.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

The authors would like to thank to Miss June Piraporn Ohata for language editing in this manuscript.

References

- [1] Ingsathit A, Avihingsanon Y, Rattanasiri S, et al. Different etiologies of graft loss and death in Asian kidney transplant recipients: a report from Thai Transplant Registry. *Transplant Proc* 42:4014-4016, 2010
- [2] Tanabe K. Interinstitutional variation in the measurement of anti-A/B antibodies: the Japanese ABO-Incompatible Transplantation Committee survey. *Transplantation* 84(12 Suppl):S13- S16, 2007
- [3] Fehr T, Cippà PE, Mueller NJ. Cytomegalovirus post kidney transplantation: prophylaxis versus pre-emptive therapy? *Transpl Int* 28:1351-1356, 2015
- [4] Kotton CN, Kumar D, Caliendo AM; Transplantation Society International CMV Consensus Group, et al. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation* 89:779-795, 2010
- [5] Sumethkul V, Ingsathit A, Jirasiritham S. Ten-year follow-up of kidney transplantation from hepatitis B surface antigen-positive donors. *Transplant Proc* 41:213-215, 2009
- [6] Lee J, Cho JH, Lee JS, et al. Pretransplant hepatitis B viral infection increases risk of death after kidney transplantation: a multicenter cohort study in Korea. *Medicine (Baltimore)* 95:e3671, 2016
- [7] Chanchaoentana W, Townamchai N, Pongpirul K, et al. The outcomes of kidney transplantation in hepatitis B surface antigen (HBsAg)-negative recipients receiving graft from HBsAg-positive donors: a retrospective, propensity score-matched study. *Am J Transplant* 14:2814-2820, 2014
- [8] Locke JE, James NT, Mannon RB, et al. Immunosuppression regimen and the risk of acute rejection in HIV-infected kidney transplant recipients. *Transplantation* 97:446-450, 2014
- [9] Boyarsky BJ, Durand CM, Palella FJ Jr, Segev DL. Challenges and clinical decision-making in HIV-to-HIV transplantation: insights from the HIV literature. *Am J Transplant* 15:2023-2030, 2015
- [10] Haywood AM. Virus receptors: binding, adhesion strengthening, and changes in viral structure. *J Virol* 68:1-5, 1994
- [11] Traylen CM, Patel HR, Fondaw W, et al. Virus reactivation: a panoramic view in human infections. *Future Virol* 6:451-463, 2011
- [12] Knipe DM, Howley PM, Griffin DE. *Fundamental Virology*, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001
- [13] Pang IK, Iwasaki A. Control of antiviral immunity by pattern recognition and the microbiome. *Immunol Rev* 245: 209-226, 2012
- [14] van de Berg PJ, van Leeuwen EM, ten Berge IJ, van Lier R. Cytotoxic human CD4(+) T cells. *Curr Opin Immunol* 20: 339-343, 2008
- [15] Chappell JD, Dermody TS. 134 - Biology of viruses and viral diseases. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 8th ed. Philadelphia: Elsevier Saunders, 1681-1693, 2015
- [16] Randall RE, Griffin DE. Within host RNA virus persistence: mechanisms and consequences. *Curr Opin Virol* 23:35-42, 2017
- [17] Kane M, Golovkina T. Common threads in persistent viral infections. *J Virol* 84:4116-4123, 2010
- [18] Khanna KM, Lepisto AJ, Hendricks RL. Immunity to latent viral infection: many skirmishes but few fatalities. *Trends Immunol* 25:230-234, 2004
- [19] Humar A. Reactivation of viruses in solid organ transplant patients receiving cytomegalovirus prophylaxis. *Transplantation* 82(2 Suppl):S9-S14, 2006
- [20] Freeman RB Jr. The 'indirect' effects of cytomegalovirus infection. *Am J Transplant* 9:2453-2458, 2009
- [21] Roman A, Manito N, Campistol JM, et al. The impact of the prevention strategies on the indirect effects of CMV infection in solid organ transplant recipients. *Transplant Rev (Orlando)* 28:84-91, 2014
- [22] Carrillo-Infante C, Abbadessa G, Bagella L, Giordano A. Viral infections as a cause of cancer (review). *Int J Oncol*

30:1521-1528, 2007

- [23] Fehérvári Z, Sakaguchi S. CD4+ Tregs and immune control. *J Clin Invest* 114:1209-1217, 2004
- [24] Razonable RR, Humar A; AST Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplantation. *Am J Transplant* 13 Suppl 4:93-106, 2013
- [25] Natori Y, Humar A, Husain S, et al. Recurrence of CMV Infection and the effect of prolonged antivirals in organ transplant recipients. *Transplantation* 101:1449-1454, 2017
- [26] Nierenberg NE, Poutsiaka DD, Chow JK, et al. Pretransplant lymphopenia is a novel prognostic factor in cytomegalovirus and noncytomegalovirus invasive infections after liver transplantation. *Liver Transpl* 20:1497-1507, 2014
- [27] Sarmiento E, Jaramillo M, Calahorra L, et al. Evaluation of humoral immunity profiles to identify heart recipients at risk for development of severe infections: a multicenter prospective study. *J Heart Lung Transplant* 36:529-539, 2017
- [28] Fernandez-Ruiz M, Silva JT, López-Medrano F, et al. Post-transplant monitoring of NK cell counts as a simple approach to predict the occurrence of opportunistic infection in liver transplant recipients. *Transpl Infect Dis* 18: 552-565, 2016
- [29] Sarmiento E, del Pozo N, Gallego A, et al. Decreased levels of serum complement C3 and natural killer cells add to the predictive value of total immunoglobulin G for severe infection in heart transplant recipients. *Transpl Infect Dis* 14:526-539, 2012
- [30] Sarmiento E, Navarro J, Fernandez-Yañez J, Palomo J, Muñoz P, Carbone J. Evaluation of an immunological score to assess the risk of severe infection in heart recipients. *Transpl Infect Dis* 16:802-812, 2014
- [31] Goldfarb NS, Avery RK, Goormastic M, et al. Hypogammaglobulinemia in lung transplant recipients. *Transplantation* 71:242-246, 2001
- [32] Kotton CN, Kumar D, Caliendo AM; The Transplantation Society International CMV Consensus Group, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* 102:900-931, 2018
- [33] Chiasakul T, Townamchai N, Jutivorakool K, et al. Risk factors of cytomegalovirus disease in kidney transplant recipients: a single-center study in Thailand. *Transplant Proc* 47:2460-2464, 2015
- [34] Hartmann A, Sagedal S, Hjelmesaeth J. The natural course of cytomegalovirus infection and disease in renal transplant recipients. *Transplantation* 82(2 Suppl):S15-S17, 2006
- [35] De Keyzer K, Van Laecke S, Peeters P, Vanholder R. Human cytomegalovirus and kidney transplantation: a clinician's update. *Am J Kidney Dis* 58:118-126, 2011
- [36] López-Oliva MO, Flores J, Madero R, et al. Cytomegalovirus infection after kidney transplantation and long-term graft loss. *Nefrología* 37:515-525, 2017
- [37] Brennan DC. Cytomegalovirus in renal transplantation. *J Am Soc Nephrol* 12:848-855, 2001
- [38] Humar A, Lebranchu Y, Vincenti F, et al. The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Am J Transplant* 10:1228-1237, 2010
- [39] Khoury JA, Storch GA, Bohl DL, et al. Prophylactic versus preemptive oral valganciclovir for the management of cytomegalovirus infection in adult renal transplant recipients. *Am J Transplant* 6:2134-2143, 2006
- [40] Kliem V, Fricke L, Wollbrink T, Burg M, Radermacher J, Rohde F. Improvement in long-term renal graft survival due to CMV prophylaxis with oral ganciclovir: results of a randomized clinical trial. *Am J Transplant* 8:975-983, 2008
- [41] Witzke O, Nitschke M, Bartels M, et al. Valganciclovir prophylaxis versus preemptive therapy in cytomegalovirus-positive renal allograft recipients: long-term results after 7 years of a randomized clinical trial. *Transplantation* 102: 876-882, 2018
- [42] Reischig T, Jindra P, Hes O, Svecová M, Klaboch J, Treska V. Valacyclovir prophylaxis versus preemptive valganciclovir therapy to prevent cytomegalovirus disease after renal transplantation. *Am J Transplant* 8:69-77, 2008
- [43] Åsberg A, Humar A, Rollag H, et al. Lessons learned from a randomized study of oral valganciclovir versus parenteral ganciclovir treatment of cytomegalovirus disease in solid organ transplant recipients: the VICTOR trial. *Clin Infect Dis* 62:1154-1160, 2016
- [44] Dierickx D, Habermann TM. Post-transplantation lymphoproliferative disorders in adults. *N Engl J Med* 378: 549-562, 2018
- [45] Dierickx D, Tousseyn T, Sagaert X, et al. Single-center analysis of biopsy-confirmed posttransplant lymphoproliferative disorder: incidence, clinicopathological characteristics and prognostic factors. *Leuk Lymphoma* 54:2433-2440, 2013

- [46] Opelz G, Döhler B, Ruhlenstroth A. Cytomegalovirus prophylaxis and graft outcome in solid organ transplantation: a collaborative transplant study report. *Am J Transplant* 4: 928-936, 2004
- [47] Green M, Michaels MG. Epstein-Barr virus infection and posttransplant lymphoproliferative disorder. *Am J Transplant* 13 Suppl 3:41-54, 2013
- [48] Morton M, Coupes B, Roberts SA, et al. Epstein-Barr virus infection in adult renal transplant recipients. *Am J Transplant* 14:1619-1629, 2014
- [49] Quinlan SC, Pfeiffer RM, Morton LM, Engels EA. Risk factors for early-onset and late-onset post-transplant lymphoproliferative disorder in kidney recipients in the United States. *Am J Hematol* 86:206-209, 2011
- [50] Caillard S, Lamy FX, Quelen C; French Transplant Centers, et al. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. *Am J Transplant* 12:682-693, 2012
- [51] Allen UD, Preiksaitis JK; AST Infectious Diseases Community of Practice. Epstein-Barr virus and posttransplant lymphoproliferative disorder in solid organ transplantation. *Am J Transplant* 13 Suppl 4:107-120, 2013
- [52] Hirsch HH, Randhawa P; AST Infectious Diseases Community of Practice. BK polyomavirus in solid organ transplantation. *Am J Transplant* 13 Suppl 4:179-188, 2013
- [53] Ambalathingal GR, Francis RS, Smyth MJ, Smith C, Khanna R. BK Polyomavirus: clinical aspects, immune regulation, and emerging therapies. *Clin Microbiol Rev* 30:503-528, 2017
- [54] Yooprasert P, Rotjanapan P. BK virus-associated nephropathy: current situation in a resource-limited country. *Transplant Proc* 50:130-136, 2018
- [55] Skulratanasak P, Mahamongkhonsawata J, Chayakulkeeree M, Larpparisutha N, Premasathiana N, Vongwiwatana A. BK virus infection in Thai kidney transplant recipients: a single-center experience. *Transplant Proc* 50:1077-1079, 2018
- [56] Fishman JA. Infection in organ transplantation. *Am J Transplant* 17:856-879, 2017
- [57] Kadambi PV, Josephson MA, Williams J, et al. Treatment of refractory BK virus-associated nephropathy with cidofovir. *Am J Transplant* 3:186-191, 2003
- [58] Kuypers DR, Vandooren AK, Lerut E, et al. Adjuvant low-dose cidofovir therapy for BK polyomavirus interstitial nephritis in renal transplant recipients. *Am J Transplant* 5: 1997-2004, 2005
- [59] Wu SW, Chang HR, Lian JD. The effect of low-dose cidofovir on the long-term outcome of polyomavirus-associated nephropathy in renal transplant recipients. *Nephrol Dial Transplant* 24:1034-1038, 2009
- [60] Nesselhauf N, Strutt J, Bastani B. Evaluation of leflunomide for the treatment of BK viremia and biopsy proven BK nephropathy; a single center experience. *J Nephropathol* 5:34-37, 2016
- [61] Faguer S, Hirsch HH, Kamar N, et al. Leflunomide treatment for polyomavirus BK-associated nephropathy after kidney transplantation. *Transpl Int* 20:962-969, 2007
- [62] Zaman RA, Ettenger RB, Cheam H, Malekzadeh MH, Tsai EW. A novel treatment regimen for BK viremia. *Transplantation* 97:1166-1171, 2014
- [63] Johnston O, Jaswal D, Gill JS, Doucette S, Fergusson DA, Knoll GA. Treatment of polyomavirus infection in kidney transplant recipients: a systematic review. *Transplantation* 89:1057-1070, 2010
- [64] Arroyo D, Chandran S, Vagefi PA, Wojciechowski D. Adjuvant ciprofloxacin for persistent BK polyomavirus infection in kidney transplant recipients. *J Transplant* 2014: 107459, 2014
- [65] Umbro I, Anzivino E, Tinti F, et al. Possible antiviral effect of ciprofloxacin treatment on polyomavirus BK replication and analysis of non-coding control region sequences. *Virology* 10:274, 2013
- [66] Lee BT, Gabardi S, Grafals M, et al. Efficacy of levofloxacin in the treatment of BK viremia: a multicenter, double-blinded, randomized, placebo-controlled trial. *Clin J Am Soc Nephrol* 9:583-589, 2014
- [67] Khalil MAM, Khalil MAU, Tan J, Khan TFT. Fluoroquinolones and BK virus nephropathy: a myth or a reality. *Indian J Nephrol* 28:257-264, 2018
- [68] Townamchai N, Thongboon A, Kittikowit W, Suankratay C, Praditpornsilpa K, Avihingsanon Y. Successful treatment of polyomavirus infection in kidney allograft recipients: case reports and literature review. *Asian Biomed* 3:151-157, 2009
- [69] Vu D, Shah T, Ansari J, Naraghi R, Min D. Efficacy of intravenous immunoglobulin in the treatment of persistent BK viremia and BK virus nephropathy in renal transplant recipients. *Transplant Proc* 47:394-398, 2015
- [70] Kable K, Davies CD, O'Connell PJ, Chapman JR, Nankivell BJ. Clearance of BK virus nephropathy by combination antiviral therapy with intravenous immunoglobulin. *Trans-*

plant Direct 3:e142, 2017

- [71] Luxemburger C, Dutta AK. Overlapping epidemiologies of Hepatitis A and typhoid fever: the needs of the traveler. *J Travel Med* 12 Suppl 1:S12-S21, 2005
- [72] Franco E, Meleleo C, Serino L, Sorbara D, Zaratti L. Hepatitis A: epidemiology and prevention in developing countries. *World J Hepatol* 4:68-73, 2012
- [73] Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. *Vaccine* 28:6653-6657, 2010
- [74] Inoue K, Yoshida M, Yotsuyanagi H, Otsuka T, Sekiyama K, Fujita R. Chronic hepatitis A with persistent viral replication. *J Med Virol* 50:322-324, 1996
- [75] Abolghasemi S, Sali S, Arabsaghari E, et al. Seroprevalence of hepatitis A in hemodialysis patient candidate for kidney transplant younger than forty years. *Nov Biomed* 2:49-53, 2017
- [76] Mariya FA, de Mello Perez R, Silva AE, Pestana JO, Ferraz ML. Prevalence of previous hepatitis A virus infection in renal transplant patients with hepatitis C: evidence of persistent anti-hepatitis A virus immune response. *Transplant Proc* 36:1500-1501, 2004
- [77] Levitsky J, Doucette K; AST Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation. *Am J Transplant* 13 Suppl 4:147-168, 2013
- [78] Jeon HJ, Ro H, Jeong JC, et al. Efficacy and safety of hepatitis A vaccination in kidney transplant recipients. *Transpl Infect Dis* 16:511-515, 2014
- [79] Stark K, Günther M, Neuhaus R, et al. Immunogenicity and safety of hepatitis A vaccine in liver and renal transplant recipients. *J Infect Dis* 180:2014-2017, 1999
- [80] Foster MA, Weil LM, Jin S, et al. Transmission of hepatitis A virus through combined liver-small intestine-pancreas transplantation. *Emerg Infect Dis* 23:590-596, 2017
- [81] Gane E, Sallie R, Saleh M, Portmann B, Williams R. Clinical recurrence of hepatitis A following liver transplantation for acute liver failure. *J Med Virol* 45:35-39, 1995
- [82] Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy. *J Hepatol* 57:442-450, 2012
- [83] Johnson DW, Dent H, Yao Q, et al. Frequencies of hepatitis B and C infections among haemodialysis and peritoneal dialysis patients in Asia-Pacific countries: analysis of registry data. *Nephrol Dial Transplant* 24:1598-1603, 2009
- [84] Blanpain C, Knoop C, Delforge ML, et al. Reactivation of hepatitis B after transplantation in patients with pre-existing anti-hepatitis B surface antigen antibodies: report on three cases and review of the literature. *Transplantation* 66:883-886, 1998
- [85] Degos F, Lugassy C, Degott C, et al. Hepatitis B virus and hepatitis B-related viral infection in renal transplant recipients. A prospective study of 90 patients. *Gastroenterology* 94:151-156, 1988
- [86] Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 50:661-662, 2009
- [87] Foster WQ, Murphy A, Vega DJ, Smith AL, Hott BJ, Book WM. Hepatitis B vaccination in heart transplant candidates. *J Heart Lung Transplant* 25:106-109, 2006
- [88] Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 148:215-219; quiz e16-e17, 2015
- [89] Fytili P, Ciesek S, Manns MP, et al. Anti-HBc seroconversion after transplantation of anti-HBc positive nonliver organs to anti-HBc negative recipients. *Transplantation* 81:808-809, 2006
- [90] Huprikar S, Danziger-Isakov L, Ahn J, et al. Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management. *Am J Transplant* 15:1162-1172, 2015
- [91] Kim CW, Chang KM. Hepatitis C virus: virology and life cycle. *Clin Mol Hepatol* 19:17-25, 2013
- [92] Ozer Etik D, Ocal S, Boyacioglu AS. Hepatitis C infection in hemodialysis patients: a review. *World J Hepatol* 7:885-895, 2015
- [93] Morales JM, Fabrizi F. Hepatitis C and its impact on renal transplantation. *Nat Rev Nephrol* 11:172-182, 2015
- [94] Morales JM, Marcén R, Andres A, et al. Renal transplantation in patients with hepatitis C virus antibody. A long national experience. *NDT Plus* 3(Suppl_2):ii41-ii46, 2010
- [95] Terrault NA, Adey DB. The kidney transplant recipient with hepatitis C infection: pre- and posttransplantation treatment. *Clin J Am Soc Nephrol* 2:563-575, 2007
- [96] Pawlotsky JM. New hepatitis C virus (HCV) drugs and the hope for a cure: concepts in anti-HCV drug development. *Semin Liver Dis* 34:22-29, 2014
- [97] Beinhardt S, Al Zoairy R, Ferenci P, et al. DAA-based antiviral treatment of patients with chronic hepatitis C in the pre- and postkidney transplantation setting. *Transpl Int* 29:999-1007, 2016

- [98] Lin MV, Sise ME, Pavlakis M, et al. Efficacy and safety of direct acting antivirals in kidney transplant recipients with chronic hepatitis C virus infection. *PLoS One* 11:e0158431, 2016
- [99] Burgess S, Partovi N, Yoshida EM, Erb SR, Azalgará VM, Hussaini T. Drug interactions with direct-acting antivirals for hepatitis C: implications for HIV and transplant patients. *Ann Pharmacother* 49:674-687, 2015
- [100] Goldberg DS, Abt PL, Blumberg EA, et al. Trial of transplantation of HCV-infected kidneys into uninfected recipients. *N Engl J Med* 376:2394-2395, 2017
- [101] Ryu WS, Bayer M, Taylor J. Assembly of hepatitis delta virus particles. *J Virol* 66:2310-2315, 1992
- [102] Adil B, Fatih O, Volkan I, et al. Hepatitis B virus and hepatitis D virus recurrence in patients undergoing liver transplantation for hepatitis B virus and hepatitis B virus plus hepatitis D virus. *Transplant Proc* 48:2119-2123, 2016
- [103] Inagaki Y, Oshiro Y, Tanaka T, et al. A nationwide survey of hepatitis E virus infection and chronic hepatitis E in liver transplant recipients in Japan. *EBioMedicine* 2:1607-1612, 2015
- [104] Haagsma EB, Niesters HG, van den Berg AP, et al. Prevalence of hepatitis E virus infection in liver transplant recipients. *Liver Transpl* 15:1225-1228, 2009
- [105] Kamar N, Selves J, Mansuy JM, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med* 358:811-817, 2008
- [106] Koning L, Pas SD, de Man RA, et al. Clinical implications of chronic hepatitis E virus infection in heart transplant recipients. *J Heart Lung Transplant* 32:78-85, 2013
- [107] Kamar N, Weclawiak H, Guilbeau-Frugier C, et al. Hepatitis E virus and the kidney in solid-organ transplant patients. *Transplantation* 93:617-623, 2012
- [108] Pischke S, Suneetha PV, Baechlein C, et al. Hepatitis E virus infection as a cause of graft hepatitis in liver transplant recipients. *Liver Transpl* 16:74-82, 2010
- [109] Kamar N, Garrouste C, Haagsma EB, et al. Factors associated with chronic hepatitis in patients with hepatitis E virus infection who have received solid organ transplants. *Gastroenterology* 140:1481-1489, 2011
- [110] Kamar N, Rostaing L, Abravanel F, et al. Pegylated interferon-alpha for treating chronic hepatitis E virus infection after liver transplantation. *Clin Infect Dis* 50:e30-e33, 2010
- [111] Kamar N, Izopet J, Tripon S, et al. Ribavirin for chronic hepatitis E virus infection in transplant recipients. *N Engl J Med* 370:1111-1120, 2014
- [112] Locke JE, Gustafson S, Mehta S, et al. Survival benefit of kidney transplantation in HIV-infected patients. *Ann Surg* 265:604-608, 2017
- [113] Roland ME, Barin B, Huprikar S, et al; HIVTR Study Team. Survival in HIV-positive transplant recipients compared with transplant candidates and with HIV-negative controls. *AIDS* 30:435-444, 2016
- [114] Frassetto LA, Tan-Tam C, Stock PG. Renal transplantation in patients with HIV. *Nat Rev Nephrol* 5:582-589, 2009
- [115] Locke JE, Mehta S, Reed RD, et al. A national study of outcomes among HIV-infected kidney transplant recipients. *J Am Soc Nephrol* 26:2222-2229, 2015
- [116] Malat GE, Ranganna KM, Sikalas N, Liu L, Jindal RM, Doyle A. High frequency of rejections in HIV-positive recipients of kidney transplantation: a single center prospective trial. *Transplantation* 94:1020-1024, 2012
- [117] Stock PG, Barin B, Murphy B, et al. Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med* 363:2004-2014, 2010
- [118] Brehm MA, Markees TG, Daniels KA, Greiner DL, Rossini AA, Welsh RM. Direct visualization of cross-reactive effector and memory allo-specific CD8 T cells generated in response to viral infections. *J Immunol* 170:4077-4086, 2003
- [119] Tanchot C, Rosado MM, Agenes F, Freitas AA, Rocha B. Lymphocyte homeostasis. *Semin Immunol* 9:331-337, 1997
- [120] Langlois AJ, Weinhold KJ, Matthews TJ, Greenberg ML, Bolognesi DP. Detection of anti-human cell antibodies in sera from macaques immunized with whole inactivated virus. *AIDS Res Hum Retroviruses* 8:1641-1652, 1992
- [121] van Maarseveen EM, Crommelin HA, Mudrikova T, van den Broek MP, van Zuilen AD. Pretransplantation pharmacokinetic curves of tacrolimus in HIV-infected patients on ritonavir-containing cART: a pilot study. *Transplantation* 95:397-402, 2013
- [122] Sawinski D, Shelton BA, Mehta S, et al. Impact of protease inhibitor-based anti-retroviral therapy on outcomes for HIV+ kidney transplant recipients. *Am J Transplant* 17:3114-3122, 2017
- [123] Miro JM, Agüero F, Duclos-Vallée JC, et al; ESCMID Study Group of Infection in Compromised Hosts. Infections in solid organ transplant HIV-infected patients. *Clin Microbiol Infect* 20 Suppl 7:119-130, 2014
- [124] Kucirka LM, Durand CM, Bae S, et al. Induction immunosuppression and clinical outcomes in kidney transplant recipients infected with human immunodeficiency virus.

- Am J Transplant* 16:2368-2376, 2016
- [125] Lopez C, Simmons RL, Mauer SM, Najarian JS, Good RA, Gentry S. Association of renal allograft rejection with virus infections. *Am J Med* 56:280-289, 1974
- [126] Martin-Gandul C, Mueller NJ, Pascual M, Manuel O. The impact of infection on chronic allograft dysfunction and allograft survival after solid organ transplantation. *Am J Transplant* 15:3024-3040, 2015
- [127] Cainelli F, Vento S. Infections and solid organ transplant rejection: a cause-and-effect relationship? *Lancet Infect Dis* 2:539-549, 2002
- [128] Borchers AT, Perez R, Kaysen G, Ansari AA, Gershwin ME. Role of cytomegalovirus infection in allograft rejection: a review of possible mechanisms. *Transpl Immunol* 7:75-82, 1999
- [129] Karuthu S, Blumberg EA. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol* 7:2058-2070, 2012
- [130] Storsley L, Gibson IW. Adenovirus interstitial nephritis and rejection in an allograft. *J Am Soc Nephrol* 22:1423-1427, 2011
- [131] Cippà PE, Schiesser M, Ekberg H, et al. Risk stratification for rejection and infection after kidney transplantation. *Clin J Am Soc Nephrol* 10:2213-2220, 2015
- [132] Mallat SG, Tanios BY, Itani HS, et al. CMV and BKPyV infections in renal transplant recipients receiving an mTOR inhibitor-based regimen versus a CNI-based regimen: a systematic review and meta-analysis of randomized, controlled trials. *Clin J Am Soc Nephrol* 12:1321-1336, 2017
- [133] Mesri EA, Feitelson MA, Munger K. Human viral oncogenesis: a cancer hallmarks analysis. *Cell Host Microbe* 15:266-282, 2014
- [134] Morath C, Mueller M, Goldschmidt H, Schwenger V, Opelz G, Zeier M. Malignancy in renal transplantation. *J Am Soc Nephrol* 15:1582-1588, 2004
- [135] Hickman LA, Sawinski D, Guzzo T, Locke JE. Urologic malignancies in kidney transplantation. *Am J Transplant* 18:13-22, 2018
- [136] Alexiev BA, Randhawa P, Vazquez Martul E, et al. BK virus-associated urinary bladder carcinoma in transplant recipients: report of 2 cases, review of the literature, and proposed pathogenetic model. *Hum Pathol* 44:908-917, 2013
- [137] Mittal A, Colegio OR. Skin cancers in organ transplant recipients. *Am J Transplant* 17:2509-2530, 2017
- [138] Dantal J, Campone M. Daunting but worthy goal: reducing the de novo cancer incidence after transplantation. *Transplantation* 100:2569-2583, 2016
- [139] Holley JL. Screening, diagnosis, and treatment of cancer in long-term dialysis patients. *Clin J Am Soc Nephrol* 2:604-610, 2007
- [140] Stallone G, Schena A, Infante B, et al. Sirolimus for Kaposi's sarcoma in renal-transplant recipients. *N Engl J Med* 352:1317-1323, 2005
- [141] de Fijter JW. Cancer and mTOR inhibitors in transplant recipients. *Transplantation* 101:45-55, 2017