REVIEW ARTICLE

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VIRAL INFECTIONS IN KIDNEY TRANSPLANT RECIPIENTS

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ABSTRACT

After transplantation, viruses are one of the most frequent sources of opportunistic infections. The particular virus encountered, the degree of immune suppression applied to avoid graft rejection, and other host characteristics influencing susceptibility all influence the likelihood of contracting a virus. Following kidney transplantation, infectious challenges have been identified as a primary source of mortality and morbidity. In order to prevent such outcome of recipient of kidney transplant, it is necessary to detect infection early and provide appropriate treatment in time. Amongst all possible infectious complications, the most common is considered to be viral infection owing to their prevalence, ability of latency and infectivity. The frequently identified virus as agents that may cause infection in case of recipients of kidney transplantation throughout the world are varicella zoster virus, herpes simplex virus, cytomegalovirus, adenovirus, Epstein-Barr virus, polyoma virus and hepatitis B. The distribution of these viruses is widespread worldwide. These microorganisms can reactivate, as these are DNA viruses, when immunosuppressive medications are given to afflicted patients. Particularly during the first six months following transplantation, these DNA viruses can result in systemic illnesses or allograft malfunction. Pretransplant evaluation, immunization, adequate prophylaxis, and preventive measures following transplant can be adopted as effective means of reducing the frequency of these viral infections. The genesis, diagnosis, prophylaxis, and management of viral infections that frequently afflict kidney transplant recipients will be covered in this review.

Key words: Virus, Opportunistic infection, Transplantation.

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INTRODUCTION:

The most suitable form of treatment for those with end-stage kidney disorders is kidney transplantation. After transplant, recipients' quality of life and lifespan are almost on par with those of healthy people. Immunosuppression is still a big concern even though kidney transplantation is preferable to long-term dialysis. Furthermore, some populations are more susceptible to infection than others, including the elderly and undernourished individuals with long-term renal disorders. Patients in underdeveloped or tropical nations are more susceptible to illness[1].

The primary source of mortality and morbidity following transplantation of kidney has been identified to be the complications due to infection, which was, in particular, noted in the population of Asia[2]. Compared to the former era of transplantation, powerful immunosuppressive medicines use, as well as, transplant in high-risk patients in Asian countries are on the rise.

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For instance, a rigorous preconditioning strategy is necessary for kidney transplants that are incompatible with a donor's blood group, nevertheless, this approach carries a significant infection risk with the BK polyomavirus (BKV) or the cytomegalovirus (CMV)[3].

Kidney transplant recipients can be affected by different viruses which is displayed in Table 1.

Table 1: Most commonly seen viral infections in renal transplant recipients:[4]

Herpes simplex virus (HSV)
Cytomegalovirus (CMV)
Adenovirus
Human papilloma virus (HPV)
Human herpes virus 6,7,8 (HHV)
Human T-Lymphotropic virus1 and 2 (HTLV)
Human immunodeficiency virus (HIV)
Hepatitis B and C viruses (HBV, HCV)
Polyomaviruses (BK, JC, SV-40)
Epstein Barr virus (EBV)

Among them, the most frequent viruses that infect recipients of kidney transplants are CMV and BKV. However, clinical manifestations differ, and skilled transplant physicians must be aware of this in order to treat patients appropriately[5,6]. A higher incidence of secondary malignancies among transplant recipients has been linked to both concomitant viral infection and intensive immunosuppression[7]. Immune system disruption may result in cancer or allograft rejection. It is evident that both kinds of problems have an impact on patient survival and limited transplant duration. Some viral infections result in cancer or are linked to transplant rejection. Physicians who perform transplants must manage the patient's immune system, too little immunosuppression might result in the graft being rejected, while excessive immunosuppression can raise the risk of infection and cancer. Therefore, it is critical to keep an eye on the patient's health following transplantation to make sure that these complications do not arise[2].

The overall concept of a viral infection in transplant recipients:

Viruses are tiny infectious organisms that can only reproduce in living host cells. Viral proteins bind to particular cell surface receptors to allow the viruses to enter live cells[8]. Viral replication occurs once the viruses have reached the host cells. For RNA viruses, the host cell's cytoplasm is where the virus replicates, for DNA and retroviruses, the host cell's nucleus is where the virus replicates. The process known as the lytic phase occurs when the cells release viral particles, which causes the cells to lyse[9]. After this stage, viruses can travel through the bloodstream or neurons to nearby or far-off uninfected cells, resulting in viral diseases[10].

Most viral infections in immunocompetent people self-limit. This is because the viruses can be removed by the immune system's intact adaptive immunity that includes subset of CD4+ helper T-cell, CD8+ cytotoxic T-lymphocyte and innate immunity involving interferon [IFN]-α and β[11]. There are two categories of persistent viral infection in immunocompetent hosts: latent and chronic categories. Latent viral infections, such as herpesviruses and polyomaviruses, are characterized by the persistence of the viral genome without replication, whereas chronic viral infections, such as HBV and HCV, exhibit continuous extended viral replication and shredding[12]. When a virus's genomes are able to evade death by staying in the cytoplasm or nucleus of infected cells, they enter a state known as latency, which makes them immune system-incompatible[13]. However, latent infection reactivation can be prevented by ongoing host immune surveillance, particularly by CD8+ T-cells, and continuous IFN-γ and

tumor necrosis factor-α production[14]. After solid organ transplantation (SOT), receiving immunosuppressive medications can lead to immunological dysregulation and viral reactivation, especially in the first six months post-transplant[15].

Cytomegalovirus (CMV)

The most prevalent virus among recipients of SOT is CMV. It typically appears in the initial few months following transplantation and is linked to both acute or chronic graft dysfunction as well as clinical infectious diseases (such as pneumonia, fever, hepatitis, gastrointestinal ulcers, and recurrent infections). Donor leukocytes, donor-transmitted viruses, and latent viruses are the sources of infection inrecipients of transplant. Between 20 and 60 percent of transplant recipients experience symptomatic CMV infection[16]. The majority of symptomatic CMV infections are typified by an episodic fever that self-limits. The CMV virus can spread to the brain, lungs, liver, pancreas, kidneys, gastrointestinal tract and can also be fatal.

CMV has been related to transplant rejection (both acute and chronic), resulting in renal allograft damage that may be difficult to distinguish from injury brought on by rejection or other causes. CMV viremia detection is the basis for current diagnostic techniques; the sensitivity of antibody testing and culture are less and cause delays in diagnosis. Nucleic acid testing (NAT) or the CMV antigenemia assay can both be used to identify viremia. A multifaceted approach is needed to treat established CMV disease, which includes reducing the use of immunosuppressive medications, antiviral medications, and occasionally adjuvant therapy. One common belief is that the cornerstone of treatment is intravenous ganciclovir. With bioavailability a 10-fold higher than oral ganciclovir, valganciclovir is an oral prodrug of ganciclovir. The majority of recent research indicates that valganciclovir may be able to take the role of intravenous and oral ganciclovir in various circumstances[17].

Herpes simplex virus (HSV) and Varicella Zoster Virus (VZV)

The double stranded DNA core of HSV and VZV is shared by both alpha herpes viruses. Latent viral replication is typically the source of infection in recipients of kidney transplant. The most common presentation of HSV infection is oral or vaginal lesions, however, it can also occasionally result in pneumonitis, encephalitis, esophagitis, or hepatitis[18,19]. Although it can spread and cause comparable visceral complications, VZV reaction typically manifests as dermal zoster. Without prophylaxis, HSV and VZV can manifest early, the detection of HSV has been noted after a month following transplant surgery, while VZV can appear as early as the first six months. For patients requiring CMV prophylaxis, ganciclovir is used as part of post-transplant prophylaxis against HSV and VZV reactions in order to prevent severe recurrences[19]. Patients can take valacyclovir or acyclovir for one to three months after transplant if they do not need CMV prophylaxis[19,20]. Polymerase chain reaction from cerebrospinal fluid or visceral tumor samples, as well as direct fluorescent antibodies for HSV and VZV from vesicular lesions, can be used to make the diagnosis. Intravenous acyclovir is used to treat disseminated infections, whilst oral acyclovir, valacyclovir, or famciclovir can be used to treat less severe infections[20].

Epstein-Barr virus (EBV)

The gamma EBV has a seroprevalence, in adults, of more than 90%. SOT recipients may experience a range of clinical manifestations of EBV infection, including pneumonitis, posttransplant lymphoproliferative disorder (PTLD), gastrointestinal disorders, hepatitis,

lung mass, lymphadenopathy, hepatosplenomegaly, andcentral nervous systemdisease. The incidences of PTLD vary for transplantation of different organs. The least common transplant procedure is kidney transplantation, which is most common after pancreas, liver, heart, lung, and small bowel transplants in that order[21]. PTLD diagnosis and classification are based on histopathology categorized in 2017 by the World Health Organization. There are still no guidelines about what should be looked for and when EBV should be evaluated. The groups with a high degree of risk for PTLD and EBV infection were not well defined. Reducing the use of immunosuppressive medications, surgery, radiation, adoptive immunotherapy, or chemotherapy can all be used for treating Parkinson's disease[22].

Polyomavirus

Three species of DNA viruses that may cause infection in humans are known to be polyomaviruses: the BK virus, the JC virus, and the SV40 virus from simians. Usually asymptomatic, the initial infection most likely spreads through the blood or respiratory system. Multiple rejection episodes and positive donor and/or recipient are known risk factors for the transplant recipient[23]. According to reports, the incidence of BK viruria is between 23% to 73%,BK virus-associated nephritis (BKVAN) incidence range from 1% to 7% and BK viremia incidence range between 8% to 15%. The highest rate of BKVAN occurs three to six months after transplantation[24].

It is advised that every month to 3 months for the initial 2 years after transplantation and after that once a year till the 5thyear, screening for BKV needs to be done with the use of quantitative DNA viral testing of the urine. Kidney histopathology, comprising tubulointerstitial nephritis with cytopathic alterations and positive immunohistochemistry utilizing antibodies typically targeting BKV antigens or cross-reacting SV40 big T-antigen, or in-situ hybridization for BKV nucleic acids, is the gold standard for BKVAN diagnosis[25].

The primary goal of BKVAN treatment is to minimize immunosuppressive medication. Withdrawing mycophenolate mofetil or tacrolimus, switching tacrolimus for cyclosporine, or stopping calcineurin inhibitors (CNIs) are several ways to do this. Antiviral therapy's effectiveness as a supplement to immunosuppression reduction remains debatable. An antiviral nucleotide counterpart of cytosine is called cidofovir. With a dose of 0.25 to 1.0 mg/kg given every one to three weeks, it has been successfully used to treat BKVAN in kidney transplant recipients[26]. Nevertheless, some research has not demonstrated the efficacy of cidofovir in the management of BKVAN[27]. Furthermore, cidofovir's nephrotoxicity is a serious issue that may impair allograft function. To prove the actual efficacy, large-scale randomized clinical trials are necessary.

Leflunomide is an additional BKV therapy option. Some facilities have employed ciprofloxacin and leflunomide together, and the results have shown possible benefits for virus reduction[28].

Hepatitis B (HBV) and C virus (HCV)

Hepatitis B transmission occurs sexually, through transfusion of blood, to child from mother, as well as via transplantation of organ. The virion DNA is stored in the hepatocyte's nucleus after infection, where it might lead to long-term consequences including persistence of infection and hepatocellular cancer or cirrhosis[29]. HBV reactivation took place following transplantation in 5% and 94% of patients with antibody to hepatitis B core antigen (antiHBc) and positive HBsAg respectively, which is a serious issue[30]. Consequently, it is essential to do a suitable pretransplant examination for HBV infection. Patients who test negative for HBV infection-related serological markers should be provided with the HBV

vaccination. Before receiving a transplant, chronic HBV infection should be assessed in case of all individuals, those not fulfilling the requirements for treatment should be given entecavir or tenofovir after transplantation[31]. Prophylaxis is still the recommended course of action for recipients with isolated anti-HBc[32]. Like HBV, HCV can spread by blood exposure, organ transplantation, sexual contact, and, less frequently, the placenta. Hepatocyte cytoplasm is where HCV can preserve its genome. Hepatocellular cancer or cirrhosis may develop in individuals suffering from chronic infection with HCV[33]. The geographic distribution of the seroprevalence of HCV in hemodialysis patients varies from 5% to 60%[34]. Data unequivocally demonstrate that patients on the waiting list do not have survival rates lower than HCV-positive recipients undergoing kidney transplantation. Comparing these people to transplant patients who are HCV-negative, however, they still have a reduced rate of graft survival[35]. Rejection of graft may occur in recipients of renal transplant who undergo IFN treatment for HCV infection, therefore this use must be carefully considered. When carefully monitored, ribavirin monotherapy can be used as a substitute for other treatments[4]. However, there are notable drug-drug interactions with ribavirin and CNIs. As a result, it is important to carefully monitor the levels of immunosuppressive medications and to modify their dosages[36].

Human immunodeficiency virus (HIV)

Kidney transplant availability may be restricted for end-stage renal failure patients who are HIV-positive. In HIV-positive individuals, however, transplantation of kidney leads to a quality of life higher than ongoing dialysis[37]. New research confirms that the prognosis for renal transplantation in suitably chosen HIV-positive patients receiving kidneys from HIV-negative donors is comparable to that of HIV-negative renal transplant recipients[18].

The primary obstacles to effectively managing HIV-positive renal transplant recipients in the clinical setting include the potential interactions between immunosuppressive medications and specific antiretroviral drug classes, as well as a greater incidence of acute rejection compared to receivers without HIV. HIV-positive patients undergoing kidney transplants may be more susceptible to acute rejection (up to 25%), and it is still unclear how best to control immunosuppression in HIV-positive patients. Rejection treatment with cytolytic drugs, such as thymoglobulin, may cause a significant increase in infection-related morbidity and a prolonged decline in CD4 levels[4].

Human papilloma virus (HPV)

Kidney transplant recipients having HPV infections can develop serious illness, including warts, dysplasia, and cancerous lesions in the oral, vaginal, and rectal regions. Ano-genital cancer and nonmelanoma skin cancer are significantly more common in recipients of renal transplants[38]. Reducing immunosuppression, topical medication, or surgery are necessary forms of treatment. Use caution when using topical immunotherapies like imiquimod[4].

Community-acquired respiratory viruses

Influenza viruses A and B, respiratory syncytial virus, parainfluenza viruses 1, 2, and 3, adenoviruses, and maybe rhinoviruses are significant community-acquired respiratory virus infections in the immunocompromised host[19]. All viruses spread through contact, with the exception of influenza, which spreads through respiratory droplets. The common cold, upper respiratory tract infections, laryngitis, pharyngitis, tracheobronchitis, influenza-like syndromes, pneumonia, and

bronchiolitis are examples of common respiratory virus syndromes. Viral shedding can last months in an immunocompromised host as opposed to days in an immunocompetent host. Supportive care and, in certain situations, the use of antiviral medications are part of the treatment for respiratory viral infections. Oseltamivir or zanamavir, which can treat both influenza A and B, are two possible treatments for influenza. Ribavirin is authorized for the treatment of respiratory syncytial virus-related lower respiratory infections. Pretransplant and annual influenza vaccinations are recommended, however, vaccine administration should not be done during early posttransplant periods as vaccine response is significantly low during this time[4].

Rejection and viral infection in kidney transplant recipients

Viral infection is also commonly linked to kidney transplant rejection. Early research at the start of the kidney transplant era revealed that 17% of patients without the viral infection had rejection episodes, compared to 72% of recipients infected with CMV. Episodes of rejection (acute or chronic) can result from viral infections. The mechanisms behind CMV-induced rejection of allografts have been sporadically investigated[39].

Numerous processes have been documented, such as the following:

(1) direct damage to endothelial cells;

(2) activation of HLA class I antigen specific T lymphocytes through cross reaction with antigen CMV;

and

(3) production of proinflammatory cytokines, such astumor necrosis factor-α, interleukin [IL]-8, IL-1, IL-6. Adhesion molecules expression on leukocytes and endothelial cells as well as HLA class II molecules on the allograft increases as a result of these intricate interactions.

Additionally, during an infection, doctors typically reduce immunosuppressive medication, which causes a rejection event[40]. Antirejection medication results in a rise in the overall state of immunosuppression, which can reawaken latent viruses, particularly polyomavirus and CMV. Moreover, an anti rejection approach could eliminate antibodies specific to a virus. As a result, patients are more vulnerable to viral infection, either primary infection or reactivation. Following transplantation, a healthy immune system and periodic surveillance for common infections are crucial[41]. When used as the primary immunosuppressive regimen, the mammalian target of rapamycin inhibitor (mTORi) (with or without CNI reduction) reduced the frequency of BK polyoma and CMV infections in comparison to the usual dose of CNI, which did not differ in the rate of acute rejection[42].

Malignancy and viral infection after kidney transplantation

Allograft survival results from the current maintenance of immunosuppressive regimes during the post-transplantation phase. The late post-transplantation phase has increased interest in problems like malignancy. One of the main causes of malignancy, as is widely known, are infections caused by virus. Human T-cell lymphotropic virus-1, human papillomavirus, EBV, Merkel cell polyomavirus, human herpesvirus-8, Kaposi's sarcoma herpesvirus, and HBV are examples of common human oncogenic viruses[43]. According to recent reports, patients who have received kidney transplants may be at risk for urothelial malignancies due to the BKV[44]. Table 2 displays the guidelines for cancer screening after kidney transplantation[45-47]. There is mounting evidence that using mTORi as part of an immunosuppressive regimen can prevent the spread of cancer and stop viral replication. Kaposi's sarcoma can be inhibited by mTORi treatment, according to compelling data[48]. Cutaneous squamous cell carcinoma is the next mTORi-based regimen's promising target[49]. Therefore screening for malignancy is necessary after kidney transplant, the protocol for which is displayed in Table-2.

Table 2 : Recommended malignancy screening protocol after kidney transplantation

Cancer	Protocol
Cervical cancer	• Ages 21 to 29 years: every 3 years Pap and HPV tests • Ages 30 to 64 years: every 5 years Pap and HPV tests • Age ≥ 65 years: discontinue if negative Pap and HPV tests for 2 years or negative Pap tests for 3 years.
Breast cancer	•Ages 40 to 54 years: mammography annually • Age ≥ 55 years: mammography biannually (discontinue if expectancy of survival is less than 10 years).
Prostate cancer	• Age ≥ 50 years: in case of male patients with a minimum of 10-years expectancy of survival, PSA with or without digital rectal examination
Colorectal cancer	• Age ≥ 50 years without family history of colorectal cancer: computed tomography colonoscopy every 5 years, every 10 years colonoscopy, every 3 years flexible sigmoidoscopy, and fecal occult blood test annually or multitarget stool DNA test every 3 years. • If family history is positive, screening should be initiated at an early age.
Skin cancer	• Every 6 to 12 months, total body examination by dermatologist.
Lung cancer	• Former smokers having quit smoking within 15 years or present smokers; aged between 55 to 74 years with history of smoking at least a 30 pack/year: low-dose computed tomography chest scan annually.
Urological cancer	• Ultrasonography every 2 to 5 years.
Posttransplant lymphoproliferative disorders	• EBV viral load during the first year post-transplantation in D+/R- recipients

CONCLUSION

Viral infections, namely CMV and BKV, continue to be a significant barrier to kidney transplant survival over the long run. Similar to other infectious disorders that affect transplant recipients, a rise in viral infections can increase the risk of rejection and malignancy following solid organ transplantation.

CONFLICT OF INTEREST

There is no conflict of interest.

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