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Reactivation of Latent Viral Infections in Transplant Recipients

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Introduction

Solid organ and hematopoietic stem cell transplantation have revolutionized the treatment of end-stage organ failure and hematologic malignancies. However, the success of transplantation is heavily dependent on lifelong immunosuppression, which, while essential for preventing rejection or Graft-Versus-Host Disease (GVHD), also compromises host defenses. This immunosuppressed state predisposes transplant recipients to a spectrum of opportunistic infections, including the reactivation of latent viruses. Many viral infections remain dormant in healthy individuals but can reactivate under conditions of immune suppression. Reactivation of latent viruses such as CytoMegaloVirus (CMV), Epstein-Barr Virus (EBV), BK polyomaVirus (BKV), Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV) is a significant cause of morbidity and mortality in transplant recipients. These viral complications can impair graft function, increase the risk of secondary infections and malignancies and affect long-term survival. This article explores the clinical implications, diagnostic challenges and management strategies for latent viral reactivation in transplant recipients [1].

Description

The most clinically significant latent virus in transplantation is CytoMegaloVirus (CMV), a β-herpesvirus that remains latent in monocytes and myeloid progenitor cells. CMV reactivation occurs in 20–60% of transplant recipients, depending on serostatus and the intensity of immunosuppression. The highest risk exists in CMV-seronegative recipients who receive organs from seropositive donors (D+/R–). CMV disease can present as a systemic syndrome with fever and cytopenias or manifest as tissue-invasive disease affecting the gastrointestinal tract, liver, lungs, or retina. Beyond direct effects, CMV exerts indirect immunomodulatory effects that increase the risk of acute and chronic rejection, secondary infections and allograft dysfunction. Monitoring of CMV DNAemia through quantitative Polymerase Chain Reaction (qPCR) is the cornerstone of early detection. Prophylactic or preemptive antiviral therapy with agents such as ganciclovir or valganciclovir is commonly employed. However, antiviral resistance, drug-related myelotoxicity and the need for prolonged surveillance pose management challenges. Epstein-Barr Virus (EBV), another member of the herpesvirus family, is particularly concerning due to its association with Post-Transplant Lymphoproliferative Disorder (PTLD). EBV persists in B lymphocytes and can become reactivated in the setting of profound T-cell immunosuppression. The risk of PTLD is highest in EBV-seronegative recipients of EBV-seropositive grafts and in those receiving T-cell depleting agents such as anti-thymocyte globulin. PTLD ranges from benign polyclonal lymphoid hyperplasia to aggressive, monoclonal non-Hodgkin lymphoma. EBV viral load monitoring using quantitative PCR allows for early detection of reactivation and guides the initiation of preemptive strategies, which may include reduction in immunosuppression, rituximab therapy, or cytotoxic chemotherapy. The management of EBV-related complications remains difficult, particularly in cases of central nervous system involvement or resistance to first-line therapies [2].

BK Virus (BKV), a polyomavirus latent in the genitourinary tract, is a significant cause of graft dysfunction in kidney transplant recipients. BK Virus-Associated Nephropathy (BKVAN) is characterized by tubulointerstitial inflammation and viral cytopathic effects, ultimately leading to fibrosis and allograft loss if left untreated. Risk factors for BKV reactivation include high levels of immunosuppression, especially tacrolimus and mycophenolate mofetil. Screening for BK viremia and viruria via PCR is recommended during the first year post-transplant. Unlike CMV, there is no effective antiviral therapy for BKV and the primary management strategy is a reduction in immunosuppression, which must be carefully balanced to avoid acute rejection. Emerging therapies, including fluoroquinolones, leflunomide and intravenous immunoglobulin (IVIG), have shown variable success.

Other herpesviruses such as herpes simplex virus (HSV) and varicella-zoster virus (VZV) also pose risks. HSV can reactivate early after transplantation, often presenting as orolabial or genital lesions, while disseminated disease may occur in the severely immunocompromised. VZV reactivation typically manifests as herpes zoster (shingles), which can lead to postherpetic neuralgia and, in some cases, disseminated disease or visceral involvement. Acyclovir prophylaxis is standard for HSV- and VZV-seropositive recipients, especially during the first months post-transplant. Vaccination with the Recombinant Zoster Vaccine (RZV) has shown promise in preventing VZV reactivation in transplant recipients, though its use must be carefully timed due to the need for sufficient immune recovery. The Human HerpesVirus 6 (HHV-6) and Human Herpesvirus 7 (HHV-7) may also reactivate, particularly in stem cell transplant recipients and are associated with encephalitis, marrow suppression and delayed engraftment. Diagnostic interpretation can be difficult, as low-level viral DNA may not represent true pathogenic reactivation. Similarly, JC virus, another polyomavirus, can reactivate and cause Progressive Multifocal Leukoencephalopathy (PML), a rare but devastating demyelinating condition of the central nervous system.

Conclusion

Reactivation of latent viral infections in transplant recipients remains a significant clinical challenge, contributing to graft dysfunction, opportunistic infections, malignancies and increased mortality. CMV, EBV, BKV, HSV and VZV are among the most critical pathogens in this context, with each virus presenting unique diagnostic and therapeutic complexities. Effective management relies on vigilant screening, early detection through molecular diagnostics and a delicate balance of immunosuppression. While antiviral therapies exist for some of these viruses, limitations in efficacy, toxicity and resistance require continued innovation. As transplantation continues to evolve, strategies such as personalized immunosuppression, virus-specific cellular therapies and broader use of recombinant vaccines hold promise for reducing the burden of viral reactivation. Ultimately, a comprehensive, multidisciplinary approach is essential to improve outcomes and ensure the long-term success of transplantation.

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Conflict of Interest

None.

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