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European perspective on human polyomavirus infection, replication and disease in solid organ transplantation

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Abstract

Human polyomaviruses (HPyVs) are a growing challenge in immunocompromised patients in view of the increasing number of now 12 HPyV species and their diverse disease potential. Currently, histological evidence of disease is available for BKPyV causing nephropathy and haemorrhagic cystitis, JCPyV causing progressive multifocal leukoencephalopathy and occasionally nephropathy, MCPyV causing Merkel cell carcinoma and TSPyV causing *trichodysplasia spinulosa*, the last two being proliferative skin diseases. Here, the current role of HPyV in solid organ transplantation (SOT) was reviewed and recommendations regarding screening, monitoring and intervention were made. Pre-transplant screening of SOT donor or recipient for serostatus or active replication is currently not recommended for any HPyV. Post-transplant, however, regular clinical search for skin lesions, including those associated with MCPyV or TSPyV, is recommended in all SOT recipients. Also, regular screening for BKPyV replication (e.g. by plasma viral load) is recommended in kidney transplant recipients. For SOT patients with probable or proven HPyV disease, reducing immunosuppression should be considered to permit regaining of immune control. Antivirals would be desirable for treating proven HPyV disease, but are solely considered as adjunct local treatment of *trichodysplasia spinulosa*, whereas surgical resection and chemotherapy are key in Merkel cell carcinoma. Overall, the quality of the clinical evidence and the strength of most recommendations are presently limited, but are expected to improve in the coming years.

Keywords: Merkel cell carcinoma, nephropathy, polyoma, progressive multifocal leukoencephalopathy, PyVAN, solid organ transplantation, *trichodysplasia spinulosa*, virus
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Hot Topics

- Pre-transplant testing of all SOT donors and all SOT recipients for HPyV-specific antibody, T-cells or DNA in urine, blood or other clinical specimens is not recommended, because current data are not sufficient for guiding organ allocation, risk stratification, immunosuppressive

therapy, screening modalities or prophylactic, preemptive or therapeutic intervention pre- or post-transplant (***BIII***).

- For SOT recipients listed for kidney transplantation after terminal renal failure due to PyVAN in native or transplanted kidneys, testing of plasma BKPyV should be considered and should be undetectable prior to (re-) transplantation or *at least* have declined by >2 $\log_{10}$ GEq/mL compared with documented peak plasma loads (***BIII***).
- All SOT recipients should have an annual skin and lip examination by a qualified health care professional with experience in diagnosing proliferative and malignant skin diseases to identify HPyV-associated skin diseases as well as melanoma and non-melanoma skin cancers (***BII***).
- Post-transplant routine *screening* of SOT recipients for any HPyV DNA (including JCPyV, MCPyV, TSpyV, KIPyV, WUPyV) in urine, blood or other clinical specimens is not recommended (with the exception of BKPyV in kidney transplant recipients), because current data are not sufficient for risk stratification, or for guiding immunosuppressive therapy, screening modalities, or prophylactic, preemptive or therapeutic intervention (***BIII***).
- All kidney transplant recipients should be regularly screened for BKPyV replication in urine (viruria) or plasma (viraemia) to identify patients at increased risk of PyVAN (***AII***).
- In kidney recipients with confirmed (sustained) plasma BKPyV loads or presumptive or proven PyVAN, maintenance immunosuppression should promptly be reduced in a step-wise fashion unless other competing risks are imminent (***AII***).

Introduction

Human polyomavirus (HPyV) species currently encompass 12 members of the genus *polyomavirus* within the family of *polyomaviridae* [1]. The first HPyVs were JC polyomavirus (JCPyV) and BK polyomavirus (BKPyV), both named after the initials of the patients from whom they were first isolated: JCPyV was detected in brain tissue from a patient with progressive multifocal leukoencephalopathy (PML) [2,3] while BKPyV was detected in urine from a kidney transplant patient with ureteric stenosis shedding 'decoy cells' [4,5]. In the past decade, 10 additional HPyVs have been identified by different molecular genetic techniques: the Karolinska Institute (KI-)PyV and Washington University (WU-)PyV in respiratory secretions of patients with unidentified cause of pneumonia [6], the MCPyV in Merkel cell carcinoma and TSPyV in *Trichodysplasia spinulosa*, two skin diseases in chronically immunocompromised patients [7,8], as well as six additional HPyVs, the clinical role of which still needs to be elucidated [9]. Seroprevalence studies indicate that HPyVs infect 30–90% of the general population and are transmitted independently of one another [7–11]. So far, the mode of transmission has not been resolved for any HPyV. However, HPyVs are frequently detectable in different body sites and fluids of healthy immunocompetent individuals, including skin, hair follicles, saliva, urine, faeces and respiratory secretions, and can be found in human sewage [9,11–13]. Thus, these hardy, non-enveloped viruses of 40- to 45-nm diameter are likely to be transmitted by direct person-to-person contact and by exposure to contaminated surfaces, foods and water.

Uncovering the respective route of transmission is hampered by the fact that characteristic clinical manifestations of primary infections have not been identified for any HPyV, presumably because of a mostly subclinical course or because of a clinically unspecific, for example flu-like, presentation. In rare cases, primary HPyV infections have been discussed as the cause of disease manifestations in the central nervous system (CNS), and in the respiratory, renourinary or gastrointestinal tract. However, supporting data (e.g. demonstrating seroconversion) are typically lacking. Evidence of biopsy-proven HPyV disease is largely confined to immunocompromised patients such as transplant recipients. Here, we review the role of HPyV infection, replication and disease (Table 1) in solid organ transplantation (SOT) patients and provide recommendations regarding the pre-transplant and post-transplant screening, and treatment and prevention using the Infectious Diseases Society of America – United States Public Health Service Grading System [14].

Diagnostic Aspects

Nucleic acid amplification testing (NAT) (e.g. by polymerase chain reaction) is the key diagnostic tool to detect HPyV

TABLE 1. Working definitions of virus infection, replication and disease in transplant patients

Virus infection – evidence of virus exposure
– by detecting specific immune responses (virus-specific antibody or T-cells)
or
– by detecting specific viral antigens, nucleic acids
Note: latent infection or low-level replication is difficult to distinguish for persisting viruses (e.g. polyoma-, herpes-, papilloma-, adenoviruses)
Virus replication – evidence of viral replication by at least one of the following
– increasing viral loads
– direct virion antigen detection
– virus isolation by culture
Note: Virus replication without compatible symptoms and signs of disease may be presymptomatic (e.g. require preemptive treatment).
Probable virus disease – evidence of viral replication above clinically relevant thresholds, or together with compatible symptoms and signs of viral syndrome or organ disease, but without histological confirmation
Note: A major contribution of other aetiologies should be excluded.
Proven virus disease – evidence of virus replication plus corresponding specific histopathology