Viral urological infections in kidney transplantation: BK polyomavirus (BKPyV)-associated diseases

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Abstract

Viral infections continue to be prevalent and a major problem in kidney transplant recipients. One of the most significant viruses for renal transplant patients is BK polyomavirus (BKPyV), the cause of BKPyV-associated nephropathy (BKVAN). BKVAN is seen in ca. 5% of renal transplant recipients and can lead to chronic allograft failure or even graft loss in up to 50% of cases. We aimed to summarize current evidence for screening and treatment of BKVAN and important findings for further research. Therefore, we summed up the evidence from well-established guidelines and searched ClinicalTrials.gov for ongoing randomized controlled trials (RCTs). Best evidence for screening for BKPyV is summarized by the American Society of Transplantation Infectious Diseases Community of Practice in 2019: They recommend screening for BKPyV viremia monthly, until month nine, and then every three months until two years post-transplant. Extended screening after two years may be considered in pediatric patients. Stepwise immunosuppression reduction is recommended for BKPyV viremia >1,000 copies/ml. There is no evidence for an effective reduction of immunosuppression or therapy for BKVAN available at the moment and high-quality studies or RCTs are missing, so further high-quality research is warranted. Promising new approaches for evaluation of therapy of BKVAN in RCTs are virus-specific T cells and targeting the viral immune response.

Summary of findings

- BK polyomavirus (BKPyV) is the most important polyomavirus for kidney transplant patients
- BKPyV-associated nephropathy (BKVAN) is the most critical disease in these patients: It is seen in 5% of renal transplant recipients and can lead to graft loss in up to 50% of cases
- Best evidence for screening for BKPyV is summarized by the American Society of Transplantation Infectious Diseases Community of Practice in 2019: They recommend screening for BKPyV viremia monthly, until month nine, and then every three months until two years post-transplant. Extended screening after two years may be considered in pediatric patients. Stepwise immunosuppression reduction is recommended for BKPyV viremia >1,000 copies/ml.
- There is no evidence for an effective reduction of immunosuppression or therapy for BKVAN available
- High-quality studies or RCTs are missing, so further high-quality research is warranted
- Promising new approaches for evaluation of therapy of BKVAN in RCTs are virus-specific T cells and targeting the viral immune response

1 Introduction

Viral infections continue to be prevalent and a major problem in kidney transplant recipients. Table 1 gives an overview of viral infections in renal transplantation according to the presenting time. These infections are especially virulent in patients with no previous contact with the virus (seronegative) or after increased immunosuppression, e.g. rejection treatment. Furthermore, recognition may be complicated by the tropism of some of the viruses for the allograft, thus deteriorating renal function and requiring differential diagnosis between viral infection and graft rejection. Complex antiviral strategies have been developed, mainly to deal with cytomegalovirus (CMV), including prophylaxis, pre-emptive therapy and therapy [1].

Table 1: Viral infections in renal transplantation according to presentation time (modified from the European Textbook of Kidney Transplantation 2017 [1])

Time to presentation	**Early (1 month after transplantation)**	**>1 month to <6 months after transplantation**	**Late (>6 months after transplantation)**
Type of infection	Nosocomial related Donor acquired Latent	Opportunistic	Community acquired Opportunistic
Virus	Herpes virus CMV	Herpes virus CMV BKPyV EBV Influenza Parainfluenza virus RSV	CMV Respiratory viruses
CMV = cytomegalovirus; BKPyV = BK polyomavirus; Epstein-Barr virus; RSV = Respiratory Syncytial Virus			

Polyomaviruses are of particular interest to kidney transplant recipients. They are small DNA viruses that were first discovered in 1971. At present, 13 different types are recognized but the most significant for renal transplant patients is BK polyomavirus (BKPyV), the cause of BKPyV-associated nephropathy (BKVAN). Furthermore, this virus can lead to hemorrhagic cystitis and ureter stenosis [1], [2]. To put it in a nutshell, BKPyV is the most important polyomavirus affecting renal transplant recipients, and adequate management of this infection may significantly impact on allograft survival. The general population is exposed to BKPyV during childhood, and 80–95% of the adults are seropositive. The virus persists in different cells from which it can be reactivated. Sometimes the infection may be transmitted with the allograft [1]. Although BKPyV has been detected in patients with heart or liver transplantation and patients with human immunodeficiency virus (HIV) infection or intestinal inflammatory disease, BKVAN is mainly described in renal transplant recipients [1], [3], [4], [5], [6].

BKVAN is seen in approximately 5% of renal transplant recipients and can lead to chronic allograft failure or even graft loss in up to 50% of cases. Some of the proposed risk factors include older age due to waning immunity, human leukocyte antigen (HLA) mismatches, acute rejection, steroid therapy and maintenance immunosuppression with tacrolimus [1], [7]. However, the common surrogate to all these factors is BKPyV viremia [1], [8].

The infection (also reactivation is possible) is initially asymptomatic, so surveillance programs are essential. The diagnosis then is based on quantitative polymerase-chain-reaction (PCR) in plasma (viremia) and urine (viruria) in the presence of acute renal failure. Unfortunately, no effective therapy is available [1].

Consequently, we aim to summarize the strategies to tackle BKVAN in kidney transplant patients from current guidelines, show results from recent randomized-controlled studies (RCT) for therapy and introduce ongoing trials in this book chapter.

2 Methods

Firstly, we searched the current guidelines on BKVAN screening and treatment, namely the European recommendations of the European Association of Urology (EAU), European Society of Clinical Microbiology and Infectious Diseases Study Group for Infection in Compromised Hosts (ESGICH), KDIGO (Kidney Disease Improving Global Outcome), Clinical practice guidelines for the care of kidney transplant recipients and the American Society of Transplantation Infectious Diseases Community of Practice.

Secondly, an evidence analysis was performed with a literature search in MEDLINE via PubMed for the period from January 2016 to 25th May 2021 [9]. We used the MeSH (Medical Subject Headings) Terms “BK virus” and “Kidney Transplantation”. Only RCTs and quasi-RCTs were included in the present analysis, case reports and reviews of all kinds were excluded. Additionally, we only included studies

about screening or therapy of BKPyV-associated nephropathy following kidney transplantation (and no other transplantations), all other studies, e.g. with BKPyV-associated hemorrhagic cystitis, were excluded. Furthermore, we followed the recommendations provided in the PRISMA reporting guidelines [10].

Thirdly, we searched ClinicalTrials.gov for ongoing RCTs and quasi-RCTs about surveillance and treatment of BKPyV-associated nephropathy following kidney transplantation with the term “BK virus nephropathy” on 27th May 2021.

3 Results

3.1 Surveillance and treatment of BKPyV-associated nephropathy – recommendations in current guidelines in kidney transplantation

European recommendations suggest that viremia should be monitored systematically during the first six months after transplantation, but no effective therapy is available at the moment. Immunosuppression should be reduced with a switch to mammalian target of rapamycin (mTOR) inhibitors if possible. Leflunomide, intravenous immunoglobulins, foscavir, brincidofovir and bortezomib have shown promising results in at least some studies of BKVAN treatment [1], [11].

The European Society of Clinical Microbiology and Infectious Diseases Study Group for Infection in Compromised Hosts (ESGICH) focuses on their recommendations on special therapies to treat the BKPyV infections in the immunocompromised host [12]. To give an example, leflunomide is a potent inhibitor of human dihydroorotate dehydrogenase and is approved to treat rheumatoid arthritis. Its immunosuppressive effects on T and B lymphocytes are through the selective inhibition of the mTOR signaling pathway. Moreover, an in-vitro inhibition of BKPyV viral DNA synthesis has been reported [13], [14], [15], [16], but ESGICH recommendation does not currently recommend leflunomide as a first-line treatment owing to the lack of definitive evidence (grade B, III) [12].

However, KDIGO Clinical practice guidelines for the care of kidney transplant recipients recommend an extended screening: Mostly, BKVAN occurs in the first two years after transplant with only 5% of cases occurring between two and five years after transplant. Accordingly, the timing and frequency of testing in recommended screening algorithms should reflect these data and balance the cost of screening with the potential to prevent BKVAN. Furthermore, it is stated that screening can reduce graft losses, because a reduction of immunosuppression can be done earlier. Still, the treatment recommendations for biopsy-proven BKVAN are unsatisfactory: reduction of immunosuppression does appear to have some impact on BKVAN, though variable rates of graft loss attributable to BKVAN have been reported even when reduction of immunosuppression has been employed. A common practice of immunosuppressive dose reduction is a withdrawal of antimetabolite (azathioprine or mycophenolate-mofetil) and reducing calcineurin inhibitors dosage by 50% [17], [18].

The newest guideline recommendations were published in 2019 by the American Society of Transplantation Infectious Diseases Community of Practice. They recommend screening for BKPyV viremia monthly, until month nine, and then every three months until two years post-transplant. Extended screening after two years may be considered in pediatric patients. Stepwise immunosuppression reduction is recommended for BKPyV viremia >1,000 copies/ml. Since properly randomized trials are lacking, there is no general recommendation for switching to certain immunosuppressive drugs [19].

3.2 Recent RCTs for surveillance and treatment of BKPyV-associated nephropathy in kidney transplantation

The literature search for primary studies yielded 561 results. Finally, two RCTs were included with a total of 240 patients (figure 1) [20], [21]. Table 2 shows the main characteristics, interventions, endpoints and results of the two studies included.

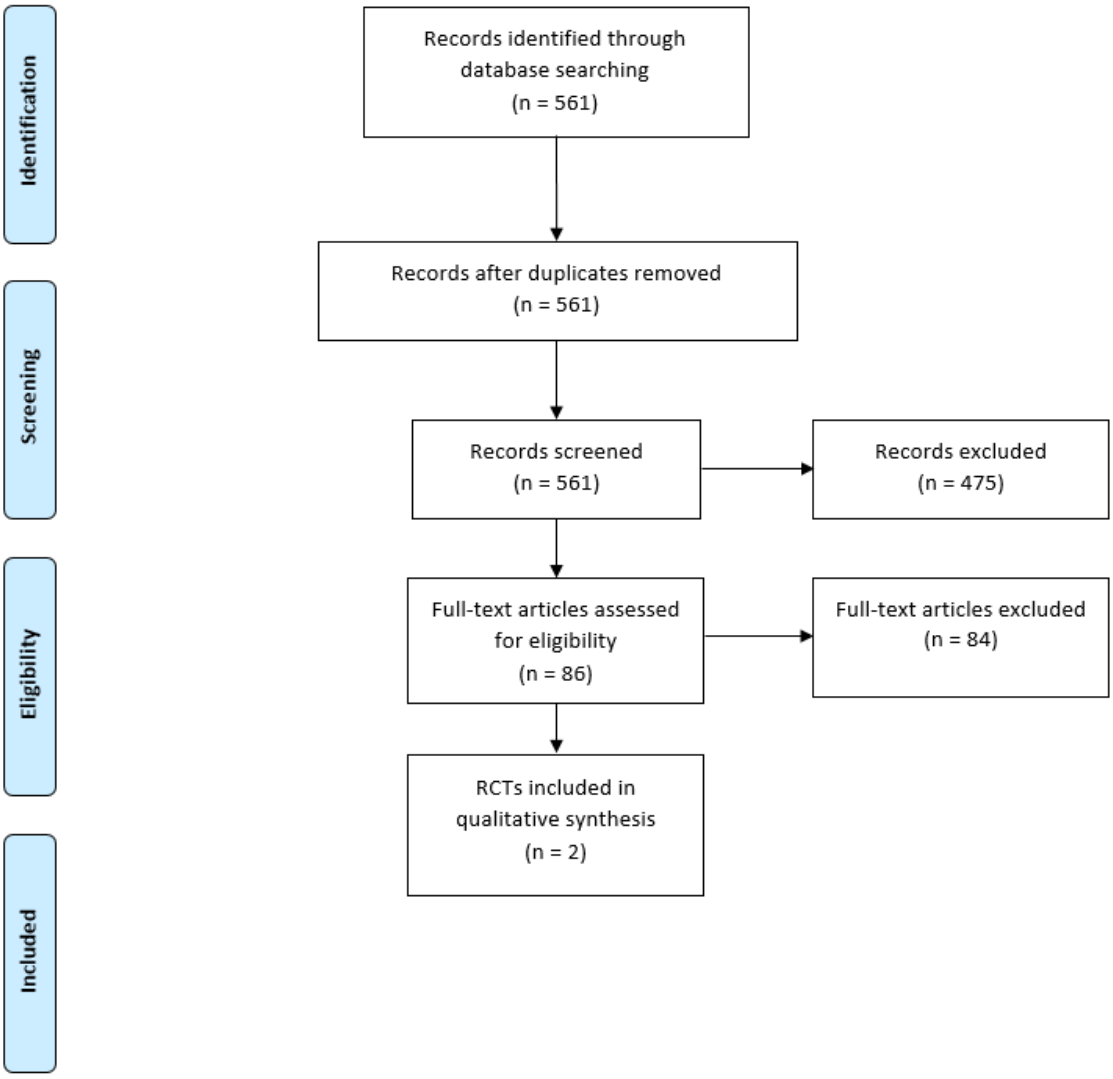

Figure 1: PRISMA Flowchart

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Table 2: Overview and characterization of all included randomized controlled trials (n = 2)

Reference	Wojciechowski et al., 2017 [20]	Patel et al., 2019 [21]
Study Design	Prospective single-center, randomized, open label pilot trial	Prospective, randomized, double-blind, placebo-controlled trial
Evidence	SIGN: 1-	SIGN: 1+
Participants	40 patients, randomized in 1:1 manner; 11 patients in everolimus and 8 patients in MMF group reached primary endpoint	200 kidney transplant recipients 2:1 (133 treatment group; 67 placebo group)
Intervention	MMF withdrawal with conversion to everolimus versus 50% reduction of MMF dose for treatment of BKPyV after kidney transplantation	250 mg ciprofloxacin twice daily oral vs. placebo for 3 months
Endpoints	Primary endpoint was a >50% reduction of BKPyV viruria or clearance of viremia at 3 months post-randomization	Primary endpoint safety and efficacy of ciprofloxacin for the prevention of BKPyV viremia in kidney transplant recipients; first 6 months post-transplant
Main Results	11 patients reached primary endpoint in everolimus and 8 in MMF group (p = 0.53). Of those with BKPyV viremia at time of enrolment, 8 of 16 and 5 of 15 cleared the viremia by month 3 in the everolimus conversation and MMF group (p = 0.47)	Higher rates of BKPyV viremia (23.3% vs. 11.9%; p = 0.06) and BKPyV nephropathy (5.8% vs. 1.5%; p = 0.26) remained at 12 months in the ciprofloxacin group. Ciprofloxacin use was associated with significantly higher rate of fluoroquinolone-resistant gram-negative infections (83.3% vs. 50%; p = 0.04).
Authors Conclusions	Conversion from MMF to everolimus in BKPyV infection demonstrated a trend toward viral clearance, but did not reach statistical significance.	A 3-month course of ciprofloxacin was ineffective at preventing BKPyV viremia in kidney transplant recipients and was associated with an increased risk of fluoroquinolone-resistant infections.

SIGN = Scottish Intercollegiate Guidelines Network; MMF mycophenolate mofetil; BKPyV = BK Polyomavirus

Wojciechowski et al. performed an RCT about a switch in immunosuppression from mycophenolate mofetil (MMF) to everolimus in BKPyV, but this failed to show significant viral clearance [20]. On the whole, a switch from MMF to everolimus cannot be recommended to treat BKPyV-associated nephropathy, but the study is underpowered. Additionally, Patel et al. had also negative results for a 3-month course of ciprofloxacin to prevent BKPyV viremia [21].

Unfortunately, both current RCTs did not find an effective strategy to tackle BKPyV infection in kidney transplant recipients.

3.3 Ongoing RCTs for surveillance and treatment of BKPyV-associated nephropathy in kidney transplantation

ClinicalTrials.gov was searched for ongoing trials (RCT) about intervention BKPyV nephropathy, eleven registered studies have been identified. Two RCTs were still ongoing and recruiting. One trial from France named “Multicenter randomized two-arms study evaluating the BK viral clearance in kidney transplant recipients with BK viremia”. This study also used everolimus as a drug and has the NTC number 03216967. Another RCT from the United States uses a new drug called viralym and is named “Study of viralym-MLYR105 in kidney transplant recipients with BK viremia (NTC 04605484)”.

4 Further research

There is a lack of evidence for screening and adequate therapy of BKPyV infections, especially BKPyV-associated nephropathy, in kidney transplant patients. High-quality RCTs are missing and there are not many ongoing RCTs. The most knowledge on this topic arises from retrospective case series. Consequently, further studies are warranted, especially RCTs about the treatment and switch of immunosuppression. That is why it is difficult to give clear recommendations.

Luckily, we can learn from experimental retrospective and prospective studies and plan proper RCTs to solve the problem. There is evidence from experimental and clinical studies that virus-specific T cells could be used to monitor and treat BKPyV infection [7], [22], [23], [24]. Furthermore, other immunological targets, like pro-inflammatory cytokines could be promising approaches to treat BKPyV disease [25].

In summary, RCTs for screening and treating of BKVAN about virus-specific T cells and targeting the immune response are most promising and also highly needed.

5 Conclusions

BKPyV is the most important polyomavirus in renal transplant recipients and leads mostly to BKVAN. This disease has a high impact on allograft survival. Unfortunately, an optimal screening strategy for viruria and viremia is missing. Furthermore, there is no established therapy or even a therapy that can be highly recommended. Best evidence is summarized 2019 by the American Society of Transplantation Infectious Diseases Community of Practice. They recommend screening for BKPyV viremia monthly until month nine, and then every three months until two years post-transplant. Extended screening after two years may be considered in pediatric patients. Stepwise immunosuppression reduction is recommended for BKPyV viremia >1,000 copies/ml. In our opinion, this strategy should be performed.

Since new high-quality research is also sparse, research in this field is warranted and necessary. Promising new targets for further evaluation in research are virus-specific T cells and targeting the viral immune response.

6 Conflict of interest

Both authors declare that they have no conflict of interest regarding this manuscript.

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Citation note: Schneidewind L, Kranz J. Viral urological infections in kidney transplantation: BK polyomavirus (BKPyV)-associated diseases. Version: 2021-12-10. In: Bjerklund Johansen TE, Wagenlehner FME, Matsumoto T, Cho YH, Krieger JN, Shoskes D, Naber KG, editors. Urogenital Infections and Inflammations. Berlin: German Medical Science GMS Publishing House; 2017-. DOI: 10.5680/lhuii000069