Management of BK-virus infection – Swedish recommendations

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ABSTRACT

BK-virus (BKV) associated nephropathy (BKVAN) and BKV associated haemorrhagic cystitis (HC) are complications of BKV infection/reactivation in renal and allogeneic haematopoietic stem cell transplantation (HSCT) patients, respectively. The task of how to manage these diseases was given to the chair by the Swedish Reference Group for Antiviral Therapy (RAV). After individual contributions by members of the working group, consensus discussions were held in a meeting on 23 January 2018 arranged by RAV. Thereafter, the recommendations were published in Swedish on November 2018. The current translation to English has been approved by all co-authors. High BKV serum levels suggest an increased risk for BKVAN and potential graft failure. For detection of BKVAN, careful monitoring of BKV DNA levels in serum or plasma is recommended the first year after renal transplantation and when increased creatinine serum levels of unknown cause are observed. Notably, a renal biopsy is mandatory for diagnosis. To reduce the risk for progression of BKVAN, there is no specific treatment, and tailored individual decrease of immunosuppression is recommended. For BKV-HC, BKV monitoring is not recommended, since BK-viruria frequently occurs in HSCT patients and the predictive value of BKV in plasma/serum has not been determined. However, the risk for BKV-HC is higher for patients undergoing myeloablative conditioning, having an unrelated, HLA-mismatched, or a cord blood donor, and awareness of the increased risk and early intervention may benefit the patients. Also for BKV-HC, no specific therapy is available. Symptomatic treatment, e.g. forced diuresis and analgesics could be of use.

KEYWORDS
BKV transplantation immunosuppression haemorrhagic cystitis BKVAN management
**Background**

Infections with BK-virus (BKV) are common and >80% of all adults have antibodies against BKV as a result of a previous infection [1-4]. It is assumed that BKV transmission occurs through the respiratory tract or by faecal-oral transmission. BKV is transmitted through solid organ transplantation, usually in the context of a renal organ transplant.

After an asymptomatic primary infection, generally occurring in early childhood, the virus establishes latency, especially in the tubular cells of the kidney. Upon immunosuppression, BKV is frequently activated thereby causing inflammation of the urinary tract and the kidneys in particular. In rare situations, other organs may also be affected. Clinical manifestations of BKV are primarily observed in patients previously undergoing renal, or allogeneic haematopoietic stem cell transplantation (HSCT) [3,4].

**BKV infection in organ transplant patients**

In renal transplant patients, both primary BKV infection and reactivation of latent BKV infection may lead to the development of BKV-associated nephropathy (BKVAN), which in turn may result in progressive dysfunction of the graft, and ultimately, the loss of the renal transplant [4]. BKVAN is rare in other solid organ transplanted patients, but it has been described, and the same accounts for BKV-associated haemorrhagic cystitis (HC), ureteral stenosis, pneumonia, encephalitis and retinitis [3,4].

Reactivation of BKV and the detection of BKV DNA in the urine and blood are frequently reported after renal transplantation. BK-viruria is found in 30–40% of the patients, and BK-viraemia in up to 29% of all renal transplanted patients, with the highest incidence of viraemia 3–6 months after transplantation [5-7]. BK-viraemia and BKVAN may occur late after transplantation and should be considered upon renal dysfunction.

**BK-virus-associated nephropathy**

It has been reported that 5–10% of all renal transplanted patients develop BKVAN, with the highest incidence between 5 and 13 months after transplantation, and with 95% of all cases occurring within 2 years after transplantation [5-7]. The variation in frequency of viruria, viraemia and BKVAN in different reports is most likely due to differences in the immunosuppressive treatment of the patients, how the patients are monitored and which PCR method is used. BKVAN does generally not result in early symptoms, although an increase in serum creatinine may be the first indication. Without decreasing immunosuppression more than 90% of the patients with BKVAN will develop a decrease in their renal function, with a loss of the graft in half the cases.

The most important risk factor for BKVAN is the immunosuppressive regimen, in which the total intensity of immunosuppression, but also the individual drugs are of importance. Other possible risk factors for BKVAN are BKV incompatibility (e.g. the combination of a BKV seropositive donor and a BKV seronegative recipient), an on-going BK-viraemia in the donor, an elderly donor

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**Table 1. Facts: evidence- and recommendation grading**

<table>
<thead>
<tr>
<th>Quality grading of evidence</th>
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<tbody>
<tr>
<td><strong>1a</strong> Systematic analysis of randomized controlled studies with homogeneity</td>
</tr>
<tr>
<td><strong>1b</strong> At least one large randomized controlled study.</td>
</tr>
<tr>
<td><strong>1c</strong> ‘All or nothing’ is ascertained when all patients died before treatment was available, but some survived after treatment, or – some survived after treatment, but after treatment all survive.</td>
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<tr>
<td><strong>2a</strong> Systematic analysis of cohort studies with homogeneity</td>
</tr>
<tr>
<td><strong>2b</strong> Individual cohort studies, including randomized controlled studies with low evidence value (poor quality, wide confidence intervals, low inclusion of some sub-groups in a study, etc.).</td>
</tr>
<tr>
<td><strong>2c</strong> ‘Outcome Research’</td>
</tr>
<tr>
<td><strong>3a</strong> Systematic analysis of case-control studies with homogeneity</td>
</tr>
<tr>
<td><strong>3b</strong> Individual case-control studies</td>
</tr>
<tr>
<td><strong>4</strong> Case series with case-control studies and cohort studies with low quality</td>
</tr>
<tr>
<td><strong>5</strong> Expert opinions without critical analysis or without being based on physiological findings, etc.</td>
</tr>
</tbody>
</table>

**Grading of recommendations**

- **A** Based on quality grading of evidence 1a, b or c
- **B** Based on quality grading of evidence 2a, b or c, 3a or b
- **C** Based on quality grading of evidence 4
- **D** Based on quality grading of evidence 5

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(>65 years of age), a male recipient, and a high degree of HLA mismatching [8].

**Monitoring and microbiological diagnostics**

For early detection of BK-viraemia, before BKVAN has developed, monitoring of BKV in plasma or serum during the first 1–2 years after renal transplantation is recommended (recommendation grade B) (Table 1). In addition, BKV should also be monitored in plasma or serum when an increased serum creatinine level cannot clearly be explained by other causes. Also patients that are treated for an acute graft rejection (and have therefore received intensified immunosuppression) should be carefully monitored for a potential BKV infection/reactivation.

Schedules for monitoring of BKV infection:

- The standard patient: Monitor the presence of BKV in plasma or serum 3, 6, 9 and 12 months after transplantation.
- Patients with intensified immunosuppression (e.g. anti-lymphocyte globulin, rejection treatment or increased general immunosuppression): Earlier, as well as more frequent and prolonged monitoring of BKV in plasma or serum than for the standard patient should be considered.

In addition, analysis of BKV DNA in serum/plasma should always be considered upon an increase of serum creatinine, that does not have any other obvious explanation, irrespective of time after transplantation. The risk to develop BKVAN is high when >10,000 BKV DNA copies/mL are observed in serum or plasma. However, BKVAN can occur (and can never be excluded) in patients with lower BKV levels (1000–10,000 BKV DNA copies/mL in serum/plasma) [5,9]. Of note, the levels of BKV DNA can vary between different sample material (plasma, serum) and between different laboratories.

**Morphological diagnostics**

A renal biopsy is mandatory to verify the diagnosis of BKVAN and should be performed upon increasing serum-creatinine levels and/or the finding of >10,000 BKV DNA copies/mL in serum/plasma. The morphological findings of BKVAN in the kidney vary depending on when after transplantation the infection is diagnosed. The diagnosis is based on immunohistochemistry using antibodies directed against SV40 (which in turn...
cross-react with BKV) (Figure 1). BKVAN is graded into classes 1–3, depending on the grade of fibrosis and the numbers of infected cells [10]. In biopsies, it may be difficult to distinguish between BKVAN in the absence vs. the presence of acute rejection. The morphology may actually be quite similar. The presence of inflammation in arteries (endarteritis) and/or microvascular inflammation suggests the presence of an acute rejection together with BKVAN.

Management/treatment of BKVAN

Today, there is no specific antiviral therapy against BKV infection, and the primary treatment strategy is to decrease immunosuppression (recommendation grade B).

At serum/plasma levels of 1000–10,000 BKV DNA copies/mL, a decrease of immunosuppression can be considered (recommendation grade D) (Table 1), but the risk for rejection should always be considered.

If serum/plasma levels are >10,000 BKV DNA copies/mL, or having a confirmed BKVAN, immunosuppression should be reduced (recommendation grade B). There is no generally accepted regimen for reduction of immunosuppression, which therefore needs to be done in collaboration with a transplantation specialist clinic, and decreasing immunosuppression should be tailored for each patient according to the clinical situation.

Possible alternatives:

- Lower the dose of tacrolimus, with the aim to lower its concentration by 25–50%.
- Lower the dose of glucocorticoids.
- Lower the dose of mycophenolate mofetil usually by 50%.

Upon an insufficient effect on the levels of BKV DNA in serum/plasma, the doses of tacrolimus or mycophenolate mofetil can be reduced even more, with the possible complete discontinuation of mycophenolate mofetil and glucocorticoid treatment. Immunosuppression with mTOR-inhibitor has in some studies been associated with lower rates of BKV [11], and changing mycophenolate mofetil to an mTOR-inhibitor can also be considered.

If treatment instead includes cyclosporine A or azathioprine, the doses of these agents can be reduced correspondingly.

The levels of BKV DNA usually decrease slowly, and viral levels can be analysed with 2–4-week intervals. Upon no change or increased levels of BKV DNA, an additional decrease of immunosuppression in line with the above should be considered. The duration of BKV DNA level monitoring is decided individually, and depends mainly on the dynamics of viral level changes, the effects on renal function, and immunological risk. Some patients can have a low BKV DNA level in serum/plasma during long periods without affecting the renal function.

As always, when immunosuppression is reduced, there is an increased risk for a rejection of the graft. The increased risk of graft rejection following reduced immunosuppression necessitates a close follow-up of renal function and consideration/determination of drug levels. A new renal biopsy should be considered if the serum-creatinine level goes up during the adjustment of the patient’s immunosuppression.

Medical treatment of BKVAN

There is no strong evidence for antiviral treatment of BKV. Several agents have been tried, although not in the context of controlled studies. When a decrease of immunosuppression has no effect, or is not possible due to a concomitant acute graft rejection, alternative treatment needs to be considered. This should always be done in collaboration with an experienced transplant physician.

- Cidofovir has in some cases been reported to decrease the risk of renal dysfunction and graft rejection in the context of BKVAN [12–14]. However, randomized controlled studies do not seem to exist. Based on existing data, treatment with cidofovir cannot be recommended, but neither can its usefulness be excluded (recommendation grade C) (Table 1).
- Brincidofovir is a prodrug of cidofovir. It results in higher concentrations of cidofovir, but less renal toxicity [15]. There are a few case reports where brincidofovir has been used for BKVAN. Brincidofovir however, has not been licensed in Sweden, and is currently not available for ‘compassionate use’ for the indication BKVAN.
- Leflunomide has immunosuppressive qualities and has been studied as an alternative to mycophenolate mofetil for inhibiting immune responsiveness during organ transplantation [16]. Leflunomide also has an antiviral effect in vitro against BKV, and some studies have reported the stabilization of renal function upon treatment of BKVAN with leflunomide. On the other hand, it has not been possible to show that
leflunomide has any additional effect other than decreasing immunosuppression [17]. Leflunomide is used in clinical practice at some transplantation centres, but due to lack of scientific documentation it cannot be recommended.

- Quinolones have activity in vitro against BKV. In two controlled studies of renal transplant patients, when giving quinolone as a prophylactic drug, no effect was observed [18,19]. This was later confirmed with a meta-analysis of eight studies, where there was no prophylactic effect of quinolones on BKVAN [20]. Quinolones can therefore not be recommended for treatment or prophylaxis against BKV infection (recommendation grade B).
- Intravenous immunoglobulin (IVIG) administration: commercial IVIG contains antibodies to BKV. Studies on IVIG have shown conflicting results and therefore no recommendation can be given.

**BKV infection in association to allogeneic hematopoietic stem cells transplantation**

BKV may induce HC in patients that have undergone an allogeneic HSCT. HC occurs in 2–66% of HSCT patients, depending on type of HSCT, conditioning and the patient’s age. Early HC occurs <1 week after HSCT and is considered being caused by a toxic effect of the conditioning regimen. Late HC occurs >1 week after HSCT, and in general at the time of engraftment, and is regarded to be due to viral infection, most commonly due to BKV reactivation/infection (but can also be due to adenovirus infection and in rare cases infections with herpes simplex virus, cytomegalovirus or JC virus). BKV associated HC (BKV-HC) usually occurs 2–8 weeks (1 week to 6 months) after HSCT. The highest risk for BKV-HC is observed after HSCT with myeloablative conditioning, with an unrelated or HLA mismatched donor, and in HSCT using cord blood donors [21–23].

**Clinical manifestations**

Clinical manifestations of BKV-HC do not differ from those of other HC, and may include dysuria, low abdominal pain, and a variable degree of haematuria. The pain can be severe and haematuria can be extensive resulting in anaemia requiring blood transfusions. Blood clotting may also occur and result in urinary tract obstruction, which in turn can lead to secondary renal failure. The degree of haematuria is graded as: Grade 1: microscopic haematuria; grade 2: macroscopic haematuria; grade 3: macroscopic haematuria with blood clots; and grade 4: renal failure due to urinary tract obstruction. The symptoms usually decrease after 3–5 weeks.

**Diagnosis**

The probability of BKV-HC increases when a triad of clinical symptoms together with haematuria grades II–IV, and the presence BKV in the urine >7 log_{10} copies/mL is found (and with the exclusion of another probable cause of HC). High BKV levels are not specific for BKV-HC, since >80% of HSCT patients secrete BKV in their urines, while only 5–20% develop BKV-HC. However, if BKV is not found in the urine, the negative predictive value is very high. The predictive value of BKV in plasma/serum for BKV-HC is still under debate [17].

**Treatment**

The treatment is primarily symptomatic with forced diuresis and analgesics. In severe cases, irrigation of the urinary bladder is performed. Upon extended bleeding and anaemia, erythrocyte and thrombocyte transfusions are given. Surgery can be necessary upon obstruction of the urinary tract (recommendation grade B). Depending on the risk for graft versus host disease (GVHD), the immunosuppression of each patient should be individualized.

Similar to BKVAN, there is a lack of controlled studies of specific treatment directed against BKV infections and therefore no recommendations can be given.

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**Disclosure statement**

The authors have no conflicts of interest.

**References**


