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ECIL guidelines for the prevention, diagnosis and treatment of BK polyomavirus-associated haemorrhagic cystitis in haematopoietic stem cell transplant recipients

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Objectives: To define guidelines for BK polyomavirus (BKPyV)-associated haemorrhagic cystitis (BKPyV-HC) after paediatric and adult HSCT.

Methods: Review of English literature and evidence-based recommendations by expert consensus.

Results: BKPyV-HC occurs in 8%–25% of paediatric and 7%–54% of adult recipients undergoing allogeneic HSCT. Diagnosis requires the triad of cystitis, macro-haematuria and high urine BKPyV loads >7 $\log_{10}$ copies/mL, and exclusion of other relevant aetiologies. BKPyV viraemia is frequent and may serve as a more specific semiquantitative follow-up marker. No randomized controlled trials are available to inform antiviral prophylaxis or treatment. However, hyper-hydration and/or bladder irrigation showed limited prophylactic value. Fluoroquinolones are not effective for prophylaxis or treatment, but rather increase antibiotic resistance. Hyperbaric oxygen or fibrin glue is marginally effective based on small case series from correspondingly equipped centres. Although cidofovir has been reported to improve and/or reduce BKPyV viraemia or viruria, the current data do not support its regular use.

Conclusions: BKPyV-HC remains a disabling unmet clinical need in HSCT that requires novel approaches supported by proper clinical trials.

Introduction

Haemorrhagic cystitis (HC) is a significant complication after HSCT, the incidence ranging from 2% to 66% according to the type and procedure of HSCT and the age of the patients. HC contributes to post-HSCT morbidity by prolonging hospital stay and severely worsening the quality of life, but its role in increasing post-HSCT mortality is controversial.[1–4] Several factors contribute to the appearance of HC, which is also reflected in the classification based on the time of onset in the post-HSCT course. Early-onset HC is defined as occurring within <1 week of HSCT, typically during or within 48 h of conditioning and is considered to result largely from direct toxicity of the conditioning regimen on the urothelial mucosa, particularly from drug metabolites and radiotherapy. Urothelial damage is worsened by inflammation leading to

haemorrhagic leakage aggravated by impaired coagulation and thrombocytopenia.

Late-onset HC, on the other hand, usually starts around the time of neutrophil engraftment, particularly in the setting of allogeneic HSCT, but can be observed from 2 weeks up to the first 6 months post-HSCT,[1,5–10] and is mostly associated with high-level BK polyomavirus (BKPyV) replication. BKPyV is one of 13 known human polyomavirus species.[4,11] The discovery of BKPyV dates back to 1971 when it was isolated from the urine of the kidney transplant patient B.K., shedding epithelial cells with nuclear viral inclusions, so-called 'decoy cells'.[11,12] A consistent link of BKPyV to disease was missing until identifying its role in HC after HSCT,[6,7] and nephropathy after kidney transplantation.[13–15] We summarize the biology, epidemiology and clinical characteristics of BKPyV-HC in haematology patients and provide recommendations that were discussed and approved at the 6th meeting of the European Conference on Infectious Disease in Leukaemia (ECIL-6)[16] held on 11–12 September 2015 in Sophia Antipolis, France.

Background

ECIL is a joint initiative supported by the European Leukaemia Network, the Infectious Diseases Working Party of the European Association for Blood and Marrow Transplantation (IDWP-EBMT), the Infectious Disease Group of European Organization for Research and Treatment of Cancer, and the Immunocompromised Host Society (ICHS). For the 6th edition, the ECIL Board decided to address BKPyV and endorsed a panel of experts to review the paediatric and adult literature and propose guidelines for affected haematology patients. The panel included two members of the ECIL Board (S. C., H. E.) and four European experts on BKPyV [T. D., C. H. R., M. K., H. H. H. (IDWP-EBMT member and current ICHS president elect)]. The ECIL-6 Consensus Conference was attended by 55 participants from 24 countries (18 European countries, 6 non-European countries). The supporting scientific societies contributed to the selection of participants by proposing 10 members each, whereas the ECIL board invited the remaining participants based on their scientific and/or clinical expertise in managing infectious complications in haematology patients.

Literature search

The literature search was performed by S. C. and A. P. using the following terms in PubMed: BK polyomavirus, haemorrhagic cystitis, and haematopoietic peripheral stem cell or bone marrow, or cord blood transplantation. Studies published until 31 August 2015 regarding biology and mechanism of pathogenesis of BKPyV as well as diagnosis, prophylaxis, and therapy of BKPyV-HC were identified, missing papers were added, and all were reviewed by all panel experts. The results of the literature search and a preliminary draft of recommendations for diagnosis, prophylaxis and treatment of BKPyV-HC were presented to the ECIL-6 conference for discussion and approval. The final recommendations were graded according to the ECIL-6 evidence-based medicine grading system, presented in Table 1.[17] An update of the search was performed on 24 January 2017, but was not found to change the current recommendations. A schematic representation of the BKPyV virion structure is shown in Figure 1 and its genome organization is shown in Figure S1 (available as Supplementary data at *JAC* Online).

Table 1. Grading systems used at ECIL-6 for levels of evidence and strength of recommendations

Grading	Criteria
Quality of evidence	
I	Evidence from at least 1 properly designed, randomized, controlled trial (oriented at primary endpoint of the trial).
II (r, t, h, u, a)[a]	Evidence from at least 1 well-designed clinical trial (including secondary endpoints) without randomization; from cohort or case–control studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies or report of expert committees.
Strength of recommendation	
A	ECIL strongly supports a recommendation for use.
B	ECIL moderately supports a recommendation for use.
C	ECIL marginally supports a recommendation for use.
D	ECIL supports a recommendation against use.

[a]Level II evidence abbreviations: r, meta-analysis or systematic review of randomized controlled trial; t, transferred evidence, i.e. results from different patient cohorts or similar immune status situation; h, comparator group was historical control; u, uncontrolled trials; a, published abstract presented at an international symposium or meeting.

An overview of BKPyV biology, immune response and disease is given in the Supplementary data.

BKPyV-HC pathogenesis, clinical presentation and diagnosis

BKPyV-HC is rare in haematology patients other than those undergoing allogeneic HSCT. BKPyV-HC occurs between 2 and 8 weeks (range 1 week–6 months) after HSCT, typically starting during the peri-engraftment period, and should be distinguished from an early-onset HC (<1 week after HSCT) caused by toxicity of the conditioning regimen such as cyclophosphamide and busulfan, or total body irradiation.[18–21] In HSCT patients, high-level BKPyV-viruria >7 $\log_{10}$ genome equivalents (gEq)/mL is associated with an increased risk for BKPyV-HC.[22–24] However, high-level BKPyV viruria is not specific for BKPyV-HC, as >80% of all HSCT patients develop high-level BKPyV viruria, while only 5%–20% develop BKPyV-HC.[4,21] High-level BKPyV viruria and BKPyV-HC are mainly observed in allogeneic HSCT patients receiving full conditioning and an unrelated human leucocyte antigen mismatched donor.[25–27] Adenovirus, herpes simplex virus, JC polyomavirus, cytomegalovirus (CMV) and other infectious (bacteria, parasite) and non-infectious aetiologies

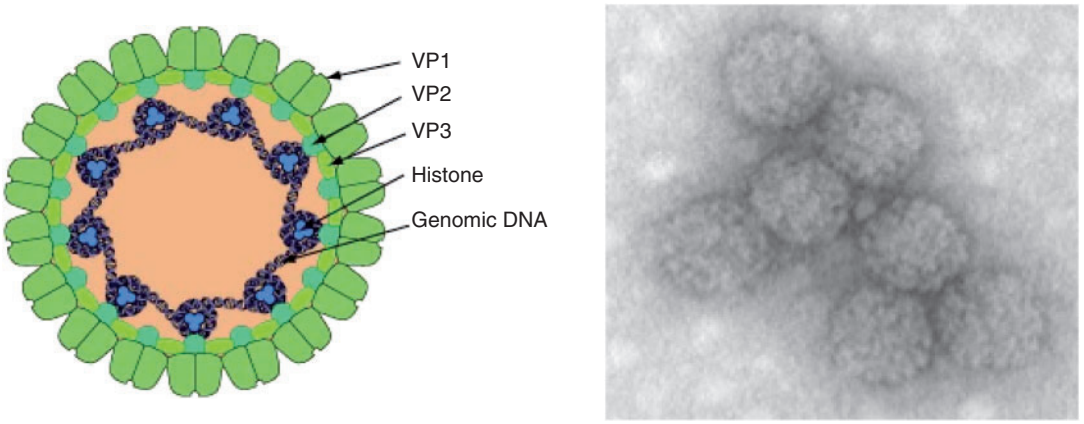

Figure 1. BK polyomavirus structure. Polyomavirus virions are small (40–45 nm), non-enveloped, and environmentally stable. Capsid consists of the structural protein VP1 on the outside and VP2 and VP3 proteins on the inside accommodating the circular 5.1 kb double-stranded DNA genome. Diagram on left summarizes the structure of the virus. Image on right is a transmission electron micrograph of purified BK polyomavirus after negative staining with 2% uranyl acetate. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 2. Triad of diagnostic criteria for BKPyV haemorrhagic cystitis

Criterion	Definition
1	clinical symptoms/signs of cystitis, such as dysuria and lower abdominal pain
2	haematuria grade 2 or higher
3	BKPyV viruria of >7 $\log_{10}$ copies/mL[a]

[a]Plasma viral loads of >3–4 $\log_{10}$ copies/mL are found in more than two-thirds of episodes of BKPyV haemorrhagic cystitis.

(bleeding disorders with or without low platelet count, primary or metastatic neoplasia, vesical catheter or ureteric stenting) may also cause HC, and must be excluded for appropriate diagnosis and management.[4,28–30] The severity of haematuria is commonly described as microscopic (grade 1); macroscopic (grade 2); macroscopic with clots (grade 3); or macroscopic with clots and post-renal failure secondary to urinary tract obstruction (grade 4).[4,21] Thus, the diagnosis of BKPyV-HC requires the triad of: (i) clinical symptoms/signs of cystitis, such as dysuria and lower abdominal pain; (ii) a haematuria grade 2 or higher; and (iii) the demonstration of BKPyV viruria, with viral loads of >7 $\log_{10}$ copies/mL (Table 2). Plasma viral loads of >3–4 $\log_{10}$ copies/mL are seen in more than two-thirds of allogeneic HSCT recipients with BKPyV-HC[1,10,31–33] and declining plasma loads have been found to correlate with clinical recovery. The pathogenesis of BKPyV-HC is not well understood as similarly high urine BKPyV loads are found in kidney transplant patients, most of whom do not develop cystitis or macro-haematuria.[34,35] Rather, a sequence of events has been suggested, starting with subclinical urothelial damage by the conditioning regimen, high-level BKPyV replication leading to viral denudation of the pre-damaged, regeneration-impaired urothelial lining and urinary leakage in submucosa followed by haemorrhagic exacerbation with abundant inflammatory cell infiltrates following allogeneic stem cell engraftment.[4,21,36] Indeed, conditioning involving cyclophosphamide, busulfan and total body irradiation has been implicated in different studies,[25,26,29] and the pronounced toxic, inflammatory properties of cyclophosphamide and its metabolite acrolein are supported by clinical and experimental studies.[37–39] Following the widespread use of hyperhydration, the exposure of the bladder urothelium to toxic metabolites can be reduced, and acute toxicity with early-onset HC has become rare.[4,21] Nevertheless, subclinical urotoxic exposure may still cause damage with rarefication of the urothelial cell layer, which combined with local inflammation stimulates BKPyV replication during impaired antiviral immune control from cytotoxic T cells. Post-engraftment, invading donor immune cells may cause further tissue damage (immune reconstitution inflammatory syndrome).[4] BKPyV-HC generally resolves after 3–5 weeks, but causes significant morbidity, prolonged hospital care with extensive nursing requirements and increases healthcare costs.[3] Moreover, bleeding may be life-threatening requiring urologic interventions including cystectomy and additional complications contributing to, e.g. renal failure may result in fatal outcome. Identifying patients at risk could therefore be an important step for preventing or pre-emptively intervening in the development of BKPyV-HC.[4]

Epidemiology and risk factors for BKPyV-HC

The observed incidence of BKPyV-HC is 8%–25% and 7%–54% in paediatric and adult patients, respectively, being higher after allogeneic than after autologous HSCT and particularly after haploidentical HSCT with post-transplant exposure to cyclophosphamide as prophylaxis for graft versus host disease (GVHD) (Table 3).[1,3,23,25,33,40–48] The lower incidence in autologous HSCT may reflect the role of immunosuppression and GVHD in allogeneic HSCT for BKPyV-HC pathogenesis.[5] Table 4 shows the main risk factors of BKPyV-HC. High-level BKPyV viruria and viraemia have both been reported as predictive factors for BKPyV-HC in patients receiving allogeneic HSCT.[1,3,8,9,23,25,30,33,40,41,49] In a paediatric study a urine BKPyV load of $>10^7$ gEq/mL had a sensitivity of 86% and specificity of 60%, while a blood BKPyV load of $>10^3$ gEq/mL had a sensitivity of 100% and a specificity of 86% for HC, respectively.[1]

Table 3. Incidence of BKPyV-HC according to type of transplant and patient age

Setting	Percentage incidence, median (range)	No. of patients	References
Allo-HSCT	13 (7–25)	2096	1,23,3,10,25,33,41–45,76
Haplo-HSCT with post-transplant cyclophosphamide exposure	24.5 (19–54)	179	46,91,47,48
Auto-HSCT	0	118	43
Adults	16 (7–54)	1413	3,46,42,45,47,48,76,91
Children	18 (8–25)	724	1,40,33,41,43,44
Adult and paediatric population	16 (13–19)	206	23,25

Allo-HSCT; allogeneic HSCT; Haplo-HSCT: haploidentical HSCT; auto-HSCT, autologous HSCT.

Table 4. Summary of the main risk factors for development of BKPyV-HC

Risk factor	No. of studies	HSCT type/total no. patients	References
BKPyV positivity in			1,8,9,23,25,30,33,40,41,49
urine	6	Allo-HSCT/507	
blood	5	Allo-HSCT/426; Auto-HSCT/25	
Other viraemia			30,33
CMV	1	Allo-HSCT/50	
HHV-6	1	Allo-HSCT/88	
Stem cell source			
UCB	2	Allo-HSCT/814	3,45
PBSC	1	Allo-HSCT/323	3
Type of donor: unrelated	1	Allo-HSCT/175	25
Type of aGVHD			9,23,45,49
aGVHD	1	Allo-HSCT/90	
II–IV grade	1	Allo-HSCT/117	
III–IV grade	1	Allo-HSCT/491	
aGVHD and high BKPyV viruria	1	Allo-HSCT/31	
Type of conditioning			
ATG	1	Allo-HSCT/117	9
cyclophosphamide	1	Allo-HSCT/200; Auto-HSCT/118	43
high-dose busulfan	1	Allo-HSCT/117	44
myeloablative conditioning	1	Allo-HSCT/175	25
Age at transplant: >7 years	1	Allo-HSCT/88	33

Allo-HSCT, allogeneic HSCT; UCB, umbilical cord blood; PBSC, peripheral blood stem cells; aGVHD, acute GVHD; ATG, serum anti-thymocyte globulin.

BKPyV IgG levels have been low or undetectable in paediatric HSCT patients with BKPyV-HC,[10] but the current data do not permit the use of BKPyV antibody titres to predict risk of BKPyV-HC. Single studies have reported CMV or human herpesvirus (HHV)-6 viraemia as independent risk factors for BKPyV-HC.[30,33] Furthermore, the stem cell source affects the risk of BKPyV-HC. Patients receiving cord blood units and peripheral blood stem cells have a higher risk of developing BKPyV-HC compared with patients receiving bone marrow grafts.[3,45] Unrelated donors and GVHD have been associated with BKPyV-HC in line with the notion that the altered allogeneic immune control contributes to pathogenesis.[25,50] Unrelated donors are associated with a higher cumulative incidence compared with mismatched or matched related donors[25] as well as acute GVHD grade II–IV alone or combined with high-level BKPyV viruria.[9,23,49] The intensity of the conditioning regimen was also found to have an impact. Myeloablative conditioning resulted in a higher risk compared with reduced intensity conditioning, with agents such as cyclophosphamide, high-dose busulfan and anti-thymocyte globulin being independent risk factors.[9,25,43,44] Notably, the age of the HSCT recipient was evaluated and patients >7 years of age had a greater risk for BKPyV-HC than younger children.[33]

Prophylaxis for BKPyV-HC

The prevention of HC including BKPyV-HC, has been explored using non-specific measures such as hyperhydration and bladder irrigation (Table 5). In a prospective, randomized study comparing hyperhydration plus forced diuresis with standard hydration plus mesna during the conditioning regimen, the incidence of HC was

Table 5. Level of evidence and recommendations for prophylaxis of BKPyV-HC

	Fluoroquinolones	Hyperhydration (during conditioning)	Bladder irrigation
No. of studies	3	1	1
References	54–56	21	51
Type of study	Retrospective, 2; cohort-prospective, 1.	Prospective, randomized.	Cohort-prospective versus historical control group.
No. of patients	294 (155 ciprofloxacin, 149 no ciprofloxacin).	147 (71 at 2 mL/kg/h + mesna vs 76 at 4 mL/kg/h and forced diuresis).	80 patients vs 40 patients (historical), 3-way Foley catheter used.
Efficacy	Reduction in BKPyV reactivation and HC incidence[54]; no efficacy in reducing rates of clinically significant HC (1 study[56]).	The incidence of HC was similar in the 2 groups (26.8% vs 23.7%).	No significant reduction of HC overall but significant reduction of HC 4 weeks after HSCT; reduction of mean duration of HC and hospitalization.
Toxicity	No adverse effects; beware bacterial resistance.	No adverse effects; beware fluid retention.	No adverse effects; beware, invasive procedure.

similar in the two study arms (26.8% versus 23.7%, respectively).[21] In a recent prospective study, bladder irrigation through a three-way Foley catheter did not result in an overall reduction of HC compared with a historical control group, although the mean duration of HC and of hospitalization was reduced.[51] The main drawbacks of these interventions are the risk of fluid overload for hyperhydration and the invasiveness of three-way Foley positioning. Supported by *in vitro* data demonstrating inhibition of BKPyV replication,[52,53] ciprofloxacin has been evaluated for preventing BKPyV-HC in two retrospective and one prospective cohort study with a total of 294 patients (155 treated with ciprofloxacin versus 149 not treated with ciprofloxacin).[54–56] The results were inconclusive as one study showed only a reduction of BKPyV reactivation, but no difference regarding BKPyV-HC,[54] while the second study reported a reduction of HC,[55] and the third study observed no impact on clinically significant HC.[56] Of note, a randomized, double-blind, placebo-controlled study on 154 kidney transplant patients showed that 3 month prophylaxis with levofloxacin failed to reduce BKPyV viruria or viraemia significantly, but was associated with increased fluoroquinolone-resistant bacterial infections and an increased rate of tendinitis.[57]

Therapy of BKPyV-HC

Cidofovir treatment of BKPyV-HC has been evaluated in 12 retrospective and 2 prospective studies with a total of 210 patients (Table 6). Cidofovir is a nucleotide analogue that inhibits a broad range of DNA viruses, and its active metabolite has a long half-life of 15–65 h that allows administration at weekly intervals. The major drawback is tubular and ocular nephrotoxicity that can be reduced by saline hydration and by probenecid, which inhibits cidofovir uptake into renal tubular epithelial cells. Although there is no agreement regarding dose, modality or frequency of administration, most authors used intravenous cidofovir 3–5 mg/kg/week or bi-weekly together with probenecid to prevent nephrotoxicity. In the absence of probenecid, cidofovir has been administered at a 3–5-fold reduced dose.[58] Disregarding the study heterogeneities, a complete clinical response was reported in 74% of patients, and at least 1 $\log_{10}$ decline in urine viral loads in 38% and in blood viral loads in 84% of patients (Table 6). Mild to moderate increases in serum creatinine concentration were seen in 18% of the patients.[5,9,10,29,32,59] In four retrospective studies, 52 patients were treated with low-dose cidofovir at 0.5–1.5 mg/kg/week without probenecid, and a complete clinical response was observed in 83% of patients, a virological response in urine in 62% and in blood in 67% of cases. Also in this group of patients, a mild to moderate increase in serum creatinine concentration was reported in 20% of patients.[60–63] To overcome the risk of nephrotoxicity, intravesical administration of cidofovir at the dose of 5 mg/kg/week has been reported for 14 patients showing a complete clinical response in 43% of patients and a virological response in ∼50%.[10,32,64,65] The use of leflunomide, an antimetabolite drug with immunomodulatory and antiviral activity, has been reported in two retrospective studies on 19 patients obtaining an overall complete and partial response rate of 63% and 26%, respectively.[66,67] Finally, complete clinical response with partial or complete virological response has been reported for two patients treated with vidarabine and one case treated with oral levofloxacin.[68–70] None of these studies provided a comparison with a control group to estimate a benefit over a spontaneous course and BKPyV-HC clearance.

Other treatments of BKPyV-HC aim at repair and regeneration of the urothelial mucosa through hyperbaric oxygen therapy or by topical application of fibrin glue (Table S1). Hyperbaric oxygen therapy was given to a total of 29 patients in different case reports or case series, with a complete clinical response rate of 86% and reduced urine BKPyV load in 65% of patients.[71–75] The main drawback of hyperbaric oxygen is its limited availability on a larger scale, the requirements for dedicated hyperbaric room facilities, the risk of ear barotrauma/pressure intolerance and claustrophobia linked to the procedure. Finally, topical applications to the damaged bladder mucosa to achieve haemostasis through cystoscopy have been reported in single-centre retrospective series of 35 patients. The complete response rate was 83%.[76] Similarly, several compounds to reduce bleeding have been used in case studies and small series, e.g. FXIII concentrate,[77] intravesical sodium hyaluronate,[78,79] oestrogens[80,81] or choreito extract granules[82] with

Table 6. Summary of studies using cidofovir for the treatment of BKPyV-HC

	CDV iv; 3–5 mg/kg/week with probenecid	CDV iv; 0.5–1.5 mg/kg/week without probenecid	CDV intravesical 5 mg/kg/week
No. of studies	6	4	4
References	[9,10,66,69,59]	[60–63]	[10,69,64,65]
Type of study	retrospective, 4; prospective, 2	retrospective, 4	retrospective, 3; prospective, 1
No. of patients	144	52	14
Efficacy			
clinical	CR (74%)	CR (83%)	CR (43%), PR (7%)
virological	Reduction in BKPyV loads in: urine 38% (26 of 61); blood: 84% (67 of 80).	Reduction in BKPyV loads in: urine: 62% (30 of 48); blood: 67% (8 of 12).	Reduction in BKPyV loads in: urine 55% (5 of 9); stable viral load in 45% (4 of 9).
Toxicity (no. episodes)	Nephrotoxicity (26), myelotoxicity (1).	Transient nephrotoxicity (11).	No adverse effects, beware invasiveness.

CDV, cidofovir, CR, complete response; iv, intravenous; PR, partial response.

response rates between 50% and 100%. Brincidofovir, a lipid conjugate of cidofovir, showed *in vitro*, on primary human urothelial cultures, a potent and long-lasting inhibitory effect on BKPyV replication,[83,84] but no data are available on the clinical use for BKPyV-HC[83] except a single case of BKPyV nephropathy after an allogeneic HSCT.[85] It is conceivable that brincidofovir might be used in the future for symptomatic HC considering the absence of alternative antiviral compounds with a better safety and tolerability profile.

The reduction of immunosuppression has been used successfully in kidney transplant patients to prevent and/or treat BKPyV-associated nephropathy,[86,87] but there is no evidence that it has a favourable risk/benefit ratio in HSCT patients due to the risk of worsening the donor versus host alloreactivity and the severity of GVHD. Unlike for BKPyV-associated nephropathy, there is no documented benefit in using intravenous immunoglobulin preparations for BKPyV-HC (see Table 7).

Cellular therapy for BKPyV-HC

Owing to the lack of an effective, clinically validated antiviral drug for the treatment of BKPyV-HC, cell therapy approaches have been explored. To induce tissue repair and immune modulatory and anti-inflammatory properties, third party mesenchymal stroma cells were infused into seven patients with BKPyV-HC.[88] In five patients, haematuria resolved with few side effects. Subsequently, a prothrombotic effect of mesenchymal stroma cells was reported[89] thus questioning this type of approach. To target BKPyV replication directly, adoptive transfer of virus-specific T cells was reported using PBMCs from 48 stem cell donors for *in vitro* stimulation using pools of overlapping peptide libraries covering 12 different immunogenic proteins from five different viruses, i.e. CMV, Epstein–Barr virus, adenovirus, HHV-6 and BKPyV. BKPyV-specific T cell responses were detected in 28 of the cell lines.[90] Administration to seven allogeneic HSCT recipients with BKPyV replication demonstrated a response in six patients. Three patients with severe BKPyV-HC showed a marked symptomatic and virological response with resolution of haematuria 2–4 weeks post-treatment. No severe toxicity was reported, although a transient episode of severe bladder pain in association with inflammation was seen in one patient and treated with steroids. These results are encouraging and support further, more comprehensive studies.

Conclusions and recommendations

BKPyV-HC remains a challenging complication after allogeneic HSCT with average rates of ∼13%. A BKPyV-HC diagnosis requires the clinical and laboratory triad of cystitis, macrohaematuria and high urine BKPyV loads >7 $\log_{10}$ gEq/mL (**AII h u**), but a significant role of other aetiologies must be excluded. Plasma BKPyV loads >1000 gEq/mL has a role for management and follow-up of triad-positive allogeneic HSCT recipients (**BII h u**). Screening of asymptomatic HSCT patients at risk remains an area of investigation and is presently not recommended, as pre-emptive therapy is not established (**DII**).

BKPyV-HC prophylaxis relies on hyperhydration (**BII t**) and bladder irrigation (**CII t**) aiming at reducing urothelial damage, particularly when using myeloablative conditioning based on cyclophosphamide, busulfan and total body irradiation. Specific antiviral prophylaxis is not available and fluoroquinolones are not recommended given the lack of significant effects on BKPyV replication and HC severity, and the selection of antibiotic resistance (**DII h t**).

BKPyV-HC treatment is based on the best supportive therapy, such as hyperhydration, bladder irrigation, platelet transfusions as needed to reduce bleeding, and pain treatment (**AIII**). The risk/benefit ratio of reduction of immunosuppression is not clear in BKPyV-HC and must be balanced with the risk of worsening or triggering acute GVHD. Antiviral treatment with intravenous cidofovir is controversial due to the absence of randomized controlled studies. Until the availability of safe and effective antivirals, the use of cidofovir may be an option although there is uncertainty of efficacy, the best dose schedule and the need to balance any benefit against its renal side effects (**CII u**). Non-specific measures aimed at speeding the healing process of the damaged urothelial lining such as hyperbaric oxygen therapy or urologic fibrin glue application have been successful in a limited number of uncontrolled studies (**CIII**). No recommendation is possible for several other treatments such as the administration of intravesical sodium hyaluronate, intravenous

Table 7. Summary recommendations for BKPyV-HC

Topic	Grading	Notes
Diagnosis		
quantitative BKPyV viruria in allogeneic HSCT	AII (h u)	High sensitivity and high negative predictive value for a cut-off $\geq 10^7$ genomic copies/mL.
BKPyV viraemia in allogeneic HSCT	BII (h u)	Some authors report a higher specificity and a positive predictive value for a cut-off $>10^3$–10^4 genomic copies/mL.
BKPyV viruria/viraemia screening of asymptomatic HSCT patients	DII	Not recommended outside of clinical studies due to lack of effective pre-emptive treatment.
Prophylaxis		
hyper-hydration during conditioning regimen	BII (t)	To prevent the urotoxic effect on cyclophosphamide and/or busulfan.
bladder irrigation during conditioning regimen	CII (t)	Invasive procedure, discomfort for the patient.
ciprofloxacin	DII (h t)	Little effect on BKPyV replication, no effect on HC.
Therapy		
best supportive therapy (hydration, platelet transfusion, analgesics)	AIII	Aim at higher platelet threshold for transfusions.
cidofovir intravenous	CII (u)	No recommendation on the dose (either 3–5 mg/kg every 1–2 weeks with probenecid or 0.5–1.5 mg/kg 1–3 times/week without probenecid.
fibrin glue application	CIII	Invasive procedure, cystoscopy needed.
hyperbaric oxygen therapy	CIII	Depending on local availability.
intravesical cidofovir, intravesical sodium hyaluronate, intravenous oestrogens, intravenous immunoglobulins, leflunomide, mesenchymal cells, adoptive immune cell therapy	no recommendation	Limited data and/or experimental procedures.

HC, haemorrhagic cystitis; h, historical control group; t, transferred evidence; u, uncontrolled study.

FXIII concentrate, leflunomide, oestrogens, mesenchymal cells and cellular immune therapy because these treatments have only been used sporadically in a very limited number of patients or are still experimental (Table 7). These evidence-based recommendations are applicable for both paediatric and adult patients.

In conclusion, despite much progress in understanding the pathogenesis, epidemiology and risk factors of BKPyV-HC, this complication still represents a disabling unmet clinical need with limited prophylactic and therapeutic options. To overcome this deficiency will require novel antiviral treatment approaches supported by proper clinical trials.

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Supplementary data

Table S1, Figure S1 and background information on BK polyomavirus biology appear as Supplementary data at *JAC* Online.

References

1 Cesaro S, Tridello G, Pillon M *et al*. A prospective study on the predictive value of plasma BK virus-DNA load for hemorrhagic cystitis in pediatric patients after stem cell transplantation. *J Pediatric Infect Dis Soc* 2015; **4**: 134–42.

2 Lunde LE, Dasaraju S, Cao Q *et al*. Hemorrhagic cystitis after allogeneic hematopoietic cell transplantation: risk factors, graft source and survival. *Bone Marrow Transplant* 2015; **50**: 1432–7.

3 Gilis L, Morisset S, Billaud G *et al*. High burden of BK virus-associated hemorrhagic cystitis in patients undergoing allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2014; **49**: 664–70.

4 Hirsch HH, Pergam SA. Human adenovirus, polyomavirus, and parvovirus infections in patients undergoing hematopoietic stem-cell transplantation. In: SJ Forman, JH Antin, FR Appelbaum, eds. *Thomas' Hematopoietic Cell Transplantation*, 5th edn. John Wiley & Sons Ltd, 2016; 1090–104.

5 Cesaro S, Brugiolo A, Faraci M *et al*. Incidence and treatment of hemorrhagic cystitis in children given hematopoietic stem cell transplantation: a survey from the Italian association of pediatric hematology oncology-bone marrow transplantation group. *Bone Marrow Transplant* 2003; **32**: 925–31.

6 Apperley JF, Rice SJ, Bishop JA *et al*. Late-onset hemorrhagic cystitis associated with urinary excretion of polyomaviruses after bone marrow transplantation. *Transplantation* 1987; **43**: 108–12.

7 Arthur RR, Shah KV, Baust SJ *et al*. Association of BK viruria with hemorrhagic cystitis in recipients of bone marrow transplants. *N Engl J Med* 1986; **315**: 230–4.

8 Erard V, Storer B, Corey L *et al*. BK virus infection in hematopoietic stem cell transplant recipients: frequency, risk factors, and association with postengraftment hemorrhagic cystitis. *Clin Infect Dis* 2004; **39**: 1861–5.

9 Gaziev J, Paba P, Miano R *et al*. Late-onset hemorrhagic cystitis in children after hematopoietic stem cell transplantation for thalassemia and sickle cell anemia: a prospective evaluation of polyoma (BK) virus infection and treatment with cidofovir. *Biol Blood Marrow Transplant* 2010; **16**: 662–71.

10 Koskenvuo M, Dumoulin A, Lautenschlager I *et al*. BK polyomavirus-associated hemorrhagic cystitis among pediatric allogeneic bone marrow transplant recipients: treatment response and evidence for nosocomial transmission. *J Clin Virol* 2013; **56**: 77–81.

11 Rinaldo CH, Tylden GD, Sharma BN. The human polyomavirus BK (BKPyV): virological background and clinical implications. *APMIS* 2013; **121**: 728–45.

12 Gardner SD, Field AM, Coleman DV *et al*. New human papovavirus (B.K.) isolated from urine after renal transplantation. *Lancet* 1971; **1**: 1253–7.

13 Binet I, Nickeleit V, Hirsch HH *et al*. Polyomavirus disease under new immunosuppressive drugs: a cause of renal graft dysfunction and graft loss. *Transplantation* 1999; **67**: 918–22.

14 Randhawa PS, Finkelstein S, Scantlebury V *et al*. Human polyoma virus-associated interstitial nephritis in the allograft kidney. *Transplantation* 1999; **67**: 103–9.

15 Drachenberg CB, Beskow CO, Cangro CB *et al*. Human polyoma virus in renal allograft biopsies: morphological findings and correlation with urine cytology. *Hum Pathol* 1999; **30**: 970–7.

16 ECIL *6—Guidelines for the Prevention, Diagnosis, and Treatment of BK Polyomavirus Disease in Stem Cell Transplant Patients*. 2016. http://www.live-sante.com/ecil/program2015.htm.

17 Cordonnier C, Cesaro S, Maschmeyer G *et al*. *Pneumocystis jirovecii* pneumonia: still a concern in patients with haematological malignancies and stem cell transplant recipients. *J Antimicrob Chemother* 2016; **71**: 2379–85.

18 Kondo M, Kojima S, Kato K *et al*. Late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation in children. *Bone Marrow Transplant* 1998; **22**: 995–8.

19 Ambinder RF, Burns W, Forman M *et al*. Hemorrhagic cystitis associated with adenovirus infection in bone marrow transplantation. *Arch Intern Med* 1986; **146**: 1400–1.

20 Binet I, Nickeleit V, Hirsch HH. Polyomavirus infections in transplant recipients. *Curr Opin Organ Transplant* 2000; **5**: 210–6.

21 Bedi A, Miller CB, Hanson JL *et al*. Association of BK virus with failure of prophylaxis against hemorrhagic cystitis following bone marrow transplantation. *J Clin Oncol* 1995; **13**: 1103–9.

22 Leung AY, Suen CK, Lie AK *et al*. Quantification of polyoma BK viruria in hemorrhagic cystitis complicating bone marrow transplantation. *Blood* 2001; **98**: 1971–8.

23 Bogdanovic G, Priftakis P, Giraud G *et al*. Association between a high BK virus load in urine samples of patients with graft-versus-host disease and development of hemorrhagic cystitis after hematopoietic stem cell transplantation. *J Clin Microbiol* 2004; **42**: 5394–6.

24 Bogdanovic G, Priftakis P, Giraud G *et al*. A related donor and reduced intensity conditioning reduces the risk of development of BK virus-positive haemorrhagic cystitis in allogeneic haematopoetic stem cell-transplanted patients. *Anticancer Res* 2006; **26**: 1311–8.

25 Giraud G, Priftakis P, Bogdanovic G *et al*. BK-viruria and haemorrhagic cystitis are more frequent in allogeneic haematopoietic stem cell transplant patients receiving full conditioning and unrelated-HLA-mismatched grafts. *Bone Marrow Transplant* 2008; **41**: 737–42.

26 Giraud G, Bogdanovic G, Priftakis P *et al*. The incidence of hemorrhagic cystitis and BK-viruria in allogeneic hematopoietic stem cell recipients according to intensity of the conditioning regimen. *Haematologica* 2006; **91**: 401–4.

27 Dalianis T, Ljungman P. Full myeloablative conditioning and an unrelated HLA mismatched donor increase the risk for BK virus-positive hemorrhagic cystitis in allogeneic hematopoetic stem cell transplanted patients. *Anticancer Res* 2011; **31**: 939–44.

28 Akiyama H, Kurosu T, Sakashita C *et al*. Adenovirus is a key pathogen in hemorrhagic cystitis associated with bone marrow transplantation. *Clin Infect Dis* 2001; **32**: 1325–30.

29 Gorczynska E, Turkiewicz D, Rybka K *et al*. Incidence, clinical outcome, and management of virus-induced hemorrhagic cystitis in children and adolescents after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2005; **11**: 797–804.

30 Han TT, Xu LP, Liu DH *et al*. Cytomegalovirus is a potential risk factor for late-onset hemorrhagic cystitis following allogeneic hematopoietic stem cell transplantation. *Am J Hematol* 2014; **89**: 55–61.

31 Erard V, Kim HW, Corey L *et al*. BK DNA viral load in plasma: evidence for an association with hemorrhagic cystitis in allogeneic hematopoietic cell transplant recipients. *Blood* 2005; **106**: 1130–2.

32 Cesaro S, Hirsch HH, Faraci M *et al*. Cidofovir for BK virus-associated hemorrhagic cystitis: a retrospective study. *Clin Infect Dis* 2009; **49**: 233–40.

33 Laskin BL, Denburg M, Furth S *et al*. BK viremia precedes hemorrhagic cystitis in children undergoing allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2013; **19**: 1175–82.

34 Funk GA, Gosert R, Comoli P *et al*. Polyomavirus BK replication dynamics in vivo and in silico to predict cytopathology and viral clearance in kidney transplants. *Am J Transplant* 2008; **8**: 2368–77.

35 Leboeuf C, Wilk S, Achermann R *et al*. BK polyomavirus-specific 9mer CD8 T Cell responses correlate with clearance of BK viremia in kidney transplant recipients: first report from the Swiss Transplant Cohort Study. *Am J Transplant* 2017; doi:10.1111/ajt.14282.

36 Li R, Sharma BN, Linder S *et al*. Characteristics of polyomavirus BK (BKPyV) infection in primary human urothelial cells. *Virology* 2013; **440**: 41–50.

37 Romih R, Koprivec D, Martincic DS *et al*. Restoration of the rat urothelium after cyclophosphamide treatment. *Cell Biol Int* 2001; **25**: 531–7.

38 Abraham P, Rabi S. Protein nitration, PARP activation and NAD+ depletion may play a critical role in the pathogenesis of cyclophosphamide-induced hemorrhagic cystitis in the rat. *Cancer Chemother Pharmacol* 2008; **18**: 18.

39 Korkmaz A, Topal T, Oter S. Pathophysiological aspects of cyclophosphamide and ifosfamide induced hemorrhagic cystitis; implication of reactive oxygen and nitrogen species as well as PARP activation. *Cell Biol Toxicol* 2007; **23**: 303–12.

40 Cesaro S, Facchin C, Tridello G *et al*. A prospective study of BK-virus-associated haemorrhagic cystitis in paediatric patients undergoing allogeneic haematopoietic stem cell transplantation. *Bone Marrow Transplant* 2008; **41**: 363–70.

41 Hatakeyama N, Suzuki N, Yamamoto M *et al*. Detection of BK virus and adenovirus in the urine from children after allogeneic stem cell transplantation. *Pediatr Infect Dis J* 2006; **25**: 84–5.

42 Lee YJ, Zheng J, Kolitsopoulos Y *et al*. Relationship of BK polyoma virus (BKV) in the urine with hemorrhagic cystitis and renal function in recipients of T cell-depleted peripheral blood and cord blood stem cell transplantations. *Biol Blood Marrow Transplant* 2014; **20**: 1204–10.

43 Megged O, Stein J, Ben-Meir D *et al*. BK-virus-associated hemorrhagic cystitis in children after hematopoietic stem cell transplantation. *J Pediatr Hematol Oncol* 2011; **33**: 190–3.

44 Peinemann F, de Villiers EM, Dorries K *et al*. Clinical course and treatment of haemorrhagic cystitis associated with BK type of human polyomavirus in nine paediatric recipients of allogeneic bone marrow transplants. *Eur J Pediatr* 2000; **159**: 182–8.

45 Rorije NM, Shea MM, Satyanarayana G *et al*. BK virus disease after allogeneic stem cell transplantation: a cohort analysis. *Biol Blood Marrow Transplant* 2014; **20**: 564–70.

46 Crocchiolo R, Bramanti S, Vai A *et al*. Infections after T-replete haploidentical transplantation and high-dose cyclophosphamide as graft-versus-host disease prophylaxis. *Transpl Infect Dis* 2015; **17**: 242–9.

47 Raiola AM, Dominietto A, Ghiso A *et al*. Unmanipulated haploidentical bone marrow transplantation and posttransplantation cyclophosphamide for hematologic malignancies after myeloablative conditioning. *Biol Blood Marrow Transplant* 2013; **19**: 117–22.

48 Ruggeri A, Roth-Guepin G, Battipaglia G *et al*. Incidence and risk factors for hemorrhagic cystitis in unmanipulated haploidentical transplant recipients. *Transpl Infect Dis* 2015; **17**: 822–30.

49 Hayden RT, Gu Z, Liu W *et al*. Risk factors for hemorrhagic cystitis in pediatric allogeneic hematopoietic stem cell transplant recipients. *Transpl Infect Dis* 2015; **17**: 234–41.

50 Mori Y, Miyamoto T, Kato K *et al*. Different risk factors related to adenovirus- or BK virus-associated hemorrhagic cystitis following allogeneic stem cell transplantation. *Biol Blood Marrow Transplant* 2012; **18**: 458–65.

51 Hadjibabaie M, Alimoghaddam K, Shamshiri AR *et al*. Continuous bladder irrigation prevents hemorrhagic cystitis after allogeneic hematopoietic cell transplantation. *Urol Oncol* 2008; **26**: 43–6.

52 Ferrazzi E, Peracchi M, Biasolo MA *et al*. Antiviral activity of gyrase inhibitors norfloxacin, coumermycin A1 and nalidixic acid. *Biochem Pharmacol* 1988; **37**: 1885–6.

53 Sharma BN, Li R, Bernhoff E *et al*. Fluoroquinolones inhibit human polyomavirus BK (BKV) replication in primary human kidney cells. *Antiviral Res* 2011; **92**: 115–23.

54 Leung AY, Chan MT, Yuen KY *et al*. Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis* 2005; **40**: 528–37.

55 Miller AN, Glode A, Hogan KR *et al*. Efficacy and safety of ciprofloxacin for prophylaxis of polyomavirus BK virus-associated hemorrhagic cystitis in allogeneic hematopoietic stem cell transplantation recipients. *Biol Blood Marrow Transplant* 2011; **17**: 1176–81.

56 Phipps C, Ng HY, Appan P *et al*. BK-virus prophylaxis: still no answer. *Bone Marrow Transplant* 2013; **48**: 1362–3.

57 Knoll GA, Humar A, Fergusson D *et al*. Levofloxacin for BK virus prophylaxis following kidney transplantation: a randomized clinical trial. *JAMA* 2014; **312**: 2106–14.

58 Rinaldo CH, Hirsch HH. Antivirals for the treatment of polyomavirus BK replication. *Expert Rev Anti Infect Ther* 2007; **5**: 105–15.

59 Kwon HJ, Kang JH, Lee JW *et al*. Treatment of BK virus-associated hemorrhagic cystitis in pediatric hematopoietic stem cell transplant recipients with cidofovir: a single-center experience. *Transpl Infect Dis* 2013; **15**: 569–74.

60 Faraci M, Cuzzubbo D, Lanino E *et al*. Low dosage cidofovir without probenecid as treatment for BK virus hamorrhagic cystitis after hemopoietic stem cell transplant. *Pediatr Infect Dis J* 2009; **28**: 55–7.

61 Ganguly N, Clough LA, Dubois LK *et al*. Low-dose cidofovir in the treatment of symptomatic BK virus infection in patients undergoing allogeneic hematopoietic stem cell transplantation: a retrospective analysis of an algorithmic approach. *Transpl Infect Dis* 2010; **12**: 406–11.

62 Lee SS, Ahn JS, Jung SH *et al*. Treatment of BK virus-associated hemorrhagic cystitis with low-dose intravenous cidofovir in patients undergoing allogeneic hematopoietic cell transplantation. *Korean J Intern Med* 2015; **30**: 212–8.

63 Savona MR, Newton D, Frame D *et al*. Low-dose cidofovir treatment of BK virus-associated hemorrhagic cystitis in recipients of hematopoietic stem cell transplant. *Bone Marrow Transplant* 2007; **39**: 783–7.

64 Bridges B, Donegan S, Badros A. Cidofovir bladder instillation for the treatment of BK hemorrhagic cystitis after allogeneic stem cell transplantation. *Am J Hematol* 2006; **81**: 535–7.

65 Rascon J, Verkauskas G, Pasauliene R *et al*. Intravesical cidofovir to treat BK virus-associated hemorrhagic cystitis in children after hematopoietic stem cell transplantation. *Pediatr Transplant* 2015; **19**: E111–4.

66 Chen XC, Liu T, Li JJ *et al*. Efficacy and safety of leflunomide for the treatment of BK virus-associated hemorrhagic cystitis in allogeneic hematopoietic stem cell transplantation recipients. *Acta Haematol* 2013; **130**: 52–6.

67 Wu KH, Weng T, Wu HP *et al*. Effective treatment of severe BK virus-associated hemorrhagic cystitis with leflunomide in children after hematopoietic stem cell transplantation. A Pilot Study. *Pediatr Infect Dis J* 2014; **33**: 1193–5.

68 Seabra C, Pérez-Simón JA, Sierra M *et al*. Intra-muscular vidarabine therapy for polyomavirus-associated hemorrhagic cystitis following allogeneic hemopoietic stem cell transplantation. *Bone Marrow Transplant* 2000; **26**: 1229–30.

69 Vianelli N, Renga M, Azzi A *et al*. Sequential vidarabine infusion in the treatment of polyoma virus-associated acute haemorrhagic cystitis late after allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2000; **25**: 319–20.

70 Toptas T, Kaygusuz-Atagunduz I, Kani HT *et al*. Levofloxacin for the treatment of severe refractory BK virus-associated hemorrhagic cystitis in hematopoietic stem cell transplantation recipients: a report of three cases. *Oncol Lett* 2014; **8**: 1775–7.

71 Focosi D, Maggi F, Pistolesi D *et al*. Hyperbaric oxygen therapy in BKV-associated hemorrhagic cystitis refractory to intravenous and intravesical cidofovir: case report and review of literature. *Leuk Res* 2009; **33**: 556–60.

72 Hosokawa K, Yamazaki H, Nakamura T *et al*. Successful hyperbaric oxygen therapy for refractory BK virus-associated hemorrhagic cystitis after cord blood transplantation. *Transpl Infect Dis* 2014; **16**: 843–6.

73 Hughes AJ, Schwarer AP, Millar IL. Hyperbaric oxygen in the treatment of refractory haemorrhagic cystitis. *Bone Marrow Transplant* 1998; **22**: 585–6.

74 Savva-Bordalo J, Pinho Vaz C, Sousa M *et al*. Clinical effectiveness of hyperbaric oxygen therapy for BK-virus-associated hemorrhagic cystitis after

allogeneic bone marrow transplantation. *Bone Marrow Transplant* 2012; **47**: 1095–8.

75 Zama D, Masetti R, Vendemini F *et al*. Clinical effectiveness of early treatment with hyperbaric oxygen therapy for severe late-onset hemorrhagic cystitis after hematopoietic stem cell transplantation in pediatric patients. *Pediatr Transplant* 2013; **17**: 86–91.

76 Tirindelli MC, Flammia GP, Bove P *et al*. Fibrin glue therapy for severe hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2014; **20**: 1612–7.

77 Demesmay K, Tissot E, Bulabois CE *et al*. Factor XIII replacement in stem-cell transplant recipients with severe hemorrhagic cystitis: a report of four cases. *Transplantation* 2002; **74**: 1190–2.

78 Cipe FE, Soygur T, Dogu F *et al*. Late onset hemorrhagic cystitis in a hematopoietic stem cell recipient: treatment with intravesical hyaluronic acid. *Pediatr Transplant* 2009; **14**: E79–82.

79 Miodosky M, Abdul-Hai A, Tsirigotis P *et al*. Treatment of post-hematopoietic stem cell transplantation hemorrhagic cystitis with intravesicular sodium hyaluronate. *Bone Marrow Transplant* 2006; **38**: 507–11.

80 Ordemann R, Naumann R, Geissler G *et al*. Encouraging results in the treatment of haemorrhagic cystitis with estrogen—report of 10 cases and review of the literature. *Bone Marrow Transplant* 2000; **25**: 981–5.

81 Heath JA, Mishra S, Mitchell S *et al*. Estrogen as treatment of hemorrhagic cystitis in children and adolescents undergoing bone marrow transplantation. *Bone Marrow Transplant* 2006; **37**: 523–6.

82 Kawashima N, Ito Y, Sekiya Y *et al*. Choreito formula for BK virus-associated hemorrhagic cystitis after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2015; **21**: 319–25.

83 Tylden GD, Hirsch HH, Rinaldo CH. Brincidofovir (CMX001) inhibits BK polyomavirus replication in primary human urothelial cells. *Antimicrob Agents Chemother* 2015; **59**: 3306–16.

84 Rinaldo CH, Gosert R, Hirsch HH. Hexadecyloxypropyl-cidofovir (CMX001) BK virus (BKV) replication in primary renal tubular epithelial cells (Abstract OP5-8). *J Clinical Virology* 2009; **46**: S12–3.

85 Papanicolaou GA, Lee YJ, Young JW *et al*. Brincidofovir for polyomavirus-associated nephropathy after allogeneic hematopoietic stem cell transplantation. *Am J Kidney Dis* 2015; **65**: 780–4.

86 Schaub S, Hirsch HH, Dickenmann M *et al*. Reducing immunosuppression preserves allograft function in presumptive and definitive polyomavirus-associated nephropathy. *Am J Transplant* 2010; **10**: 2615–23.

87 Hirsch HH, Babel N, Comoli P *et al*. European perspective on human polyomavirus infection, replication and disease in solid organ transplantation. *Clin Microbiol Infect* 2014; **20** Suppl 7: 74–88.

88 Ringdén O, Uzunel M, Sundberg B *et al*. Tissue repair using allogeneic mesenchymal stem cells for hemorrhagic cystitis, pneumomediastinum and perforated colon. *Leukemia* 2007; **21**: 2271–6.

89 Moll G, Rasmusson-Duprez I, von Bahr L *et al*. Are therapeutic human mesenchymal stromal cells compatible with human blood? *Stem Cells* 2012; **30**: 1565–74.

90 Papadopoulou A, Gerdemann U, Katari UL *et al*. Activity of broad-spectrum T cells as treatment for AdV, EBV, CMV, BKV, and HHV6 infections after HSCT. *Sci Transl Med* 2014; **6**: 242ra83.

91 Raiola A, Dominietto A, Varaldo R *et al*. Unmanipulated haploidentical BMT following non-myeloablative conditioning and post-transplantation CY for advanced Hodgkin's lymphoma. *Bone Marrow Transplant* 2014; **49**: 190–4.