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Review

BK Virus Associated Haemorrhagic Cystitis. A systematic review of current prevention and treatment strategies

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ABSTRACT

Background: BK virus is a major cause of late onset haemorrhagic cystitis in patients undergoing Haematopoietic Cell Transplantation (HCT). The evidence for the management of BK Virus Associated Haemorrhagic Cystitis (BKV-HC) is limited. Much of the published data consists of non-randomised case series and case reports. To our knowledge this is the first systematic review for the management of BKV-HC in both paediatric and adult populations.

Our primary outcome was to examine the evidence for strategies of 1) prevention and 2) cessation of haematuria associated with BKV. Secondary outcomes were to assess the toxicity of treatment strategies and devise management recommendations for clinicians.

Materials and methods: We performed a systematic review of the PubMed and Central databases to evaluate the current evidence. A search protocol was prepared and registered with the PROSPERO database (CRD42017082442). The review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement and AMSTAR (Assessing the methodological quality of systematic reviews) guidelines. Results were classified by treatment type. Qualitative analysis of included articles was performed, and grades of recommendations were devised for each treatment.

Results: Of 896 titles screened, 44 articles were included for qualitative analysis. The overall quality of evidence was low. There is insufficient evidence to recommend prophylactic quinolones. 40 studies evaluated treatments for established BKV-HC. There are no high-quality comparative studies. Cidofovir is the most studied treatment but quality of evidence is low, and grade of recommendation is weak. Hyperbaric oxygen therapy, Fibrin glue, Leflunomide, Sodium Pentosan Polysulfate, Intravesical Alum and Radiological embolisation have all been described but the effectiveness of these treatments is unclear.

Conclusion: There remains no clear specific treatment for BKV-HC. An effective multi-disciplinary approach leading to early recognition and initiation of treatment is encouraged. The development of novel therapies followed by well-designed clinical studies are urgently needed.

1. Introduction

BK virus (BKV) is a polyoma virus found in most adults, with subclinical primary infection [1]. In the context of immunosuppression, the dormant virus reactivates and replicate in an unrestricted fashion. In renal transplant, this causes nephritis and ureteric obstruction, whereas in Haematopoietic Cell Transplantation (HCT), BKV causes haemorrhagic cystitis (HC). Leung et al. (2005) [2] suggested a 3-phase model for the development of HC (Fig. 1). When the immune system reconstitutes, there is an immune response to the virus, leading to inflammation and damage to the bladder mucosa ultimately causing bleeding, pain, frequency and urgency.

HC is not uncommon after haematopoietic cell transplantation (HCT) and can be graded I-IV (Supplementary figure 1) [3]. Approximately 16% of all patients undergoing allogenic- HCT develop some form of HC [4]. Severe cases are associated with treatment related mortality. The link between BK viruria and HC is complex. BK viruria is detected in approximately 50% in patients undergoing HCT, however the incidence of late onset HC is much lower (10–15%) [5]. Several studies have correlated high BK virus titre with the development of HC, however additional risk factors such as the conditioning regimen and development of graft versus host disease (GVHD) have also been

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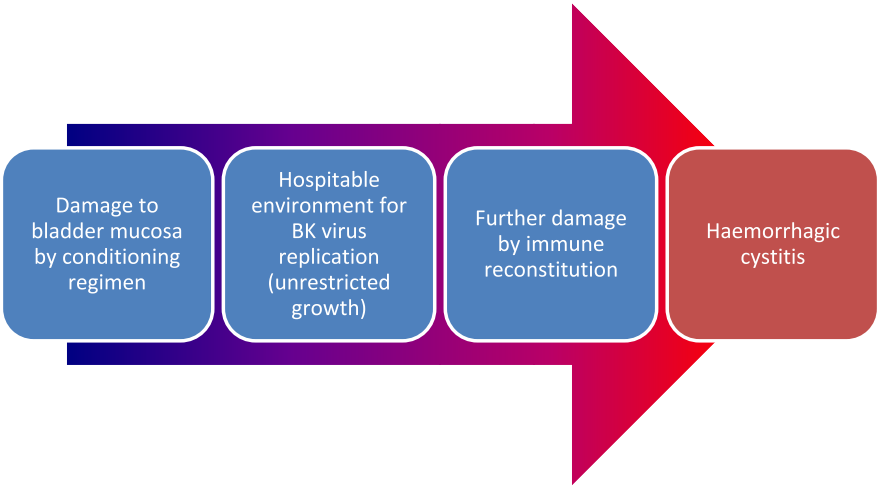

Fig. 1. Model for development of haemorrhagic cystitis.

implicated, indicating a multifactorial aetiology [6].

The evidence for the management of post engraftment BK Virus Associated Haemorrhagic Cystitis (BKV-HC) is limited. Much of published data consists of non-randomised case series and case reports. To our knowledge this is the first systematic review for the management of BKV-HC in both paediatric and adult populations.

2. Objective

Objectives were determined utilising the PICO framework

Population: Adults or children with BKV-HC

Intervention: Any prevention or treatment strategy

Comparison: Supportive management alone (Where comparison available)

Outcome: Prevention or cessation of haematuria.

We evaluated the evidence for the prevention and management of BKV-HC in patients who have undergone HCT. Our primary outcome was to examine the evidence for strategies of 1) prevention and 2) cessation of haematuria. Secondary outcomes were to assess the toxicity of treatments and devise management recommendations for clinicians as well as identify areas for further research.

3. Material and methods

3.1. Search strategy

A search protocol was prepared and registered with the PROSPERO database (CRD42017082442). Electronic search of PubMed and CENTRAL databases were performed by two independent reviewers in November 2017 (MA) and March 2018 (TT). Searches terms included: “BK”, “haemorrhagic”, “hemorrhagic”, “cystitis”. Results were reported as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.

3.2. Data collection and analysis

After initial screening of titles and abstracts, we identified original articles reporting an intervention for the prevention or treatment of BK virus haematuria with a reported clinical outcome. All English language articles in humans (paediatric and adult) were included. No restriction was placed on date of publication and conference abstracts were included to maximise evidence utilisation.

Articles without primary data such as reviews were excluded from qualitative review, however references were examined to detect any missed articles. Case reports were excluded unless a novel treatment modality was reported. We excluded articles where HC was caused by radiation therapy and primary urinary tract malignancy. Articles where BKV had not been determined were excluded.

After full text review, data was extracted from included studies pertaining to patient characteristics, study design, intervention and reported endpoints. Our primary interest was clinical response to the intervention. Where reported, we also collected information regarding virologic response and treatment related toxicity. Due to marked heterogeneity for included studies, meta-analysis was not possible. The results of the systematic review were classified into prevention and treatments. Included studies were critically appraised for bias and rated in accordance with the 2009 Oxford Centre Evidence Based Medicine Levels of Evidence (Supplementary table 1). Summary grades of recommendation were devised for each treatment.

4. Results

Our initial search identified 896 articles with 10 additional titles identified from references. After screening of titles and abstracts, we identified 70 relevant studies for full text review. We excluded 26 articles (14 no primary data, 6 not BKV-HC, 6 solitary case report) however they were retained for the discussion section. The remaining 44 articles were included for qualitative assessment. Fig. 2 illustrates our search.

4.1. Prevention

Four articles have investigated the utility of prevention techniques specific to BKV-HC.

4.1.1. Mesna

Mesna is a medication that binds to urotoxic metabolites of chemotherapy agents (cyclophosphamide, ifosfamide) inactivating them into harmless compounds excreted in the urine. A single randomised control trial (RCT) compared mesna to forced diuresis in 147 patients undergoing HCT [7] and found no difference in the incidence of HC (26.8 vs 23.7%). This was the only RCT in this systematic review (Level 2b).

4.1.2. Quinolones

Quinolones have demonstrated some in-vivo and in-vitro anti-viral activity and are frequently used as prophylaxis in neutropenic patients after HCT. The efficacy of extending prophylactic quinolones for BKV-

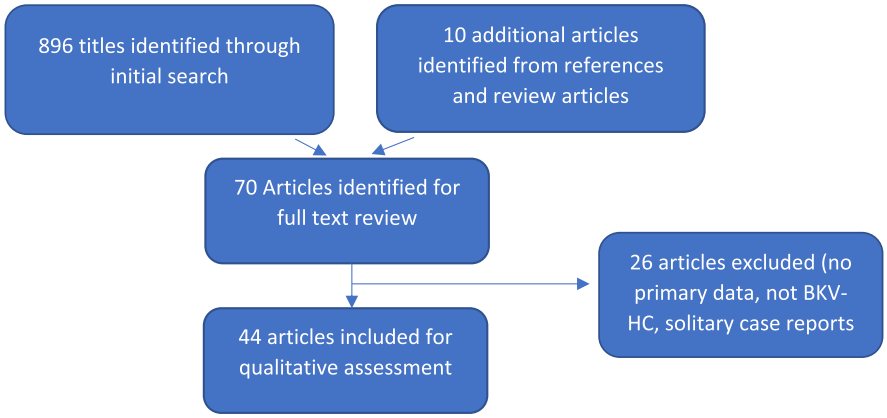

Fig. 2. Illustration of search results.

Table 1
Studies evaluating effect of prophylactic quinolones.

Author	Patients	Intervention	Results	Study type	Level of Evidence
Leung 2005 [8]	22/68	Ciprofloxacin vs Cephalosporin	Reduced BK viruria in cipro group. Inconclusive clinical data	Retrospective case control	4
Miller 2011 [9]	44/92	Ciprofloxacin 60 days	Significant reduction incidence of BKV-HC 2.6 vs 20.9%	Retrospective case control	4
Phipps 2013 [10]	76/134	Ciprofloxacin 56 days	No difference	Prospective case control	4

Table 2
Studies evaluating the effect of intravesical cidofovir.

Author	Number of patients	CR (Clinical Response)	VR (Virologic Response)	Pain	Level of Evidence
Rao 2009	6	6 out of 6	3 out of 4	not reported	4
Cesaro 2009 (subgroup)	5	3 out of 5	not reported	not reported	4
Rascon 2015	4	0 out of 4	not reported	not reported	4
Sakurada 2016	4	4 out of 4	2 out of 4	not reported	4
Foster 2016	10	not reported	"not significant"	Significant	4
Total	29				

HC prevention has been investigated in 3 studies (Table 1) [8–10] with conflicting results. No significant toxicities were reported including no increased incidence of clostridium difficile infection.

4.1.3. Continuous bladder irrigation (CBI)

No studies specifically evaluated the role of CBI in BKV-HC prevention. A multicentre prospective observational study of 450 patients undergoing HCT did not observe any difference in the development of HC with the following: hyperhydration, mesna, urinary alkalisation and urinary catheter [11]. In contrast, Hadjibabaie et al.'s case control study reported CBI significantly reduced incidence of late onset HC (BKV not confirmed; 30.2 vs 39.6, $p < 0.001$) [12].

Due to conflicting reports, quinolones and continuous bladder irrigation cannot be recommended for prevention of BKV-HC.

4.2. Treatments

Several modalities have been explored to treat BKV-HC. Our search collected 40 articles reporting treatment outcomes of patients with proven BKV-HC.

4.2.1. Quinolones

Toptas reported on 3 cases of severe refractory BKV-HC treated with levofloxacin for 60 days [13]. Successful resolution of HC occurred in all cases, with concurrent reduction in BKV urinary load. However, patients underwent simultaneous supportive care and therefore the role of levofloxacin in resolution is uncertain, hence no recommendation can be made.

4.2.2. Cidofovir

Cidofovir (CDV) is a long acting anti-viral drug with a broad spectrum of anti-viral activity.

A single case control [14] and 16 case series [15–30] have reported the use of cidofovir as a therapy for BKV-HC in a combined cohort of 297 patients. These are mainly low-quality studies with wide-ranging clinical response rates. CDV dosing and route varied, resulting in a heterogenous case mix.

4.2.2.1. Intravesical. Five studies included data specific to 29 patients treated with intravesical cidofovir at 5 mg/kg/week (Table 2) [15,16,22,23,25]. Where reported, clinical response (CR) was seen in 14/19 patients (73.7%; range 0–100%). Reduction in BK viruria was reported in 5/8 patients in 2 studies and reported as not significant in a third study of 10 patients.

4.2.2.2. Intravenous. Thirteen studies have reported the use of intravenous (IV) cidofovir in a total of 268 patients (study size range 5–57). Findings are summarised in Table 3. There were marked patient heterogeneity with varied dosing regimens and severity of HC. The average reported complete clinical response rate was 77.2% (range 60–86%). All of these studies were retrospective series [14,17–21,23,24,26,28–30].

Reporting and definitions of virologic response (VR) was variable depending on serum or urine BK load measurements and cut off values

Table 3
Studies evaluating the effect of Intravenous cidofovir.

Author	Design	Route	No	CR (%)	Comments	Toxicity	Limitations	Level of Evidence
Gaziev 2010	Case Series	IV Mixed dose	19	100	Paediatric cohort. 69% virologic response (urine - 2 log) at 4 weeks No difference in time to resolution compared to 11 control patients treated irrigation only. Severity in CDV group higher		Heterogenous CDV dosing. Heterogenous conditioning regimens.	4
Cesaro 2013	Case series	IV Mixed dose	32	84.4	CR associated with reduction of BK viremia load	28% nephrotoxic.	Heterogenous CDV dosing.	4
Cesaro (subgroup) 2009	Case series	IV Mixed dose	57	66.7	Paediatric and adult mixed. 81% virologic response (blood), 20% clearance (urine). BK viremia increased after 4 weeks in cases of PR or failure.	4 deaths not directly related to HC. 10% nephrotoxicity	Heterogenous dosing and use of probenecid. 32% had concurrent treatments e.g. HBOT 8, leflunomide 4, bladder GCSF 3	4
Koskenvuo 2013	Case series	IV 5 mg/kg + Intravesical (3)	6	66.7	Paediatric cohort 4/6 CR with VR (blood - 2 log reduction)		Small cohort of mixed management. Unclear detail on CR	4
Ganguly 2010	Case series	IV 0.5 mg/kg	18	72.2	With accompanying virologic response-urine	17% nephrotoxicity	Grade of HC not described	4
Faraci 2009	Case series	IV 1 mg/kg	7	85.7	Paediatric cohort 1 Death of pneumonia. Remainder CR. Reduced urinary viral load in 5/6 surviving patients.	No AKI	Small numbers.	4
Lee 2015	Case series	IV 1 mg/kg	8	87.5	80% virologic response (urine - 1 log)	37.5% nephrotoxicity	All patients also received quinolone and hyaluronic acid.	4
Savona 2007	Case series	IV 1 mg/kg	19	84.2	47% virologic response (urine - 1 log)	26% nephrotoxicity	Definition of clinical response vague. All patients also received quinolone. High incidence of GVHD	4
Perez-Huertas 2016	Case series	IV 3–5 mg/kg	5	60.0	Paediatric cohort 60% complete response. 20% partial.		No access to full text	4
Kwon 2013	Case series	IV 5 mg/kg + probenecid	12	100.0	Paediatric cohort 92% virologic response (urine - 1 log)		Included grade 1 HC.	4
Gorczynska 2005	Case series	IV 5 mg/kg + probenecid	19	78.9	Paediatric cohort Accompanied by resolution of viremia		All patients had conjugated oestrogen. Reporting of viral response unclear	4
Phillippe 2016	Case series	IV 5 mg/kg + probenecid	27	81.5		29% nephrotoxicity	29% of patients grade 1 HC! Heterogenous frequency of administration.	4
Gilis 2013	Case series	IV 5 mg/kg	39	64.1	Failures successfully treated with HBOT 7, Alum 5, cautery/embolisation 7, cystectomy 1		Virology response not reported. 13 grade 1 patients included. Probenecid use unclear	4
		Total	268	77%				

for significance. Cesaro (2009) noted that in patients with clinical response, 81% had clearance of serum BKV; however only 20% had urinary clearance. Partial response or failure to respond to CDV was associated with increased serum BKV load [23].

There was variation in the reporting and definition of Acute Kidney Injury (AKI). The largest multi-centre series by Cesaro (2009) [23] reported a 10% incidence of AKI using predominately 5 mg/kg dosing.

Four smaller series have reported the use of low dose cidofovir (0.5–1 mg/kg) without probenecid, with comparable rates of clinical and virologic response.

4.2.3. Hyperbaric oxygen therapy (HBOT)

HBOT has been successfully utilised in the management of refractory haemorrhagic cystitis in the context of pelvic radiation. It is hypothesised that increasing the oxygen gradient promotes capillary angiogenesis and regeneration of healthy urothelium.

In the context of BKV-HC, four case series have described their experience treating 42 patients with BKV-HC [20,31–33]. Savva-Bordalo treated 16 patients with an average of 13 sessions (90 min sessions, 5 days/week) with 94% complete resolution [32]. Prospective serial measurements noted an average 2.1 log reduction of urinary BKV load.

HBOT is safe with the main drawback of restricted access to hyperbaric oxygen chamber. Although only demonstrated in low quality case series; the reported outcomes are particularly promising given their success in refractory cases and the low toxicity.

4.2.4. Leflunomide

Leflunomide is an immunosuppressant typically used in rheumatoid arthritis. It has demonstrated in-vivo anti-viral activity and demonstrated efficacy in treating BKV associated nephropathy after renal transplantation.

Three studies reported the outcomes of treatment of oral leflunomide 100 mg in 23 patients with BKV-HC [34–36] (Table 4).

These studies are all considered poor Level 4 studies. Whilst potentially promising, the results are not overwhelming and higher quality studies are needed to and therefore no recommendation can be given.

4.2.5. Adoptive T cell transfer

Pello [37] at el described a novel technique of adoptive immunotherapy where donor cells highly enriched in BKV-specific T-cells were transferred to a patient as a treatment for BKV-HC. There was a complete resolution of patient's symptoms and substantial decrease in the urine BKV load from 3.3 million copies/mL to 1360 copies/mL. No GVHD or recurrence of symptoms have been observed to date (162 days after transplantation, 76 days after adoptive transfer). This innovative modern technique shows promise although further research is needed to generate a recommendation for clinical use.

4.2.6. Oestrogens

Oestrogens have been thought to treat HC through stabilisation of microvasculature. Heath et al. [38] reviewed the use of intravenous (25–100 mg/day) followed by oral oestrogen (5–10 mg/day) therapy in the management of HC in 10 paediatric patients with heterogenous virology (5 with documented BKV). There was complete resolution of visible haematuria in 6 patients. Another series by Ordemann [39] included three patients with BKV-HC treated with oral oestrogen (4–12 mg daily) which resolved with treatment, but one patient had a relapse. The main adverse side effect noted was bladder spasms.

Conversely, whilst not confirmed BKV, Mousavi et al. investigated the use of oral conjugated oestrogen in a RCT of 56 HCT patients with late onset HC and did not demonstrate any benefit [40].

The small numbers in these low quality (Level 4) studies combined with extrapolated conclusions from Mousavi's RCT means that oestrogens cannot be recommended.

Table 4
Studies evaluating the effect of leflunomide to treat BKV-HC

Author	Design	Number	Patient characteristics	Result	Comments
Wu 2014	Case-control	5 vs 7 control	Paeds, BKV-HC grade 3 or more	12 vs 121 days duration of HC. BKV urine/blood load reduced significantly. Undetectable in blood 4/5 patients. No significant difference in pt characteristics or initial BKV load. No side effects	Well reported but limited numbers and huge difference between control group. Possible of bias in reporting of resolution.
Park 2016	Case series	4	BKV-HC grade 3 or more, after 2 weeks of supportive treatment	50% complete resolution, 50% partial response (1 of whom died of leukaemia relapse). All had GVHD. No significant adverse effects	Small sample size. Heterogenous initial management
Chen 2013	Case series	14	BKV-HC grade 2 or more	50% complete resolution. 35% partial. 14% VR in urine (1 log) despite CR. 2 failures. 5 had adverse effects	No long-term data despite 4 year delay to publication. Simultaneous reduction in immunosuppression

4.2.7. Clotting factors

Off label use of clotting factors in patients without specific deficiencies have been contemplated. Demesmay (2002) published a small series demonstrating clinical resolution in 2/4 patients treated with factor XIII [41]. Only 1 patient in this series was diagnosed with BKV and did not respond.

Recombinant activated factor VII has been reported but not specific to BKV-HC [42]. There is therefore insufficient evidence to make any recommendation for the use of clotting factors.

4.2.8. Keratinocyte growth factor (KGF)

Two individual case reports describe the use of KGF to manage refractory BKV-HC [43,44]. Both patients had undergone a range of invasive treatment modalities and so resolution of symptoms cannot be attributed purely to KGF.

4.2.9. Intravesical prostaglandin

It has been hypothesised that intravesical prostaglandin causes platelet aggregation and vasoconstriction and thus reducing bleeding.

Laszlo [5] reported 10 cases of BKV-HC managed with prostaglandin E2 intravesical infusions (PGE2) with resolution in all patients. The main side effect was bladder spasms. In contrast, Cesaro (2003) [45] reported a significantly lower success rate for PGE2 compared to HBOT; at 37% (7/19) vs 78.5% (11/14) respectively ($P = 0.002$).

This inconsistent evidence and lack of confirmatory studies do not demonstrate adequate evidence for a recommendation.

4.2.10. Intravenous immunoglobulin (IVIG)

A single case report by Alavi et al. reported clinical resolution and reduction in urinary BK viral load by treating a child with intravenous immunoglobulin [46]. It is impossible to delineate the precise impact of IVIG given it is one case report and it was used in conjunction with intravenous ciprofloxacin.

4.2.11. Oral sodium pentosan polysulfate (SPP)

Oral SPP replenishes the glycosaminoglycans layer of the bladder urothelium, thereby reversing damage to urothelial surface. SPP has been utilised successfully in radiation cystitis [47]. Duthie et al. (2011) [48] designed a protocol using SPP 100 mg TDS and catheter avoidance. Although not all patients had confirmed BKV, five patients were compared to five historical control patients. Four of the control patients died with HC and none in the protocol group. They observed 88% lower blood transfusion rate, and all recovered from the HC without side effects. Whilst this may reflect the potential of SPP, there is marked heterogeneity in patient characteristics and no further studies have been found to corroborate these findings.

4.2.12. Fibrin glue (FG)

Tirindelli (2014) [49] reported the application of FG in 35 adults with BKV-HC. FG was applied to bleeding areas cystoscopically using the "Vivostat®" system whilst the bladder was insufflated with CO2 at 12 mmHg. No side effects were experienced. There was initial complete response in 83% of patients although a quarter had a relapse of HC. BK viruria remained unchanged. This treatment appears safe and effective although requires a general anaesthetic in most cases for administration. Further studies to confirm these results are required.

4.2.13. Intravesical formalin

Formalin has been used in refractory HC of varying aetiology since the 1970s. Formalin precipitates proteins on the bladder surface and occludes telangiectasia thereby reducing bleeding. Formalin can result in significant bladder fibrosis, perforation and vesicoureteral reflux; causing permanent renal damage and systemic toxicity.

The utilisation of formalin in BKV-HC is limited to case reports in the context of failed conservative management. In a report from Cheuk et al., the HC resolved and the patient remained well at 14.3 years follow up [50].

Whilst formalin appears to be effective based on extrapolated evidence, the toxicity risk is high due to permanent lasting damage to the bladder. It can be reserved as a last resort measure.

4.2.14. Intravesical alum

Intravesical alum has been utilised since 1982 for radiation HC [51]. It precipitates protein at the cell surface, hardening capillary endothelium without permeating cells and therefore does not cause tissue inflammation and fibrosis.

The main risk is aluminium toxicity, which is more common in patients with renal impairment. Whilst no dedicated studies have assessed its efficacy for BKV-HC, 5 patients who failed cidofovir treatment were successfully treated with intravesical alum irrigation in the aforementioned article from Gilis (2013) [20]. Further studies are needed to assess the long-term efficacy.

4.2.15. Selective embolisation of vesical arteries

Selective embolisation of vesical arteries can be used for multiple causes of HC. Three cases are reported by two authors reporting successful management of severe refractory cases of BKV-HC [52,53]. One of these cases required 2 procedures to achieve complete response with long term follow up.

Embolisation appears safe. Although not proven BKV, Han et al. (2008) [54] achieved response in 8/10 patients with late onset post-HCT HC (2 patients required 2nd treatment). The remaining 2 patients died of non-related complications. No major complications were seen, and 2 patients experienced transient buttock pain. Embolisation can therefore be considered an option in severe cases although further studies in the context of BKV-HC are required.

4.2.16. Urinary diversion

The use of urinary diversion has been described in several case reports. The mechanism of action is thought to be due to a) decreased bladder distension and thereby reduced microtrauma, and b) protection from urinary urokinase, which prevents clot formation and subsequent bladder mucosal healing and bleeding cessation.

The simplest method of diversion is percutaneous nephrostomy. Ebiloglu [55] reports two patients with BKV-HC managed with bilateral nephrostomy. Both patients underwent several treatment modalities including clot evacuation. One died of septic shock and the other was asymptomatic for one month.

A larger case series is needed to evaluate the effectiveness of urinary diversion.

4.2.17. Cystectomy

Cystectomy is a major operation which carries significant morbidity and mortality. In refractory cases of HC, cystectomy can be contemplated. Garderet [56] described their experience in 3 cases where cystectomy and enterocystoplasty diversion was performed and the patients survived.

Whilst these excellent results are to be commended, cystectomy carries substantial risk in immunocompromised patients and positive outcomes in case reports will often be over-represented due to publication bias. Cystectomy should only be reserved as a last resort procedure.

5. Discussion

BKV-HC carries significant morbidity, prolongs hospitalisation, and occasionally may be fatal. There remains no definitive treatment for BKV-HC. The standard of care for the management is supportive with irrigation and blood product replacement. In some cases, additional intervention does not change the course of the disease with spontaneous resolution occurred with irrigation alone [57].

Table 5
Summary of recommendations.

Recommendation	Grade of Recommendation/Level of Evidence
Prevention	
Mesna is not superior to forced diuresis in the prevention of HC	B-2b
Insufficient or inconsistent evidence for the routine use of prophylactic continuous bladder irrigation or quinolones	D-4
Treatment	
Intravenous cidofovir can be used as a systemic treatment at either low or normal dose (1–5 mg/kg). Insufficient evidence to recommend intravesical cidofovir	C-3
Hyperbaric oxygen therapy appears to be a safe and effective option	C-4
Intravesical fibrin glue appears to demonstrate modest benefit in arresting bleeding from BKV-HC	C-4
Oral sodium pentosan polysulfate (SPP) has demonstrated some benefit in radiation cystitis and may also be beneficial in BKV-HC	D-4
Intravesical alum has demonstrated benefit in radiation cystitis and may also be beneficial in BKV-HC	D-4
Radiological embolisation appears to be a safe option to treat refractory cases	D-4
Intravesical formalin and cystectomy can be considered as last resort options to manage refractory cases	D-5
Adoptive T cell transfer and leflunomide may be beneficial but further research needed and insufficient evidence for recommendation	No recommendation
Quinolones, oestrogens, clotting factors, KGF, IV immunoglobulins and Intravesical prostaglandins have insufficient evidence to suggest benefit for treatment of BKV-HC.	No recommendation

To our knowledge, this is the first systematic review evaluating all the current available evidence for adult and paediatric populations. Meta-analysis was not possible due to considerable heterogeneity in the management and reporting.

Of the various treatment strategies, considerable focus has been on anti-viral drugs. Cidofovir has been the most extensively studied treatment and has become increasingly utilised, although the evidence for its use is disappointing with no quality comparative studies. The single attempt at comparison with a historical control group was poorly matched for severity and did not show benefit for CDV compared to conservative measures [14]. Regarding intravenous CDV, the largest analysis from Cesaro demonstrated 67% complete clinical response in patients with grade 3–4 HC [23]. Most of BKV-HC cases settle with the conservative measures alone, so the effectiveness of any proposed treatment is unclear without randomisation against a control group.

Table 5 summarises our recommendations from this Systematic Review.

Patients with BKV-HC present unique challenges to the urologist due to immunocompromise. Recent guidelines for haematologists in 2018 [58] (European Conference on Infections in Leukaemia – ECIL) have published recommendations in concordance with the findings of our review. Our review includes non-specific intravesical and surgical therapies more familiar to urologists in the context of intractable radiation HC.

Numerous treatments such as quinolones, oestrogens, clotting factors, KGF, IVIG and intravesical prostaglandins have been reported sporadically over the years with small numbers, inconsistent evidence and lack of supporting studies. Their benefit is somewhat uncertain, and no recommendation can be made. More modern approaches using immune cellular therapy shows promise however should still be considered experimental.

Oral SPP and intravesical hyaluronic acid are licensed for use in interstitial cystitis. Whilst few studies have reported of their use in BKV-HC, several reports and case series have demonstrated potential benefit in HC from other aetiologies. These can be considered as areas for further study in the context of BKV-HC and are particularly attractive due to their favourable safety profile [47,59].

HBOT has demonstrated consistent evidence for its benefit in radiation and chemical induced HC. The main limitation is access to a HBOT chamber.

Cystoscopic clot evacuation is often required with electrocoagulation to control bleeding. The relatively large case series by Tirindelli describing the use of fibrin glue provides a potentially helpful adjunct in the cystoscopic management although the results are modest. Further supporting evidence would be helpful for this novel application which is infrequently used by urologists.

Emergency cystectomy should be avoided due to considerable risk of mortality. In severe cases, embolisation presents itself as an attractive alternative option.

Urologists and haematologists bring different approaches and attitudes towards the management of BKV-HC [60]. It is our recommendation that patients are treated in a multi-disciplinary approach during the early phase of HC for prompt and best appropriate care.

6. Conclusions

Patients with BKV-HC are a relatively rare and unwell group of patients who are frequently given compassionate poly-treatment in the best effort to improve their condition. Due to the non-standardisation of care, the quality of evidence for the prevention and management of BKV-HC is low with a high degree of heterogeneity in management.

Despite the lack of robust clinical evidence, clinicians are challenged into selecting effective treatment options from a myriad of options. Cidofovir requires randomised comparative studies to clarify its benefit for this group of patients despite its common use. Conservative measures remain the mainstay of management. The priority in management should be early recognition and initiation of treatments.

This review highlights the need for higher quality research. We also highlight the need for further multi-disciplinary research focus on intravesical and bladder protection strategies due to the inter-relation between the BK Virus and the bladder urothelium.

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Ethical approval

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Author contribution

M Aldiwani: Project development, Data collection, Data analysis, Manuscript writing.
T Tharakan: Data collection, Data analysis Manuscript writing.
A Al-hassani: Manuscript writing.
N Gibbons: Project development.
J Pavlu: Manuscript editing.
D Hrouda: Project development, Manuscript editing.

Conflicts of interest

There are no conflicts of interest to declare.

Trial registry number

PROSPERO Registry Number CRD42017082442.

Guarantor

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Declarations of interest

None.

Data statement

All original search results pertaining to list of included and excluded papers are available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.01.019.

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