ECIL 6 - Guidelines for the Prevention, Diagnosis, and Treatment of BK Polyomavirus Associated Hemorrhagic Cystitis in Stem Cell Transplant Patients

Working Group

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ESFIG –ESCMID score

Strength of a recommendation	
Grade A	ESCMID strongly supports a recommendation for use
Grade B	ESCMID moderately supports a recommendation for use
Grade C	ESCMID marginally supports a recommendation for use
Grade D	ESCMID supports a recommendation against use
Quality of Evidence	
Level I	Evidence from at least one properly designed randomized, controlled trial
Level II*	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

*Added index:

$_r$: Meta-analysis or systematic review of randomized controlled trials.

$_t$: Transferred evidence, that is, results from different patients' cohorts, or similar immune-status situation.

$_h$: Comparator group is a historical control.

$_u$: Uncontrolled trial.

$_a$: Published abstract (presented at an international symposium or meeting).

Ullmann et al. Clin Microbiol Infect 2012; 18 (S7): 1-8

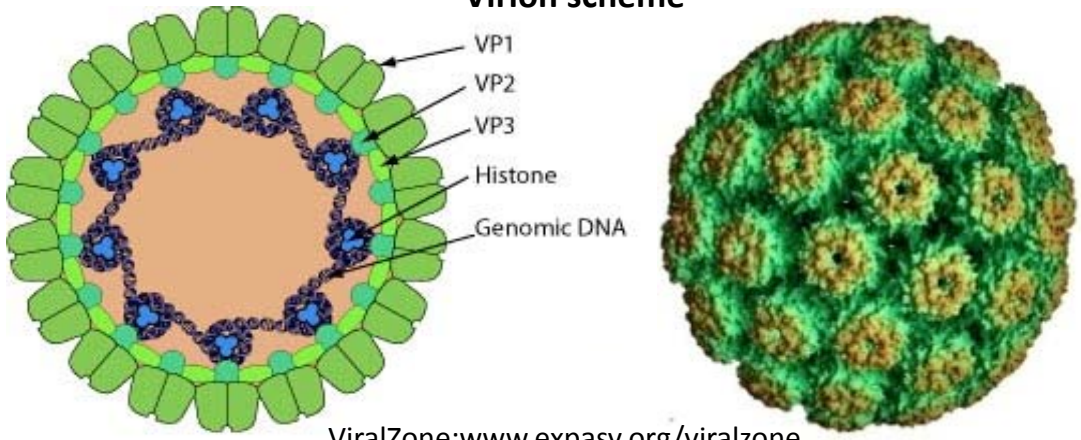
Outline

1. Virus biology
2. Epidemiology of BKPyV
3. BKPyV Disease
4. Pathogenesis
5. Diagnostic criteria
6. Diagnosis of BKPyV-HC
7. Epidemiology of BKPyV-HC
8. Prophylaxis of BKPyV-HC
9. Therapy of BKPyV-HC
10. Experimental therapy
11. Summary recommendations

BK Polyomavirus (BKPyV): Discovery, Classification and Morphology

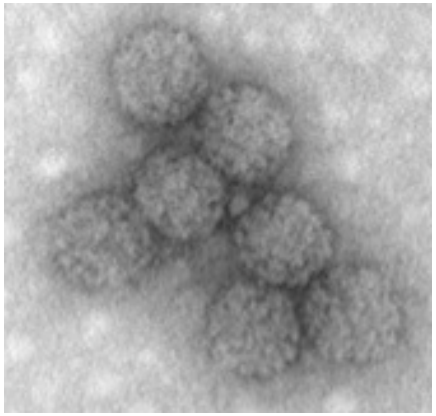
- 1971 first report of a human PyV isolation from urine of a kidney transplant patient[1]
- Family *Polyomaviridae*, genus Orthopolyomavirus[2]
- PyV virions are small (40-45nm) and non-enveloped[3]
  - Environmentally stable
  - Capsid : 360 VP1 proteins outside (VP2 and VP3 protein on the inside)
  - Small DNA genome of 5100 bp

Virion scheme



ViralZone:www.expasy.org/viralzone,
Swiss Institute of Bioinformatics

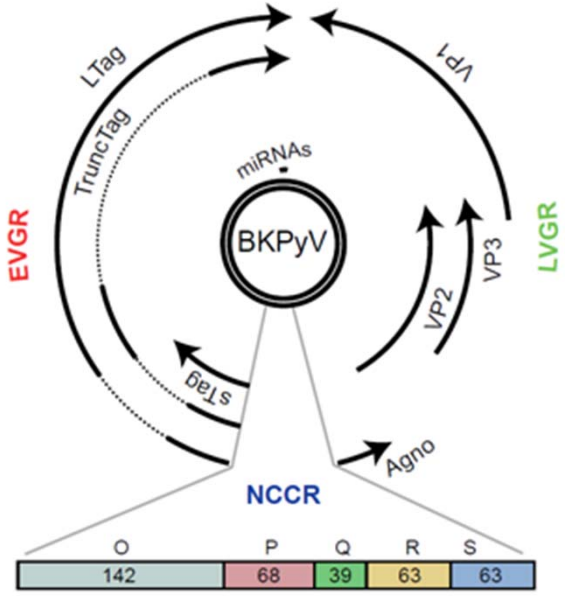
Electron microscopy



1. Gardner et al. (1971) Lancet 297: 1253
2. Johne et al. (2011) Arch Virol 156: 162
3. Rinaldo et al. (2013) APMIS 121: 728

Small Genome Encoding Few Proteins and No Classic Antiviral Targets

- Early viral gene region (EVGR): regulatory small and large tumour antigens (sTag, LTag), and miRNA
- Late viral gene region (LVGR): capsid proteins VP1, VP2, VP3, and regulatory agnoprotein
- Non-coding control region (NCCR): *ori*, promoter/enhancer elements define viral replication strength: some variants are more virulent in immunodeficient patients
- Does not encode a viral DNA polymerase or protease

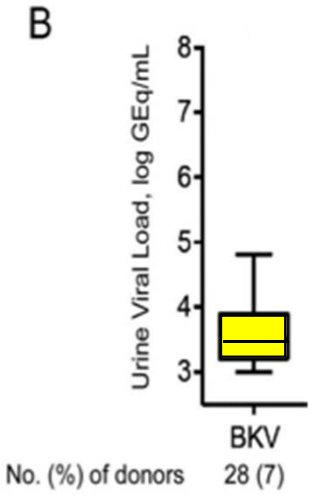


BKPyV genome:
5100 bp double-stranded DNA

Rinaldo et al. (2013) APMIS 8: 728
Gosert et al. (2008) J Exp Med 205: 841
Bethge et al. (2015) J Virol 89: 3396

BKPyV Natural Infection

- Primary infection is mostly subclinical and usually occurs in *early childhood*
- Transmission route(s) are undefined, but likely oral and/or respiratory
- Persistent infection is established in epithelial cells of the reno-urinary tract
- Asymptomatic shedding in urine is seen in 5% - 10% of healthy blood donors
  - BKPyV detectable in sewage waters
- BKPyV rarely causes disease in immunocompetent individuals

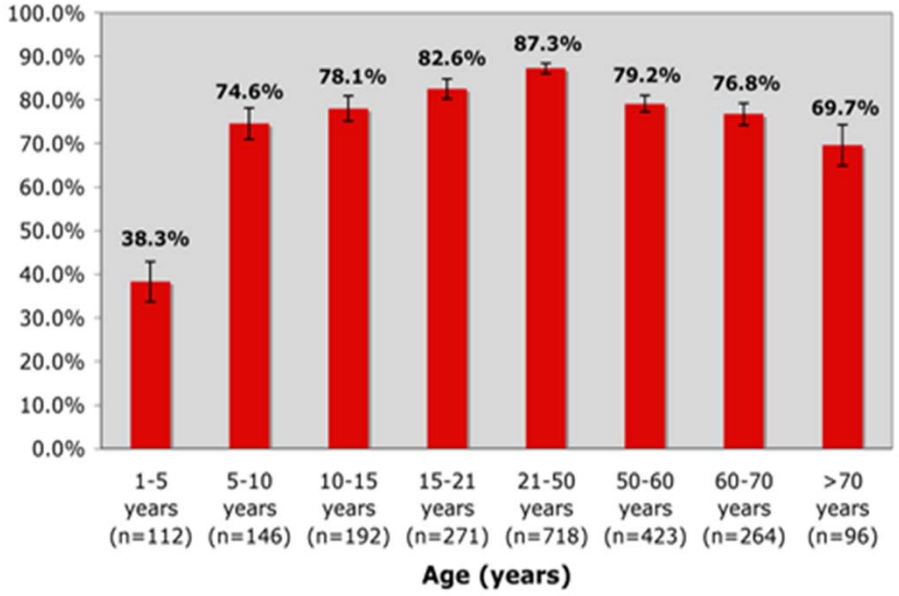


Asymptomatic urine shedding in
28 of 400 blood donors in Basel

Egli et al. (2009) J Infect Dis 199: 837

BKPyV-specific Immunity (I)

- Seroconversion starts in early childhood reaching 80%-90% by early adulthood[1,2,3]
- With increasing age, IgG antibody titres (and seroprevalence rates) decrease[1,2,3,4]
- BKPyV-specific T-cell responses follow a similar pattern [4]
- Adaptive immune responses are more pronounced for capsid protein VP1 than for regulatory protein LTag[5,6]

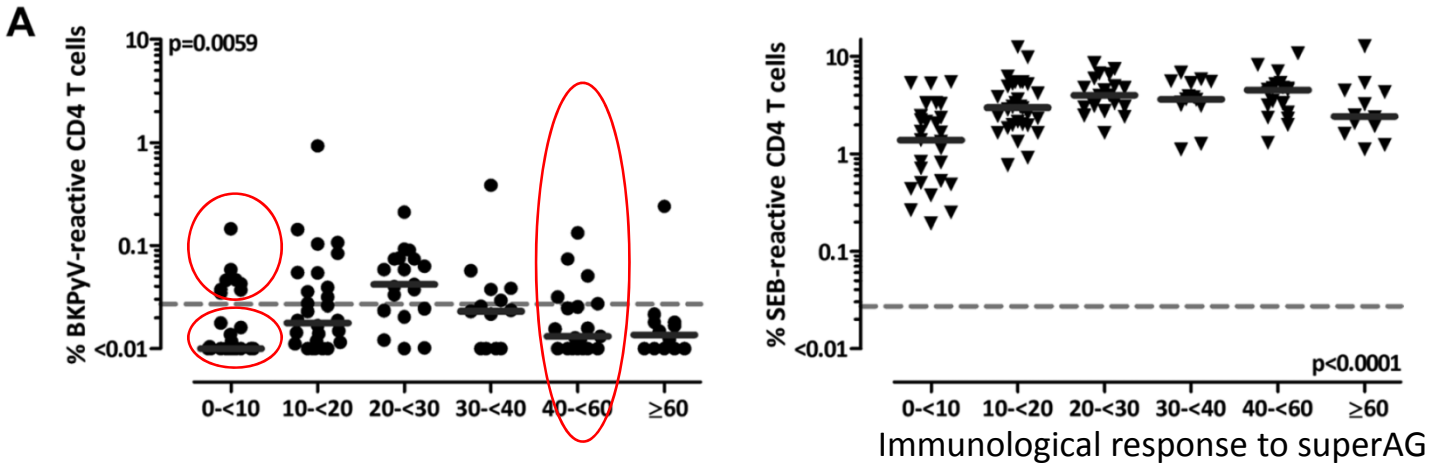


BKPyV IgG in 1501 blood donors (≥21 years); and 721 children <21 years)[2]

1. Knowles et al. (2003) J Med Virol 71: 115
2. Kean et al. (2009) PLoS.Pathog. **5**:e1000363
3. Egli et al. (2009) J Infect Dis 199: 837
4. Schmidt et al. (2014) Am J Transplant 14: 1334
5. Leuenberger et al. (2007) Clin Vacc Immunol 14: 959
6. Bodaghi et al. (2009) J Clin Microbiol 47:2577

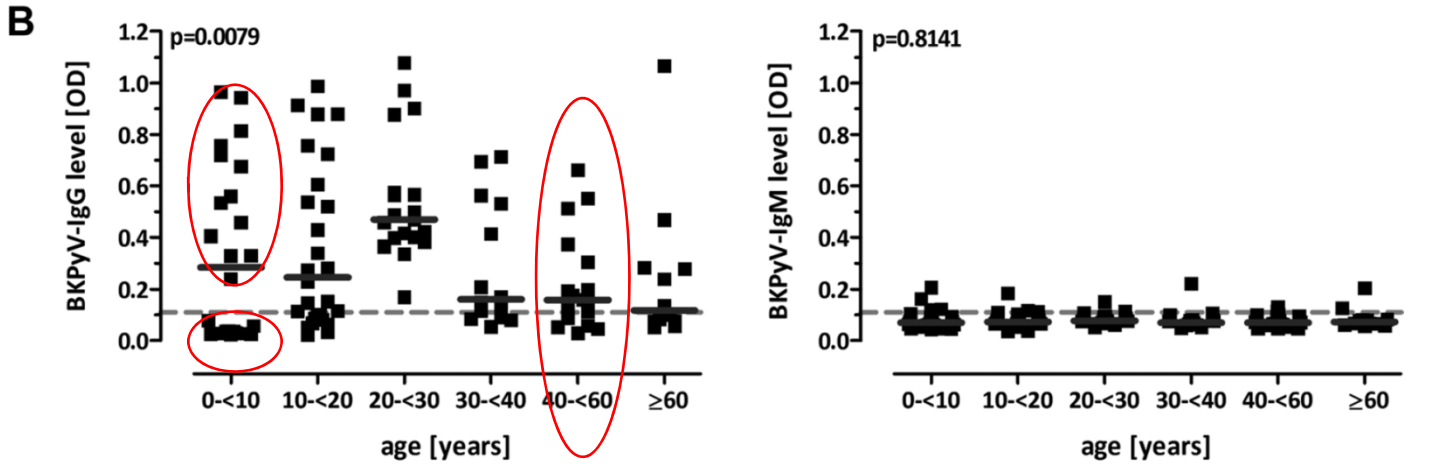
BKPyV-specific Immunity (II)

CD4 T-cells



Immunological response to superAG

Antibody levels



Schmidt et al. (2014) Am J Transplant 14: 1334

Major BKPyV Diseases

- Specific mechanism(s) promoting BKPyV reactivation are not precisely defined
- BKPyV replication is necessary, but not sufficient for disease
- BKPyV disease involves:
  - Uncontrolled viral replication in combination with impaired immunity
  - Additional factors, associated with different clinical settings

- BKPyV-associated hemorrhagic cystitis (BKPyVHC)
  - Mainly in allogenic HSCT recipients
- BKPyV-associated nephropathy (BKPyVAN)
  - Mainly in kidney transplant patients

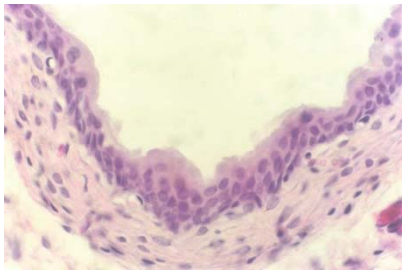
Pergham, Hirsch (2016) Thomas' textbook Hematology (in press).
Hirsch HH (2005) Clin Inf Dis 41: 354
Hirsch & Steiger (2003) Lancet Inf Dis 3: 611

Other BKPyV-associated diseases affecting HSCT patients

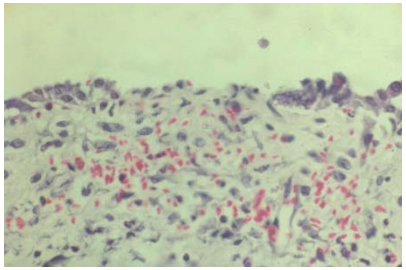
Disease	N° of patients references	HSCT setting
Nephropathy	3[2,10,11]	Allo-HSCT
Ureteral stenosis	1[5]	Allo-HSCT
Encephalitis	4[3,4,6,7]	Allo-HSCT
Respiratory tract infections	2[1,9]	Allo-HSCT
Skin eruption	1[8]	Allo-HSCT

1) Akazawa Y et al (2012) Transpl Infect Dis 14:142;
2) Aksenova M et al (2015) Pediatr Transplant 19:29;
3) Behre G et al (2008) BMT 42:499;
4) Chittick P et al (2013) Ann Pharmacother 47: 1229;
5) Hwang YY et al (2013) BMT 48:745;
6) Lee SY et al (2013) Blood Res 48:226;
7) Lopes da Silva R et al (2011) Pediatr Infect Dis 13:161;
8) Medeiros PV et al (2011) Pediatr Dermatol 28:76;
9) Sandler ES et al (1997) BMT 20:163;
10) Verghese N et al (2009) Pediatr Transplant 13:913;
11) Abudayyeh A et al. (2016) Am J Transplant DOI: 10.1111/ajt.13635

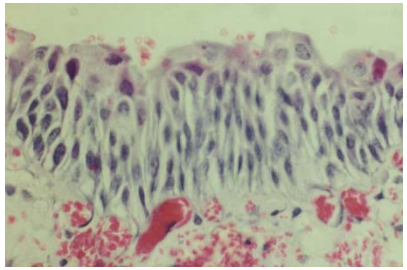
Conditioning Regimens Often Induce Damage of the Urothelium



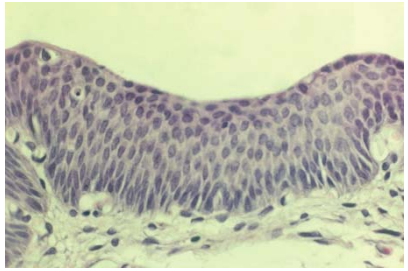
Normal 3-layered urothelium from rat. In humans the urothelium consists of 3-6 cell layers.



Urothelium 1 day after cyclophosphamide injection:
➔denuded areas



Urothelium 5 days after cyclophosphamide injection:
➔enlarged intercellular space and marked hemorrhage

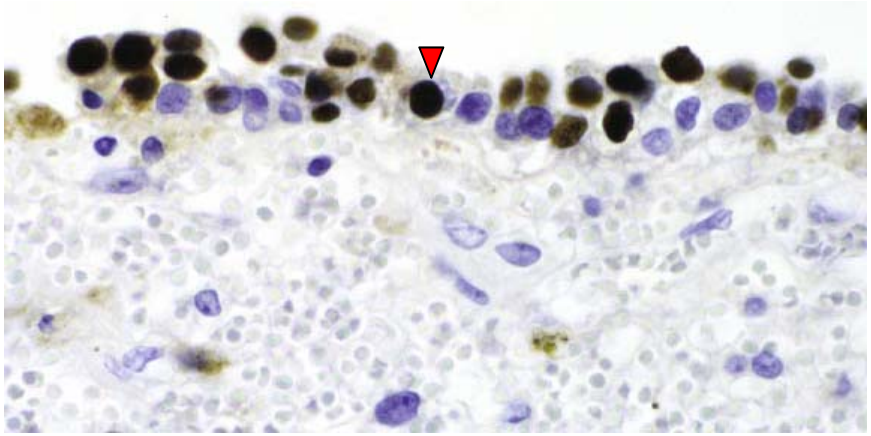


Urothelium 10 days after cyclophosphamide injection:
➔hyperplastic, no hemorrhage

Modified from Lee et al. (2014) Biomed Res Int :473536

Suggested Pathogenesis of BKPyV-HC

1. Urothelium damaged by myeolablative conditioning regimens (e.g.cyclophosphamide)
2. Reactivation of BKPyV in renal tubular epithelial cells and possibly urothelial cells
3. High-level BKPyV replication in urothelial cells - immune control lacking
4. Significant denudation, followed by hemorrhage and inflammation
5. Exacerbation upon recovery of immunity post-engraftment – especially if the graft is from an unrelated donor and conditioning was myeloablative

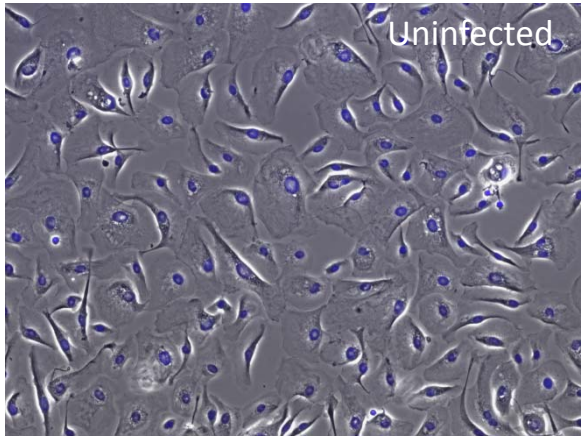


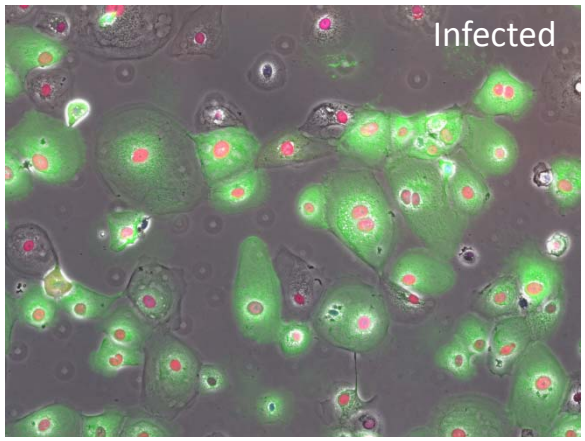
www.pathology.mc.duke.edu.

Urinary bladder biopsy from a BKPyV-HC patient showing denudation and BKPyV infected cells (▼) staining positive for viral large T-antigen in nucleus

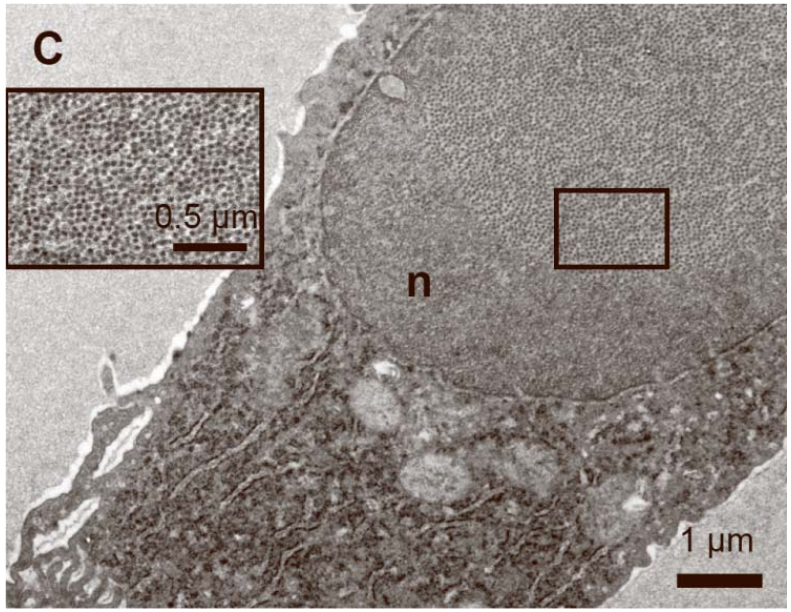
Pergham and Hirsch (2016) Thomas' textbook Hematology (in press)
Binet et al. (2000) Curr Op Org Transpl 5: 210
Giraud et al. (2006) Haematologica 91: 401
Giraud et al. (2008) Bone Marrow Transplant 41:737

BKPyV Infection of Human Urothelial Cells in Cell Culture





Immunofluorescence staining of uninfected and BKPyV-infected urothelial cells 4 days after infection. Infected cells are pink (LTag) or pink and green (LTag and agnoprotein). Notice the enlarged cells and denudation in infected culture.



Electron microscopy of BKPyV infected urothelial cell 3 days after infection. The nucleus is filled with viral particles (insert).

Li et al (2013) Virology 440: 41

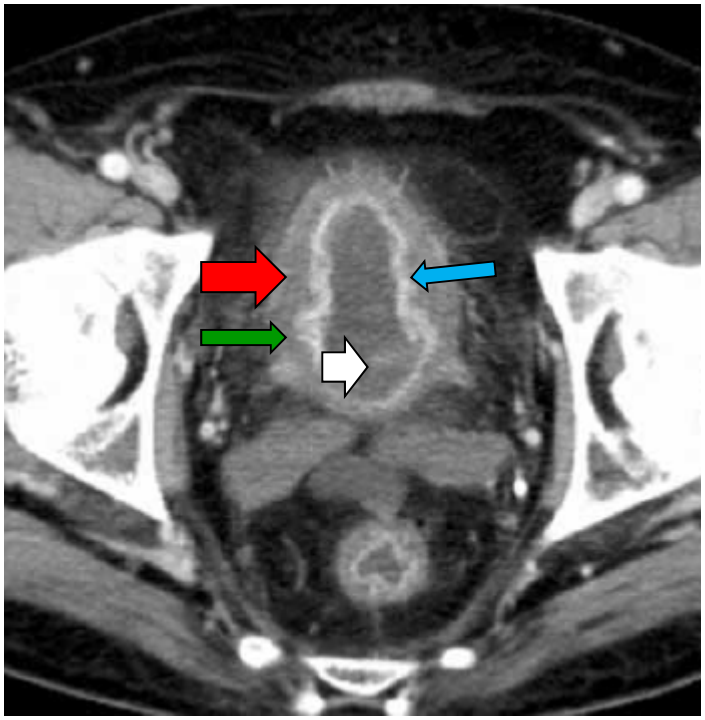
Hemorrhagic Cystitis: Clinical Diagnosis

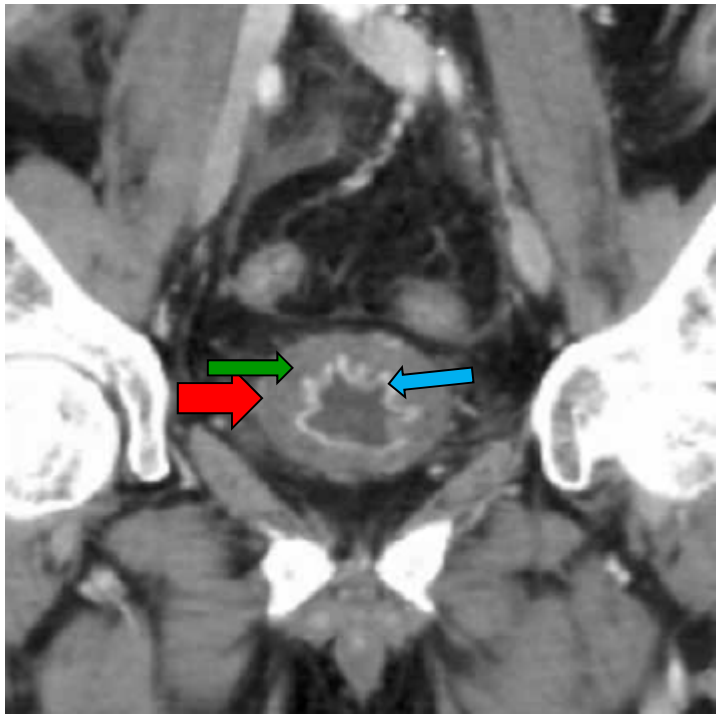
Requires clinical symptoms and signs of cystitis *plus* haematuria Grade II -IV

- Clinical symptoms and signs of cystitis
  - Dysuria, urge, frequency, lower abdominal pain, ...
- Hematuria Grade
  - Grade I >100 erythrocytes /HPF ≥2 consecutive days
  - Grade II macroscopic hematuria
  - Grade III macroscopic hematuria with clots
  - Grade IV macrohematuria, clots, increasing creatinine or cystatine C reflecting renal or bladder dysfunction
- Adjunct diagnostic work-up:
  - Radiological correlates
    - Bladder wall changes by sonography, MRI, CT (but *cave* contrast)
  - Urologic /cystoscopic correlates
  - Histopathology

Arthur et al. (1986) New Engl J Med 315: 230
Bedi et al. (1995) J Clin Oncol 13: 1103
Hirsch HH & Pergam SA (2016) Thomas' Hematology
Leung et al. (2001) Blood 98: 1971
Wong et al. (2007) Clin Infect Dis 44: 830

CT images of BKPyV-HC grade III in adult patient, 53 years, allo SCT for CML





Main findings:

Thickening of bladder wall

Mural edema

Increased enhancement of mucosa

Small bladder capacity

Intraluminal clot

Schultze et al. (2008) Acta Radiologica 49: 1187

BKPyV-associated Hemorrhagic Cystitis

Diagnosis requires the triad of

1. Clinical signs of cystitis
2. Hematuria Grade II and higher
3. Viral replication
    - BKPyV Urine viral load >7 log10 cp/mL [1,2,4,5]

Plasma viral loads often associated to BKPyV viruria (even increasing > 3-4 log10 [3,5] cp/mL). Negative plasma viral load does not rule out a diagnosis of BKPyV-HC.

Evaluate and if possible treat major contribution of other etiologies

- Infectious: bacterial, fungal, viral (JCPyV, CMV, HAdV, HSV), parasite
- Urotoxic: Onset within 1-2 weeks after conditioning, cyclophosphamide, busulfan, TBI, insufficient uroprotection (diuresis, mesna)
- Hematologic: low platelets, bleeding disorders, graft-versus-host disease
- Malignant: Urothelial carcinoma, other primary or metastasizing neoplasia
- Mechanical: Catheter, ureteric stenosis, stenting, or other device

1. Leung et al. (2001) Blood 98: 1971
2. Wong et al. (2007) Clin Inf Dis 44: 830
3. Erard et al. (2005) Blood :
4. Hirsch HH & Pergam SA (2016) Thomas' Hematology (in press)
5. Cesaro et al. (2015) Ped Infect Dis J

Diagnostic Approaches to Risk and Surveillance (1)

BKPyV genome detection

- After allogeneic HSCT, the rate of BKPyV detection increases to more than 80% of patients
- Qualitative detection of BKPyV in urine by NAT (PCR) is not informative and therefore discouraged.
- All patients with BKPyV-HC have significant urine viral loads that usually exceeds 7 log10 cp/mL
- Most, but not all, patients with BKPyV-HC develop BKPyV viremia >10^3 genomic copies/ml, which may precede the clinical diagnosis of BKPyV-HC
- Some centres use high-level viruria and/or viremia to identify patients at increased risk for BKPyV-HC, but in the absence of established therapies, no recommendations can be made for interventions at this time

Arthur et al. (1988) J Inf Dis 158: 563
Leung et al. (2001) Blood 98: 1971
Erard et al. (2005) Blood 106: 1130
Koskenvuo M et al. (2013) J Clin Virol 56:77
Egli et al. (2009) J Inf Dis 199: 837
Laskin et al. (2013) Biol Blood Marrow Transplant 19: 1175
Cesaro et al. (2015) Pediatr Infect Dis J Soc 4: 134

Diagnostic Approaches to Risk and Surveillance of BKPyV-HC (1)

Potential utility of serology in donors or recipients

- Most patients undergoing allogeneic HSCT are BKPyV-IgG positive
- Adult allogeneic HSCT recipients with higher pre-transplant BKPyV antibody titres may be at risk for higher urine BKPyV loads
- Pediatric allogeneic HSCT recipients with undetectable BKPyV-IgG may be at risk of nosocomial infection

Despite that

- Current data are insufficient to suggest the use of BKPyV antibody titres to predict risk, or guide surveillance, or prophylaxis strategies

Arthur et al. (1986) New Engl J Med 315: 230
Leung et al. (2001) Blood 98: 1971
Wong et al. (2007) Clin Inf Dis 44: 830
Koskenvuo et al. (2013) J Clin Virol 56:77
Bogdanovic et al. (1998) Pediatr Transplat 2:288

Epidemiology of HC (with or without BKPyV)

Setting	Incidence % Median (range)	N° of patients	References
Allo-SCT	17 (5,8-66)	4161	1-9, 11-20, 23, 25-27
Haplo-HSCT with cyclophosphamide exposure posttransplant	31,5 (19-61)	179	10, 21, 22, 24
Auto-HSCT	0 (0-1)	930	1, 3, 19, 25, 26
Adults	23 (2-61)	2071	7, 10, 16, 17, 19, 21-24, 26, 27
Children	19 (3.6-26)	2299	1-3, 6, 11, 13-15, 18, 20
Mixed population	23.5 (12.2-53.3)	900	4, 5, 8, 9, 12, 25

1) Cesaro S et al (2003) BMT 32:925;
2) Cesaro S et al (2008) BMT 41:363;
3) Cheuk DK et al (2007) Transpl Int 20:73;
4) El-Zimaity M et al (2004) Blood 103: 4674;
5) Gargiulo G et al (2014) Ecancermedicalscience 8:420;
6) Gaziev J et al (2010) BMT 16:662;
7) Gilis L et al (2014) BMT 49:664;
8) Giraud G et al (2006) Haematologica 91:401;
9) Giraud G et al (2008) BMT 41:737;
10) Crocchiolo R et al (2015) Transpl Infect Dis 17:242.
11) Gorczynska E et al (2005) Biol Blood Marrow Transplant 11:797;
12) Han TT et al (2014) Am J Hemaol 98:55;
13) Hatakeyama N et al (2006) Pediatr Infect Dis 25:84;
14) Kloos RQ et al, (2013) Biol Blood Marrow Transplant 19:1263;
15) Laskin BL et al (2013) Biol Blood Marrow Transplant 19:1175;
16) Lee GW et al (2003) J Korean Med Sci 18:191;
17) Lee YJ et al (2014) Biol Blood Marrow Transplant 20:1204;
18) Megged O et al (2011) J Pediatr Hematol Oncol 33:190
19) Mori Y et al (2012) Biol Blood Marrow Transplant 18:458;
20) Peinemann F et al (2000) Eur J Pediatr 159:182;
21) Raiola A et al (2014) BMT 49:190;
22) Raiola A et al (2013) BBMT 19:117;
23) Rorije NM et al (2014) Biol Blood Marrow Transplant 20:564;
24) Ruggeri A et al (2015) Transpl Infect Dis
25) Shakiba E et al (2011) Exp Clin Transpl 9:405;
26) Tirindelli MC et al (2009) Transfusion 49:170;
27) Yaghobi R et al (2009) Transplant Proc 41:2900.

Epidemiology of BKPyV-HC

Setting	Incidence % Median (range)	N° of patients	References
Allo-SCT	13 (7-25)	2046	1-3, 5-11, 14, 16
Haplo-HSCT with cyclophoshamide exposure posttransplant	24,5 (19-54)	179	4, 12, 13, 15
Auto-HSCT	0	118	10
Adults	16 (7-54)	1413	4, 5, 9, 12-16
Children	18 (8-25)	724	2, 3, 7, 8, 10, 11
Mixed population	16 (13-19)	206	1, 6

1) Bogdanovic G et al (2004) J Clin Microbiol 42:5394;
2) Cesaro S et al (2008) BMT 41:363;
3) Cesaro S et al (2015) Pediatr Infect Dis J 4:134;
4) Crocchiolo R et al (2015) Transpl Infect Dis 17:242.
5) Gilis L et al (2014) BMT 49:664;
6) Giraud G et al (2008) BMT 41:737;
7) Hatakeyama N et al (2006) Pediatr Infect Dis J 25:84;
8) Laskin BL et al (2013) Biol Blood Marrow Transpl 19:1175;
9) Lee YJ et al (2014) Biol Blood Marrow Transpl 20:1204;
10) Megged O et al (2011) J Pediatr Hematol Oncol 33:190;
11) Peinemann F et al (2000) Eur J Pediatr 159:182;
12) Raiola A et al (2014) BMT 49:190;
13) Raiola A et al (2013) BBMT 19:117;
14) Rorije NM et al (2014) Biol Blood Marrow Transpl 20:564;
15) Ruggeri A et al (2015) Transpl Infect Dis
16) Tirindelli MC et al (2014) Biol Blood Marrow Transpl 20:1612.

Clinical studies and risk factors significantly associated with BKPyV-HC (I)

Risk Factor (Parameters investigated)	N° of studies	HSCT setting/ Total N° patients	References
BKPyV positivity in:			
- urine	6	Allo-HSCT/507	1; 2; 5; 7; 9; 10
- blood	5	Allo-HSCT/426	2; 3; 4; 8; 11
		Auto-HSCT/25	4
Other viremia: - CMV	1	Allo-HSCT/50	8
- HHV6	1	Allo-HSCT/88	11
Stem cell source: - UCB	2	Allo-HSCT/	6; 12
- PBSC	1	Allo-HSCT/	6
Type of donor: Unrelated	1	Allo-HSCT/175	7

1) Bogdanovic G et al (2004) J Clin Microbiol 42:5394;
2) Cesaro S et al (2008) BMT 41:363;
3) Cesaro S et al (2015) Pediatr Infect Dis J 4:134;
4) Erard V et al (2004) Clin Infect Dis 39:1861;
5) Gaziev J et al (2010) Biol Blood Marrow Transpl 16:662;
6) Gilis L et al (2014) BMT 49:664;
7) Giraud G et al (2008) BMT 41:737;
8) Han TT et al (2014) Am J Hematol 89:55;
9) Hatakeyama N et al (2006) Pediatr Infect Dis J 25:84;
10) Hayden RT et al (2015) Transpl Infect Dis17:234
11) Laskin BL et al (2013) Biol Blood Marrow Transpl 19:1175;
12) RoriJe NM et al (2000) Biol Blood Marrow Transpl 20:564

Clinical studies and risk factors significantly associated with BKPyV-HC (II)

Risk Factor (Parameters investigated)	N° of studies	HSCT setting/ Total N° patients	References
Type of aGVHD:			
- aGVHD	1	Allo-HSCT/90	4
- II-IV grade	1	Allo-HSCT/117	2
- III-IV grade	1	Allo-HSCT/491	8
- aGVHD+high BK viruria	1	Allo-HSCT/31	1
Type of conditioning:			
- ATG	1	Allo-HSCT/117	2
- Cyclophosphamide	1	Allo-HSCT/200 Auto-HSCT/118	6
- High-dose busulphan	1	Allo-HSCT/117	7
- Myeloablative conditioning	1	Allo-HSCT/175	3
Age at transplant: > 7 yrs	1	Allo-HSCT/88	5

1) Bogdanovic G et al (2004) J Clin Microbiol 42:5394;
2) Gaziev J et al (2010) Biol Blood Marrow Transpl 16:662;
3) Giraud G et al (2008) BMT 41:737;
4) Hayden RT et al (2015) Transpl Infect Dis17:234;
5) Laskin BL et al (2013) Biol Blood Marrow Transpl 19:1175;
6) Megged O et al (2011) J Pediatr Hematol Oncol 33:190;
7) Peinemann F et al (2000) Eur J Pediatr 159:182;
8) Rorije NM et al (2000) Biol Blood Marrow Transpl 20:564.

Prophylaxis for BKPyV-HC

	Fluoroquinolones	Hyper-hydration (during conditioning)	Bladder irrigation
N° of studies	3	1	1
References	Leung AY et al (2005) Clin Infect Dis 40:528; Miller AN et al (2011) Biol Blood Marrow Transplant 17:1176; Phipps C et al (2013) BMT 48:1362.	Bedi A et al (1995) J Clin Oncol 13: 1103	Hadjibabaie M et al (2008) Urol Oncol 26:143.
Type of Study	Retrospective, 2 (Cipro) Cohort-prospective, 1 (Cipro)	Prospective, randomized, 1	Prospective, 1
N° of patients	294 (155 Cipro vs 149 no Cipro)	147 (71 at 2 ml/kg/h + mesna vs 76 at 4 ml/kg/h + forced diuresis)	80 vs 40 (historical control)
Efficacy	Reduction in BKPyV reactivation (Leung) and HC incidence (Miller). No efficacy in reducing rates of clinically significant HC (1 study-Phipps). In kidney patients, levofloxacin prophylaxis failed to reduce onset or levels of BKPyV viruria/viremia (Knoll et al. JAMA 2014)	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. 3-way Foley catheter used
Toxicity	No adverse effects Cave bacteria resistance	No adverse effects Cave fluid retention	No adverse effects, Cave invasive procedure
Grading	**D II h,t**	**B II t**	**C II t**

Therapy of BKVPyV-HC (I)

	CDV i.v 3 to 5 mg/kg/wk With probenecid	CDV i.v. 0.5 to 1.5 mg/kg/wk Without probenecid	CDV intravesical 5 mg/kg/wk
N° of studies	6	4	4
References	Cesaro S et al (2009) Clin Infect Dis 49:233; Cesaro S et al (2013) BMT 48:809; Gaziev J et al (2010) Biol Blood Marrow Tranplant 16:662; Gorczynska E et al (2005) Biol Blood Marrow Transplant 11:797; Koskenvuo et al (2013) J Clin Virol 56:77; Kwon HJ et al (2013) Transpl Infect Dis 15:569;	Faraci M et al (2009) Pediatr Infect Dis J 28:55; Ganguly N et al (2010) Transpl Infect Dis 12:406; Lee SS et al (2015) Korean J InternMed 30:212; Savona MR et al (2007) BMT 39:783	Bridges B et al (2006) Am J Hematol 81:535; Cesaro S et al (2009) Clin Infect Dis 49:233; Koskenvuo et al (2013) J Clin Virol 56:77; Rascon J et al (2015) Pediatr Transplant;
Type of Study: •Retrospective •Prospective	 4 2	 4 0	 3 1
N° of patients	144	52	14
Efficacy: • Clinical: • Virological:	 CR (74%) Reduction in BKPyV loads in: - Urine: 38% (26/61) - Blood: 84% (67/80)	 CR (83%) Reduction in BKPyV loads in: - Urine: 62% (30/48) - Blood: 67% (8/12)	 CR (43%), PR (7%) Reduction in BKPyV loads in urine: 55% (5/9); stable viral load: 45% (4/9).
Toxicity (N° episodes)	Nephrotoxicity (26), myelotoxicity (1)	Transient nephrotoxicity (11)	No adverse effects cave invasiveness
Grading	**C II u**	**C II u**	**Few data No recommendation**

Therapy of BKVPyV-HC (II)

	Vidarabin im/iv	Levofloxacin oral	Leflunomide oral
N° of studies	2	1	2
References	Seabra C et al (2000) BMT 26:1229; Vianelli N et al (2000) BMT 25:319	Toptas et al (2014) Oncol Lett 8:1775	Chen XC et al (2013) Acta Haematol 130:52; Wu KH et al (2014) Pediatr Infect Dis 33:1193
Type of Study: Retrospective	Retrospective, 2	Retrospective, 1	Retrospective, 2
N° of patients	2	3	19
Efficacy: • Clinical: • Virological:	CR (100%) BK viruria negative (50%)still positive (50%).	CR (100%) BK viruria decreased >90% (100%)	CR (63%), PR (26%) Reduction in BK viruria (100%)
Toxicity (N° episodes)	No adverse effects	No adverse effects	GI symptoms (1), neutropenia (2) Cave: hepatic toxicity
Grading	**Few data** **No recommendation**	**Few data** **No recommendation**	**Few data** **No recommendation**

Therapy of BKVPyV-HC (III)

	Hyperbaric oxygen	Fibrin glue	Choreito extract granules
N° of studies	5	1	1
References	Focosi D et al (2009) Leuk Res 33:556; Hosokawa K et al (2014) Transpl Infect Dis 16:843; Hughes AJ et al (1998) BMT 22:585; Savva-Bordalo J et al (2011) 47:1095; Zama D et al (2013) Pediatr Transplant 17:86	Tirindelli MC et al (2014) Biol Blood Marrow Transplant 20:1612	Kawashima N et al (2015) Biol Blood Marrow Transplant 21:319
Type of Study: Retrospective	Retrospective, 5	Retrospective, 1	Retrospective, 1
N° of patients	29	35	6
Efficacy: • Clinical: • Virological:	CR (86%) Reduction in BKPyV loads in urine (65%)	CR (83%) BK viruria remained positive in 83% of patients achieving CR.	CR (100%) Reduction in BKV loads in urine
Toxicity (N° episodes)	Ear barotrauma (1), pressure intolerance (1), claustrophobia (1) Cave:feasibility , claustrophobia, earache	No adverse effects	No adverse effects
Grading	**C III u**	**C III u**	**Few data** **No recommendation**

Other therapies of HC

	FXIII concentrate	Hyaluronic acid/ sodium hyaluronate intravesical	Estrogen
N° of studies	1	2	2
References	Demesmay K et al (2002) Transplantation 74:1190	Cipe FE et al (2010) Pediatr Transplant 14:79; Miodosky M et al (2006) BMT 38:507	Ordemann R et al (2000) BMT 25:981; Heath JA et al (2006) BMT 37:523
Type of Study: Retrospective	Retrospective, 1	Retrospective, 2	Retrospective, 20
N° of patients	4	8	20
Efficacy: • Clinical:	CR (50%), PR (25%)	CR (75%), PR (12%)	CR (70%), PR (5%)
Toxicity (No. episodes)	No adverse effects	No adverse effects	Hepatotoxicity (2)
Grading	**Few data** **No recommendation**	**Few data** **No recommendation**	**Few data** **No recommendation**

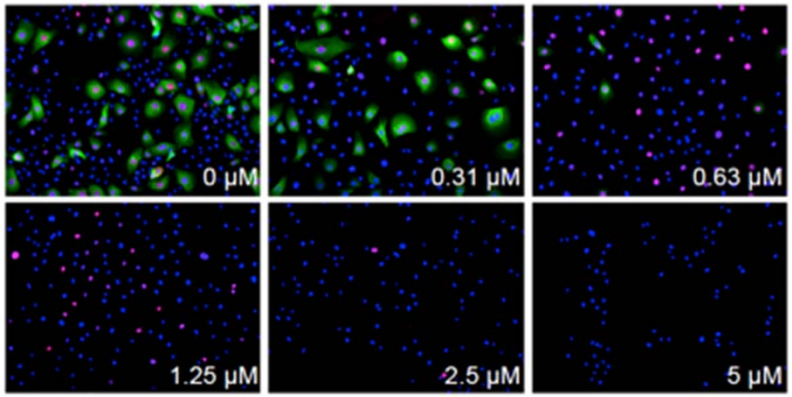
Experimental Immune Therapy of BKPyV-HC (I)

	Mesenchymal cells	Cellular immune therapy (*in vitro*)	Notes
N° of studies	1[1]	1[3]	
References	Ringdén et al. Leukemia (2007) 21,2271-2276; Moll et al. Stem Cells (2012) 7,1565-74;	Papadopoulou et al, Sci Transl Med (2014) 6,242:242ra83	
Type of Study:	Prospective, 1	Prospective, 1	
N° of patients	7 (4 died) hematuria resolved	48 donors (28/48 anti BKPyV activity)	
Efficacy: Clinical/Virological	Decrease in hematuria -	14 lines against 5 vir 9 lines against 4 vir 12 lines against 3 vir 11 lines against 2 vir	3/3 HC patients with lines against BKPyV had clinical and virological responses
Toxicity	Instant blood mediated inflammatory reaction[2]	No adverse effects? IRIS	
Grading	**Few data** **No recommendation**	**Few data** **No recommendation**	

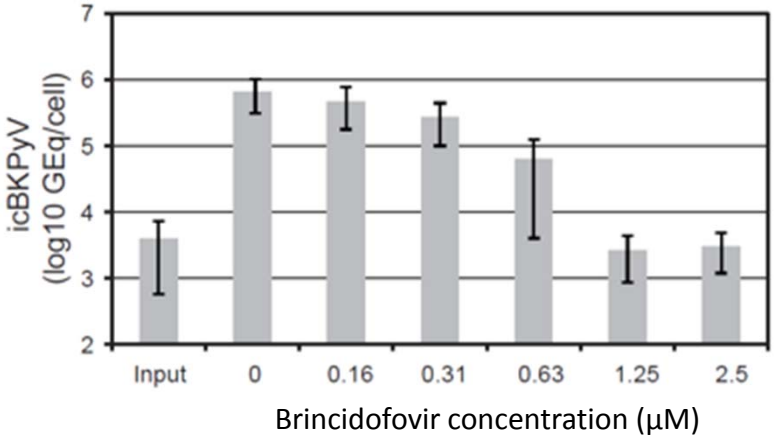
Experimental Therapy: Brincidofovir?

- Brincidofovir (CMX001): an oral ether-lipid ester conjugated prodrug of cidofovir
- Uptake into cells by diffusion - independent of transporters (unlike cidofovir)
- In phase 3 clinical trials for adenovirus and cytomegalovirus
- *In vitro* strong reduction of BKPyV replication, but also cytostatic effects
- Would possibly give the best effect, if given intravesically in a solution

Human primary urothelial cells infected with BKPyV and treated with Brincidofovir for 3 days (LTag/Agno/DNA)



Intracellular BKPyV genomes per urothelial cell 3 days post treatment start



Tylden et al. (2015) AAC 59:3306

Summary-Recommendations for diagnosis of BKPyV-HC

Issue **For diagnosis of BKPyV-HC**	**Grading**	**Notes**
Quantitative BKPyV viruria in allo HSCTs	A II h,u	High sensitivity and high negative predictive value for a cut-off $\geq 10^7$ genomic copies/ml
BKPyV viremia in allo HSCTs	B II h,u	Some authors report a higher specificity and positive predictive value for a cut-off $> 10^3$ genomic copies/ml
BKPyV viruria/viremia screening in asymptomatic HSCTs	D II	Not recommended outside clinical studies

Summary-Recommendations for prophylaxis of BKPyV-HC

Issue **Prophylaxis**	**Grading**	**Notes**
Hyper-hydration during conditioning	B II t	Useful to prevent the urotoxic effect of Cy or BU
Bladder irrigation	C II t	Invasive procedure, discomfort for the patient
Ciprofloxacin	D II h,t	Little effect on BKPyV replication No effect on HC

Summary-Recommendations for therapy of BKPyV-HC

Issue Therapy	Grading	Notes
Best supportive therapy (analgesics, PLT transfusion, hydration)	A III	Aim at higher PLT threshold for transfusion
Hyperbaric Oxygen Therapy	C III	Depending on local availability
Fibrin glue application	C III	Invasive treatment requiring cystoscopy
Cidofovir, i.v.	C II u	No recommendation of dose (either 3-5 mg/kg with probenecid OR 0.5-1.5 mg/kg without probenecid)
Cidofovir, intravesical	No recommendation	Limited experience