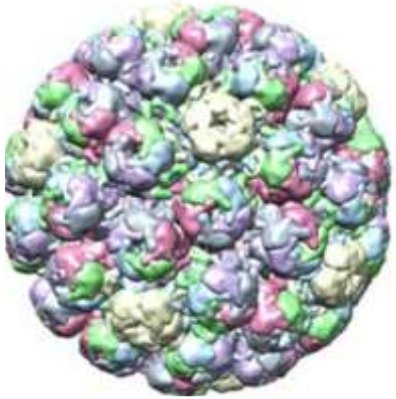


NAKİL SONRASI ÖNEMLİ VİRAL ENFEKSİYONLAR

POLYOMAVİRUSLAR

Dr Vildan AVKAN-OĞUZ
Dokuz Eylül Üniversitesi Tıp Fakültesi
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD.
İSTANBUL EYLÜL 2024

Sunum planı

- Polyomaviruslar

- SOT - BKV özellikleri
  - Epidemiyoloji
  - Patogenez
  - Risk faktörleri
  - Klinik tablolar
  - Tanı ve Tedavi

Polyomaviruslar

- Papillomavirus genusu - Papovaviridea ailesi (dsDNA)
- 1953 ; Farelerde – lenfoma etkeni
  (Mouse polyomavirus)
- 1960 ; Maymunlarda –Simian virus 40 (SV40)
- 1971 ; İlk insan polyomavirusları tanımlama
  Böbrek transpant alıcısında BKV
  PML bir hastanın beyin dokusunda JCV

Polyomaviruslar

- 2007; Tanımlanan bölgeye göre isimlendirme

  Washington University polyoma virus (WUPyV)
  Karolinska Institute polyoma virus (KIPyV)
  Malawi polyoma virus (MWPyV)

  İnsanda patojen - 14 farklı tür

Polyomaviruslar

PyV lar Onkojenik

Üroepitelial kanser
Orofarengial kanser
Akciğer kanseri
Agresif adenoid kistik karsinom

Ambalathingal et al. Clin Microbiol Rev 2017; 30:503-528

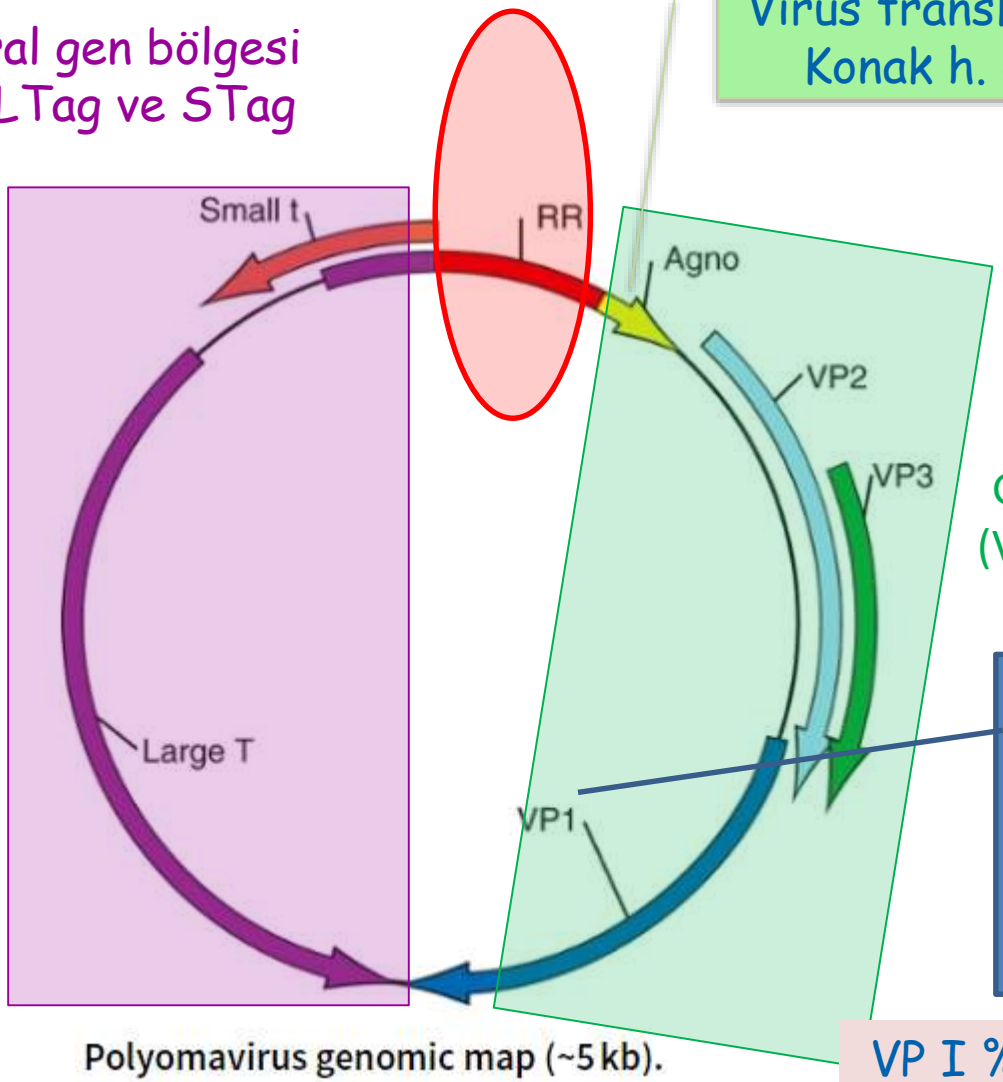
Polyomaviruslar

Kodlama yapmayan kontrol bölgesi (NCCR)
ori ve düzenleyici sekansları

Erken viral gen bölgesi
(EVGR); LTag ve STag

Virus transkripsiyonu
Konak h. onarımı

miRNAs
Viral genom-hücre
histonları ile ilişki
Viral rep. kontrolü



Polyomavirus genomic map (~5 kb).

Geç viral gen bölgesi (LVGR);
(VP1,VP2,VP3) ve agnoprotein

VP1 sekans değişikliği ile dört farklı genotip (I, II, III, IV)

VP I %70-80; VP IV % 10-20
10 subtip

Mandell 2020

BKV-Malignite

- LTAg, STAg ekspresyonu ve Agnoprotein

  LTAg – En önemli

  STAg - mitojen aktive protein kinaz (MAPK) akt.

  Agnoprotein - DNA tamir proteinini inhibe etmesi- translasyona katkı

- BKV-LTA-p53 protein kompleksinin prostat kanser dokusunda saptanması,

- Pankreas, beyin ve üroepitelyal tümorlerde BKV-DNA sının gösterilmesi

Bulaşma yolu

- Solunum yolu

  Üst solunum yolu, tonsiller, waldeyer halkası

- Oral-fekal - Kanalizasyon bulaşı

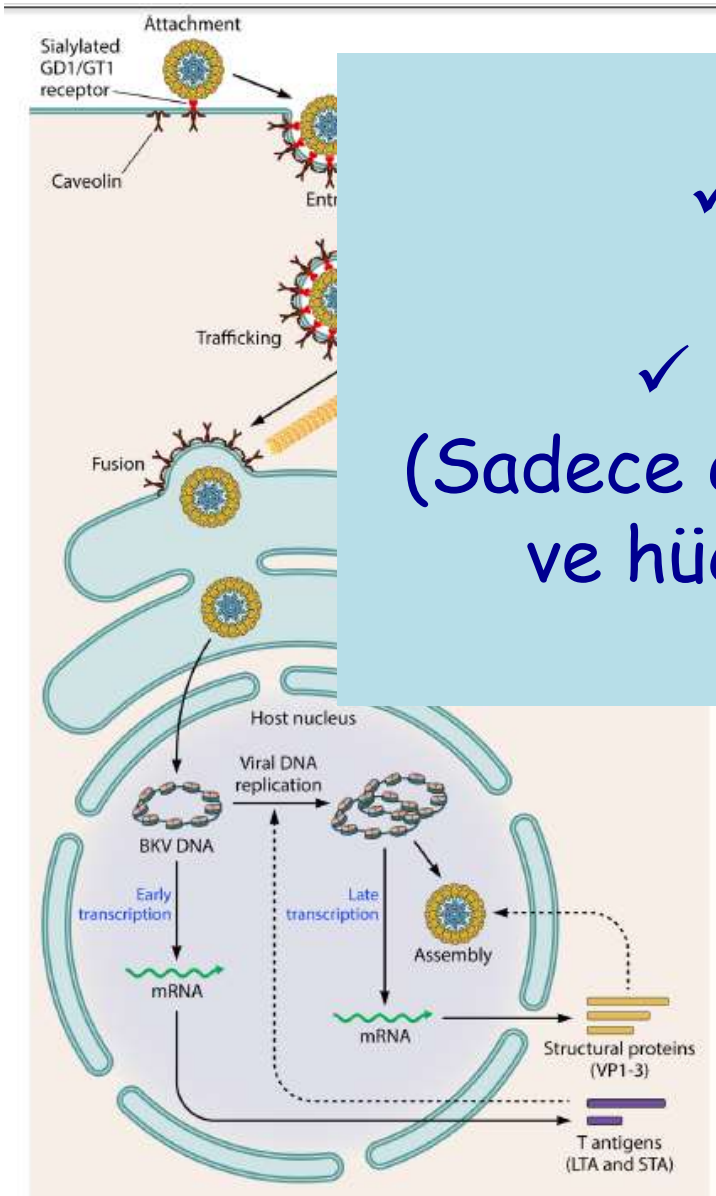
- Kan transfüzyonu – Lökositler

- Transplasental -fetus

BKV-patogenez

Gangliozidler; GD1b, GT1b

Kaveol - pinositik veziküller



✓ Litik infeksiyon

✓ Abortif infeksiyon
(Sadece erken gen transkripsiyonu ve hücre transformasyonu)

- Viral rep. – geç bölge gen ekspres.
- Agnoprotein- virionun olgunlaşması
- Virus partiküllerinin hücre membranına taşınması
- Ekzositoz ile salınımı

Ambalathingal et al. Clin Microbiol Rev 2017; 30:503-528

(*Transplantation* 2005;79: 1277–1286)

Polyomavirus-Associated Nephropathy in Renal Transplantation: Interdisciplinary Analyses and Recommendations

Hans H. Hirsch,[1,15] Daniel C. Brennan,[2] Cinthia B. Drachenberg,[3] Fabrizio Ginevri,[4] Jennifer Gordon,[5] Ajit P. Limaye,[6] Michael J. Mihatsch,[7] Volker Nickeleit,[8] Emilio Ramos,[9] Parmjeet Randhawa,[10] Ron Shapiro,[11] Juerg Steiger,[12] Manikkam Suthanthiran,[13] and Jennifer Trofe[14]

Received: 11 February 2019 | Accepted: 26 February 2019

DOI: 10.1111/ctr.13528

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY Clinical TRANSPLANTATION The Journal of Clinical and Translational Research

BK polyomavirus in solid organ transplantation—Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice

Hans H. Hirsch[1,2] | Parmjeet S. Randhawa[3,4] | on behalf of AST Infectious Diseases Community of Practice

BKV - epidemiyoloji

- Primer infeksiyon yaşamın ilk 10 yılı

  4 yaş - seropozitiflik % 90 ve üzeri

- Latent: Ürogenital Sistem, Böbrek ve Sinir sistemi

- Sağlıklı kişilerde spontan reaktivasyon % 0 - 20
  (Özellikle gebe ve çocuklarda)

  Viruri % 7 Viremi ϕ

BKV - epidemiyoloji

Seropozitiflikte coğrafik bölgeye göre - % 40-95

ABD'de	% 90
İngiltere'de	% 81
isviçre'de	% 82
Ülkemizde	% 78.5

(11-17 yaş grubunda % 89)

Us D, et al. *Mikrobiyol Bul.* 1991;25(2):173-177.
Us D. Enfekiyon Hast ve Mikr. 2017: 1514

BKV - epidemiyoloji

- İmmunsupresif konakta;

  % 30-60 idrarla atılım

  Böbrek transpl. - % 1-10 nefropati

  HSCT - % 5-15 hemorajik sistit

  Diğer transplantasyon tipleri - ?

BKV – böbrek dışı nakil epidemiyoloji

Crowhurst et al. BMC Infectious Diseases (2020) 20:600
https://doi.org/10.1186/s12879-020-05292-0

BMC Infectious Diseases

CASE REPORT Open Access

BK virus-associated nephropathy in a lung transplant patient: case report and literature review

Thomas Crowhurst[1,2*], James Nolan[3], Randall Faull[1,4], Mark Holmes[1,2] and Chien-Li Holmes-Liew[1,2]

CASE REPORT | RELATO DE CASO

BK virus nephropathy in a heart transplant recipient

Nefropatia pelo vírus BK em um receptor de transplante cardíaco

JBN-2020-0049 DOI: https://doi.org/10.1590/2175-8239-

Monitoring the BK Virus in Liver Transplant Recipients: A Prospective Observational Study

Kubra Demir-Onder,[1] Vildan Avkan-Oguz,[1] Tarkan Unek,[2] Sulen Sarioglu,[3] Ozgul Sagol,[3] Ibrahim Astarcioglu[2]

Experimental and Clinical Transplantation (2014) 5: 429-436

BKV – karaciğer transplantasyonu

Monitoring th … ts:
A P…

Kubra Demir-… u,[3]

Materials and Methods: **T… study comprised patients o… consecutively received liver… l to December 31, 201… examined once, every 2… months after transplant.… evaluated on each examin… samples were collected,… assessed with real-time pol… and the presence of decoy c… cells with large… inclusions) in the uri… were followed-up for 1 year to see if rejection occurred.**

…8%) showed BK …ed BK viruria, and … No statistically …between BK virus …especting demo- …er functions, and …vity in blood was …sessment in urine …in reaction test

Karaciğer transplantasyonu
Ocak-Aralık 2011
2 hf da bir / 3 ay
İdrar Decoy, PZR
Kan PZR

39 hasta

Decoy h. 13 (% 33,3)
Viruri 11 (% 28.2)
Viremi 5 (% 12.8)

Demir-Onder K, et al. Expert Clin Transpl. 2014;5;429-36

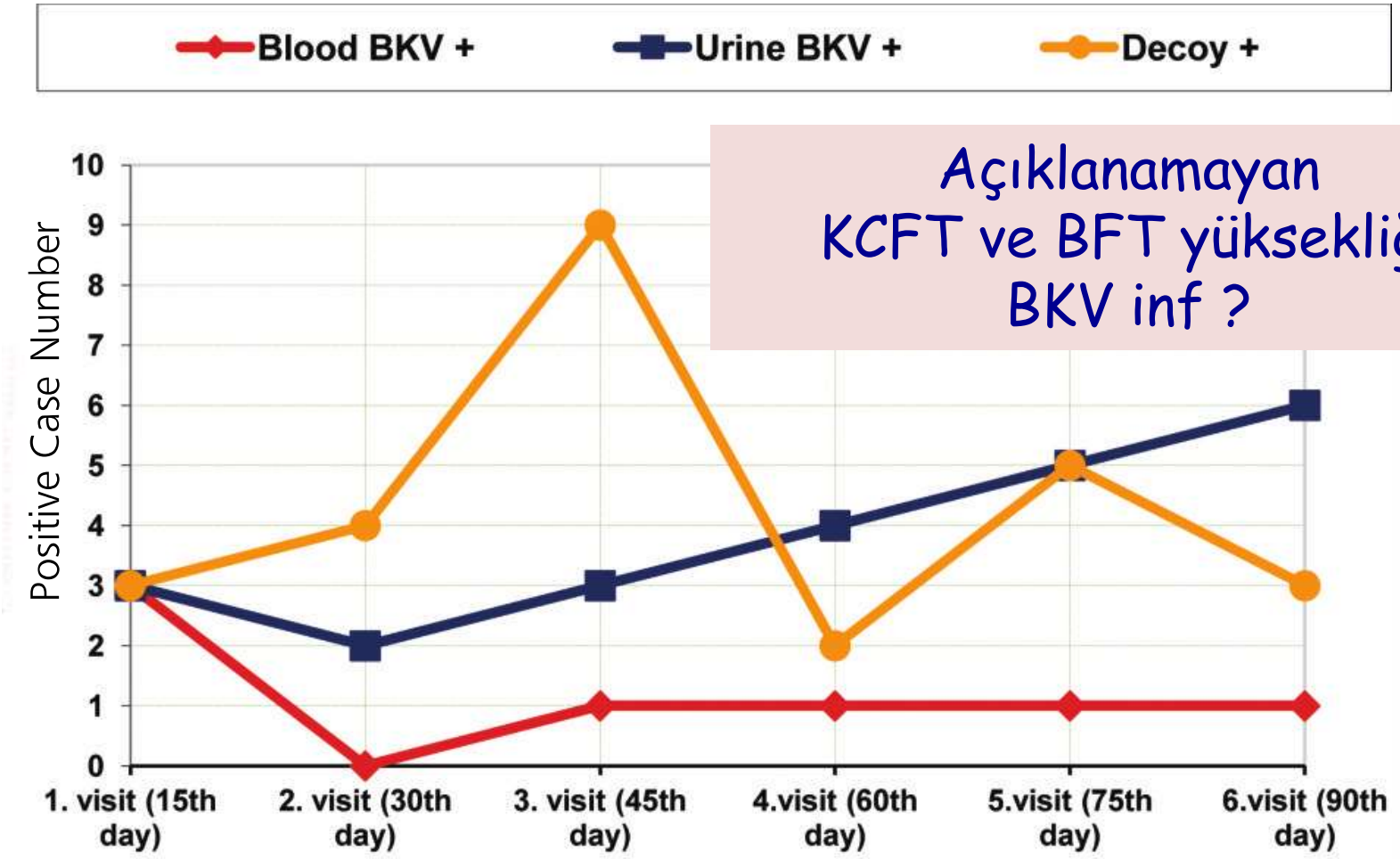
BKV – karaciğer transplantasyonu

Table 2. The Newcastle-Ottawa Quality Assessment Scale for Studies Included in the Meta-Analysis

Method	Patient Number n=39 (%)	Sample Number n=207 (%)
Urine decoy	13 (33.3)	26 (12.5)
Urine PCR	11 (28.2)	23 (11.1)
Blood PCR	5 (12.8)	7 (3.3)
Decoy + urine PCR	0 (0.0)	*
Decoy + blood PCR	2 (5.1)	*
Urine + blood PCR	2 (5.1)	*
Decoy + urine PCR+ blood PCR	0 (0.0)	*

Demir-Onder K, et al. Expert Clin Transpl. 2014;%;429-36

BKV – karaciğer transplantasyonu



Açıklanamayan
KCFT ve BFT yüksekliği
BKV inf ?

Demir-Onder K, et al. Expert Clin Transpl. 2014;%;429-36

BKV – HSCT epidemiyoloji

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

Setting	Percentage incidence, median (range)	No. of patients
Allo-HSCT	13 (7–25)	2096
Haplo-HSCT with post-transplant cyclophosphamide exposure	24.5 (19–54)	179
Auto-HSCT	0	118
Adults	16 (7–54)	1413
Children	18 (8–25)	724
Adult and paediatric population	16 (13–19)	206

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

Cesaro S, et al. J Antimicrob Chemother 2018; 73:12-21

BKV – Risk faktörleri

ALICI;

- İleri yaş, E cinsiyet,
- ABO kan grubu?, HD ?
- D-vit. eksikliği,
- Antinötrofil sitoplazmik antikorlar,
- interferon gama gen polimorfizmi,
- BKV İgA veya genotip spesifik nötralizan antikor titrelerinin düşüklüğü veya yokluğu,
- BKV spesifik T hücre yanıtı eksik./yokluğu

VERİCİ;

- ✓ Kadavra, kadın cinsiyet
- ✓ Virüri varlığı,
- ✓ BKV antikor titreleri ve yüksek viral yük,
- ✓ HLA uyumsuzluğu

BKV risk ?
Reaktivasyon
İnfeksiyon

YÖNETİM ? Soğuk iskemi süresi ? ureteral stentler, akut tubuler nekroz, akut rejeksiyon ve anti-rejeksiyon/steroid ? immunsupresyonun ?

The Second International Consensus Guidel on the Management of BK Polyomavirus in Kidney Transplantation

Camille N. Kotton, MD,[1] Nassim Kamar, MD, PhD,[2] David Wojciechowski, MD,[3] Michael Eder, MD,
Helmut Hopfer, MD,[5] Parmjeet Randhawa, MD,[6] Martina Sester, PhD,[7] Patrizia Comoli, MD,[8]
Helio Tedesco Silva, MD, PhD,[9] Greg Knoll, MD,[10] Daniel C. Brennan, MD,[11] Jennifer Trofe-Clark, Pharm
Lars Pape, MD, PhD,[14] David Axelrod, MD, MBA,[15] Bryce Kiberd, MD,[16]
Germaine Wong, MBBS, MMed, PhD,[17,18,19] and Hans H. Hirsch, MD[20,21]; on behalf of The Transplantation Society International BK Polyomavirus Consensus Group*

Abstract. BK polyomavirus (BKPyV) remains a significant challenge after kidney transplantation. International experts reviewed current evidence and updated recommendations according to Grading of Recommendations, Assessment, Development, and Evaluations (GRADE). Risk factors for BKPyV-DNAemia and biopsy-proven BKPyV-nephropathy include recipient older age, male sex, donor BKPyV-viruria, BKPyV-seropositive donor/-seronegative recipient, tacrolimus, acute rejection, and higher steroid exposure. To facilitate early intervention with limited allograft damage, all kidney transplant recipients should be screened monthly for plasma BKPyV-DNAemia loads until month 9, then every 3 mo until 2 y posttransplant (3 y for children). In resource-limited settings, urine cytology screening at similar time points can exclude BKPyV-nephropathy, and testing for plasma BKPyV-DNAemia when decoy cells are detectable. For patients with BKPyV-DNAemia loads persisting >1000 copies/mL, or exceeding 10 000 copies/mL (or equivalent), or with biopsy-proven BKPyV-nephropathy, immunosuppression should be reduced according to predefined steps targeting antiproliferative drugs, calcineurin inhibitors, or both. In adults without graft dysfunction, kidney allograft biopsy is not required unless the immunological risk is high. For children with persisting BKPyV-DNAemia, allograft biopsy may be considered even without graft dysfunction. Allograft biopsies should be interpreted in the context of all clinical and laboratory findings, including plasma BKPyV-DNAemia. Immunohistochemistry is preferred for diagnosing biopsy-proven BKPyV-nephropathy. Routine screening using the proposed strategies is cost-effective, improves clinical outcomes and quality of life. Kidney retransplantation subsequent to BKPyV-nephropathy is feasible in otherwise eligible recipients if BKPyV-DNAemia is undetectable; routine graft nephrectomy is not recommended. Current studies do not support the usage of leflunomide, cidofovir, quinolones, or IVIGs. Patients considered for experimental treatments (antivirals, vaccines, neutralizing antibodies, and adoptive T cells) should be enrolled in clinical trials.

(*Transplantation* 2024;108: 1834–1866).

The Second International Consensus Guidelines on the Management of BK Polyomavirus in Kidney Transplantation

Camille N. Kotton, MD,[1] Nassim Kamar, MD, PhD,[2] David Wojciechowski, MD,[3] Michael Eder, MD,[4] Helmut Hopfer, MD,[5] Parmjeet Randhawa, MD,[6] Martina Sester, PhD,[7] Patrizia Comoli, MD,[8] Helio Tedesco Silva, MD, PhD,[9] Greg Knoll, MD,[10] Daniel C. Brennan, MD,[11] Jennifer Trofe-Clark, PharmD,[12,13] Lars Pape, MD, PhD,[14] David Axelrod, MD, MBA,[15] Bryce Kiberd, MD,[16] Germaine Wong, MBBS, MMed, PhD,[17,18,19] and Hans H. Hirsch, MD[20,21]; on behalf of The Transplantation Society International BK Polyomavirus Consensus Group

BKPyV-DNAemia[a]		Biopsy-proven BKPyV-nephropathy[b]	
Risk factor	**Evidence level[c]**	**Risk factor**	**Evidence level[c]**
Donor factors		Donor factors	
Urinary BKPyV shedding	Low, C	Urinary BKPyV shedding	Low, C
BKPyV genotypes and subgenotypes	Very low, D	BKPyV genotypes and subgenotypes	Very low, D
BKPyV-seropositive antibody[d] status (D^+) if antibody levels are very high in living donors	Low, C	BKPyV genotypes different from the recipient (mismatching)	Very low, D
BKPyV genotypes different from the recipient (mismatching)	Very low, D	*LVGR* polymorphisms	Very low, D
Recipient factors		Recipient factors	
Older recipient age	Moderate, B	Older recipient age	Low, C
Male recipient sex	Moderate, B	Male recipient sex	Low, C
BKPyV-seronegative recipient antibody status (R^-) if the donor is BKPyV-seropositive D^+	Moderate, B		
Low recipient neutralizing antibody[e] levels against the donor BKPyV serotype	Very low, D	Low recipient neutralizing antibody levels[e] against the donor BKPyV serotype	Very low, D
Previous kidney transplantation	Low, C		
HLA class I (absence of A2, B7, B8, B51, B44, B51, B13, CW7)	Very low, D		
HLA class II (DR15)	Very low, D	HLA-E*01:03 vs protective HLA-E*01:01	Very low, D
Interferon-γ gene rs2435061	Very low, D		
Younger pediatric recipient age	Very low, D		
Obstructive uropathy as primary renal disease of pediatric recipients	Very low, D		
Transplantation factors		Transplantation factors	
Tacrolimus (compared with cyclosporine A)	High, A	Tacrolimus (compared with cyclosporine A)	High, A
Lymphocyte-depleting agents	Low, C	Lymphocyte-depleting agents	Low, C
Acute rejection	Low, C	Acute rejection	Low, C
Corticosteroids (higher maintenance; cumulative, rejection therapy)	Moderate, B	Corticosteroids (higher maintenance; cumulative, rejection therapy)	Moderate, B
mTOR inhibitors (decrease risk)	Low, C	mTOR inhibitors (decrease risk)	Low, C
Ureteric stents	Low, C	Ureteric stents	Low, C
ABOi kidney transplantation	Low, C	BKPyV genome rearranged *NCCR*	Low, C

Transplantation 2024;108: 1834-66

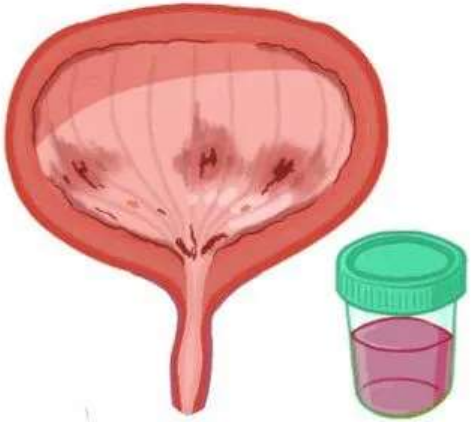
BKV-Klinik

- Böbrek transplant alıcılarında
  - Asemptomatik hematüri, kreatinin yüksekliği
  - Nefropati (% 1-10)
  - Uretral stenoz

- Allojenik hemapoietik kök hücre alıcıları (HSCT)
  - Hemorajik sistit (% 5-15)
  - İntertisyel pnömoni
  - Meningoensefalit

BK VIRUS (BKV)

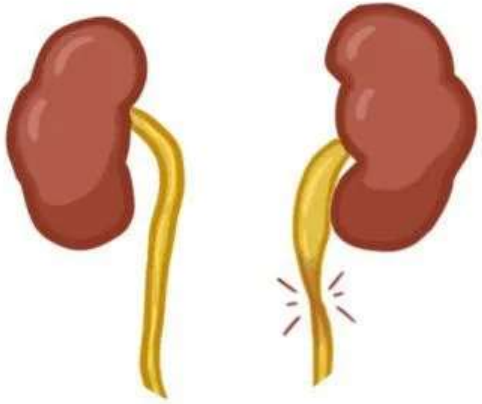
CLINICAL MANIFESTATIONS



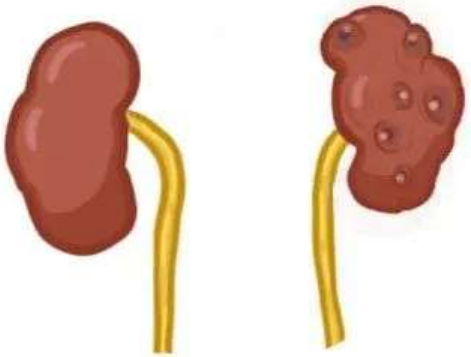
HEMORRHAGIC CYSTITIS

↳ BLOODY URINE

↳ BONE MARROW TRANSPLANT RECIPIENTS



URETERAL STENOSIS



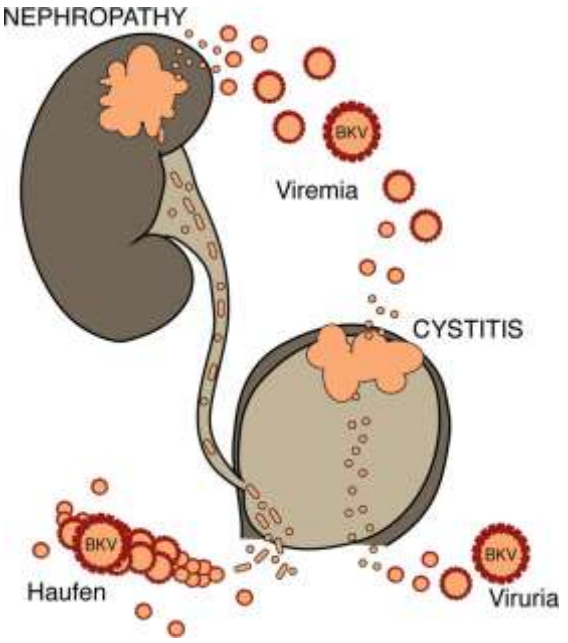
NEPHROPATHY

↳ KIDNEY TRANSPLANT

Transplantasyon sonrası (6 gün -5 yıl)
Ortalama 10-13 ay

HSCT sonrası
2-8 hafta (1hafta- 6 ay)

BKV – Klinik



Nefropati

- Kaynak ?

  Verici kaynaklı infeksiyon

  Alıcıda reaktivasyon

- İlk 2 yıl önemli

- BKV spesifik antikor yanıtı ve T hücre yanıtı

- Akut tübülointertisyel nefrit tablosu

  Epitelde litik inf.- proksimal tübül nekrozu-bazal membran harabiyeti

BKV – Klinik

Uretral stenoz

- Virusun, ureterdeki transizyonel epitel hücrelerinin proliferasyonunu indüklemesi
- Uretra epitelyumundaki sitopatik etki, ülserasyon ve enflamasyon ile obstrüktif üropati gelişimi
- Yüksek serum kreatinin düzeyleri

BKV- KLİNİK Hemorajik sistit

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

Simone Cesaro[1]*†, Tina Dalianis[2], Christine Hanssen Rinaldo[3,4], Minna Koskenvuo[5], Anna Pegoraro[1], Hermann Einsele[6], Catherine Cordonnier[7] and Hans H. Hirsch[8,9]† on behalf of the 6th European Conference on

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.

J Antimicrob Chemother 2018; 73;12-21

BKV-Tanı


BKV gösterilmesi
Viral sitopatik bulgular
BKV TANI
İmmunolojik yanıt
Histopatoloji

The Second International Consensus Guidelines on the Management of BK Polyomavirus in Kidney Transplantation

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Nakil sonrası
İlk 9 ay – Ayda bir kez
9 ay- 2yıl –Üç ayda bir
Greft fonksiyon bozukluğu ? Biopsi ?

Consensus recommendations: diagnostics

Screening

- *We recommend* regular screening of kidney transplant recipients for BKPyV replication to identify patients for treatment of probable/presumptive/biopsy-proven BKPyV-nephropathy (**strong, A**)
- *We recommend* screening kidney transplant recipients for plasma BKPyV loads *monthly* until mo 9, then *every* 3 mo until 2 y posttransplantation (**stron**
- If plasma
- In kidney 2–4 wk
- In kidney DNAem
- In resourc the abc
- If blood sampling is not available or considered inappropriate for screening, *we suggest* measuring urine BKPyV-DNA loads by QNAT at similar time points as recommended above (**weak, D**)
- If urine decoy cells or urine BKPyV-DNA loads of >10 million copies/mL (or equivalent) are detected, *we recommend* measuring plasma BKPyV-DNA loads to guide clinical management (**strong, B**)
- For combined kidney/solid organ transplants, including pancreas, *we suggest* extending screening for BKPyV-DNAemia every 3 mo up to 36 mo post-transplant (**weak, C**)
- For non-kidney solid organ transplant recipients, *we recommend to not* routinely screen for BKPyV-DNAemia (**strong, B**)
- For non-kidney solid organ transplant recipients presenting with declining renal function, in the absence of other reasons for the renal compromise, *we suggest* testing for BKPyV-DNAemia and looking for BKPyV-nephropathy if a renal biopsy is performed (**weak, C**)

- Plazma BKPyV-DNA 1000-10 000 c/mL - 2-3 hf içinde doğrulama
- > 1000 c/mL ; BKPyVDNAemi 2-4 haftada izlem
- İmmunsupresyon arttırılmesi gerekiyor veya rejeksiyon tedavisi yapılacaksa ayda bir 3 ay izlem

Transplantation 2024;108: 1834-66

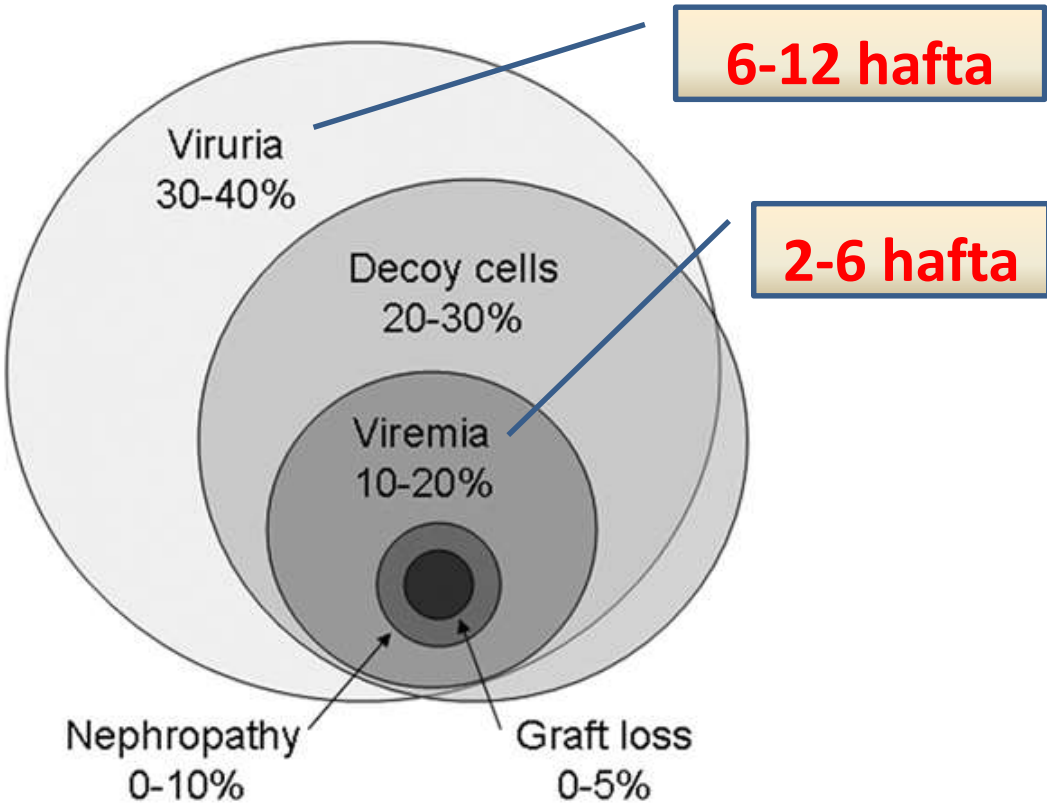
BKV-Tanı

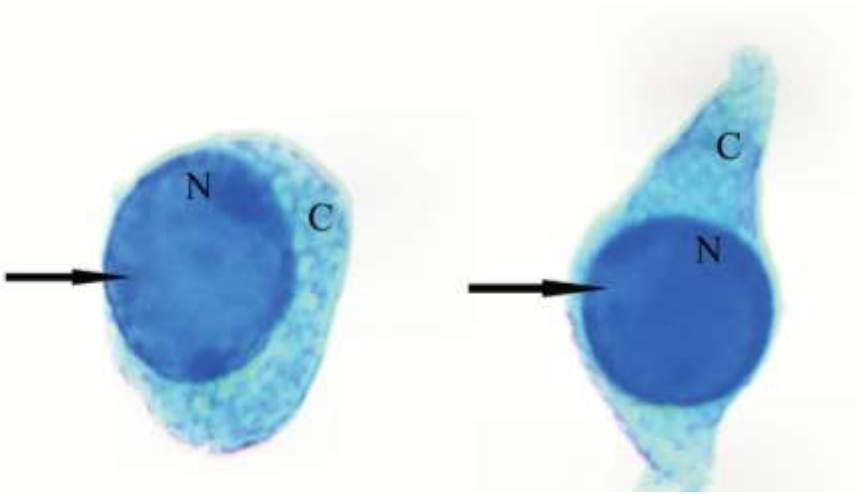
İdrarda decoy hücresi

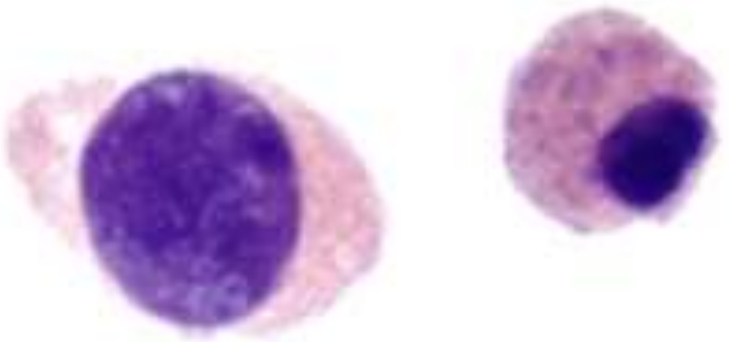
İdrarda PZR

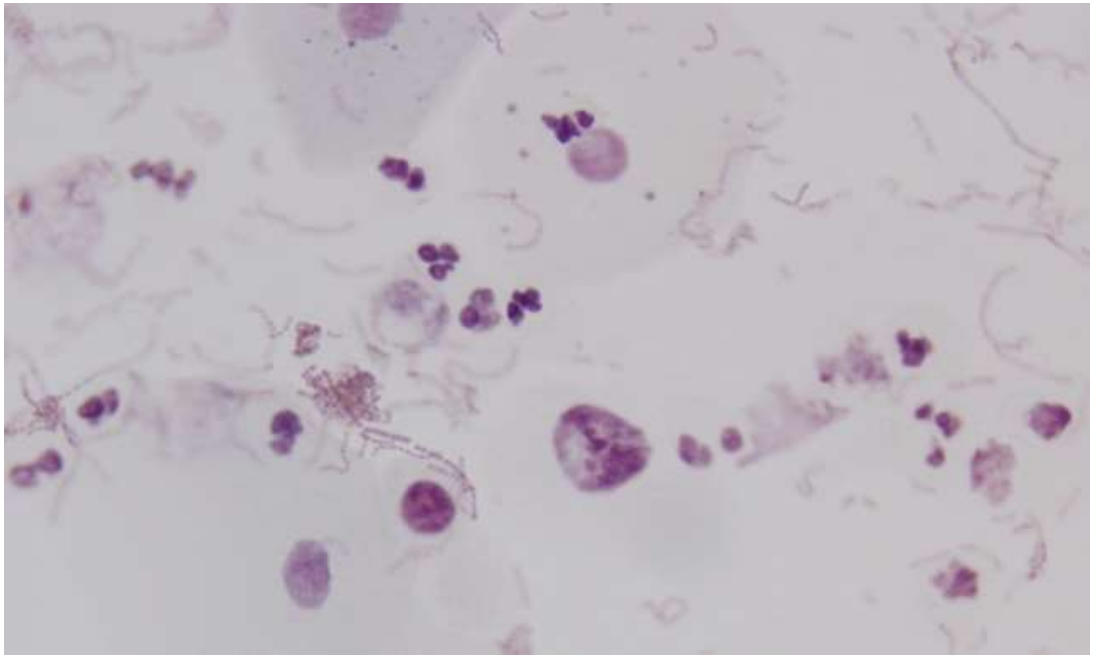
Kanda PZR

Histopatoloji









Demir-Onder K, et al. Expert Clin Transpl. 2014:29-36

The Second International Consensus Guidelines on the Management of BK Polyomavirus in Kidney Transplantation

Camille N. Kotton, MD,[1] Nassim Kamar, MD, PhD,[2] David Wojciechowski, MD,[3] Michael Eder, MD,[4] Helmut Hopfer, MD,[5] Parmjeet Randhawa, MD,[6] Martina Sester, PhD,[7] Patrizia Comoli, MD,[8] Helio Tedesco Silva, MD, PhD,[9] Greg Knoll, MD,[10] Daniel C. Brennan, MD,[11] Jennifer Trofe-Clark, PharmD,[12,13] Lars Pape, MD, PhD,[14] David Axelrod, MD, MBA,[15] Bryce Kiberd, MD,[16] Germaine Wong, MBBS, MMed, PhD,[17,18,19] and Hans H. Hirsch, MD[20,21]; on behalf of The Transplantation Society International BK Polyomavirus Consensus Gr

Aynı örnek, aynı laboratuvar

Laboratory testing

- *We recommend* that the same specimen type and assay be used in the same diagnostic laboratory to avoid uncertainty because of assay variability when monitoring the dynamics of BKPyV-DNAemia (**strong, B**)
- *We recommend* using QNAT assays that target conserved BKPyV genome sequences to permit the detection of all genotypes and variants (**strong, C**)
- *We recommend* using QNAT assays with a short amplicon size of <150 bp to avoid significant underquantification (**strong, C**)
- *We recommend* that clinical virology laboratories serving transplantation programs participate in external quality assurance programs for quantitative BKPyV-DNA load testing (**strong, C**)

Statements

- Further data are needed:
  - before pretransplant BKPyV serology of donor or recipient can be recommended for risk stratifying kidney transplant recipients for posttransplant BKPyV-DNAemia/-nephropathy
  - before pretransplant BKPyV-specific CMI measurement can be recommended for routine clinical use to predict posttransplant BKPyV-DNAemia/-nephropathy
  - before posttransplant BKPyV serology can be recommended for routine clinical use to predict the course of BKPyV-DNAemia/-nephropathy
  - before posttransplant BKPyV-specific CMI can be recommended for routine clinical use to predict the course of posttransplant BKPyV-DNAemia/-nephropathy
  - before posttransplant BKPyV-specific CMI can be used to safely guide changes in immunosuppression
  - before recommendations can be made as to how best to screen for BKPyV-associated urothelial carcinoma in kidney transplant recipients with ongoing BKPyV-DNAemia/-nephropathy

Transplantation 2024;108: 1834-66

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Böbrek Transplantasyonu

Transplantasyon sonrası;
- ✓ İlk 9 ay - Ayda bir
- ✓ 9 ay-2 yıl - Üç ayda bir

Graft fonksiyon bozukluğu?
Biopsi yapılırsa ?

Çocuklarda
3 ayda bir -3 yıl izlem
İdrarda Decoy h.
BKPvDNAuria (10 milyon c/mL)
Plazma BKPyVDNAemi izlemi

BKPyV DNAemi

no

yes

BKPyVDNAemi
1 000-10 000 c/mL iki kez > 2 hafta

VEYA

BKPyVDNAemi
> 10 000 c/mL bir kez

Yüksek immünolojik risk

yes

Böbrek biopsisi
Klinik+lab+virolojik bulgular ve önceki biopsi bulguları ile yorumla

no

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The Second International Consensus Guidelines ... f BK Polyomavirus in ... n

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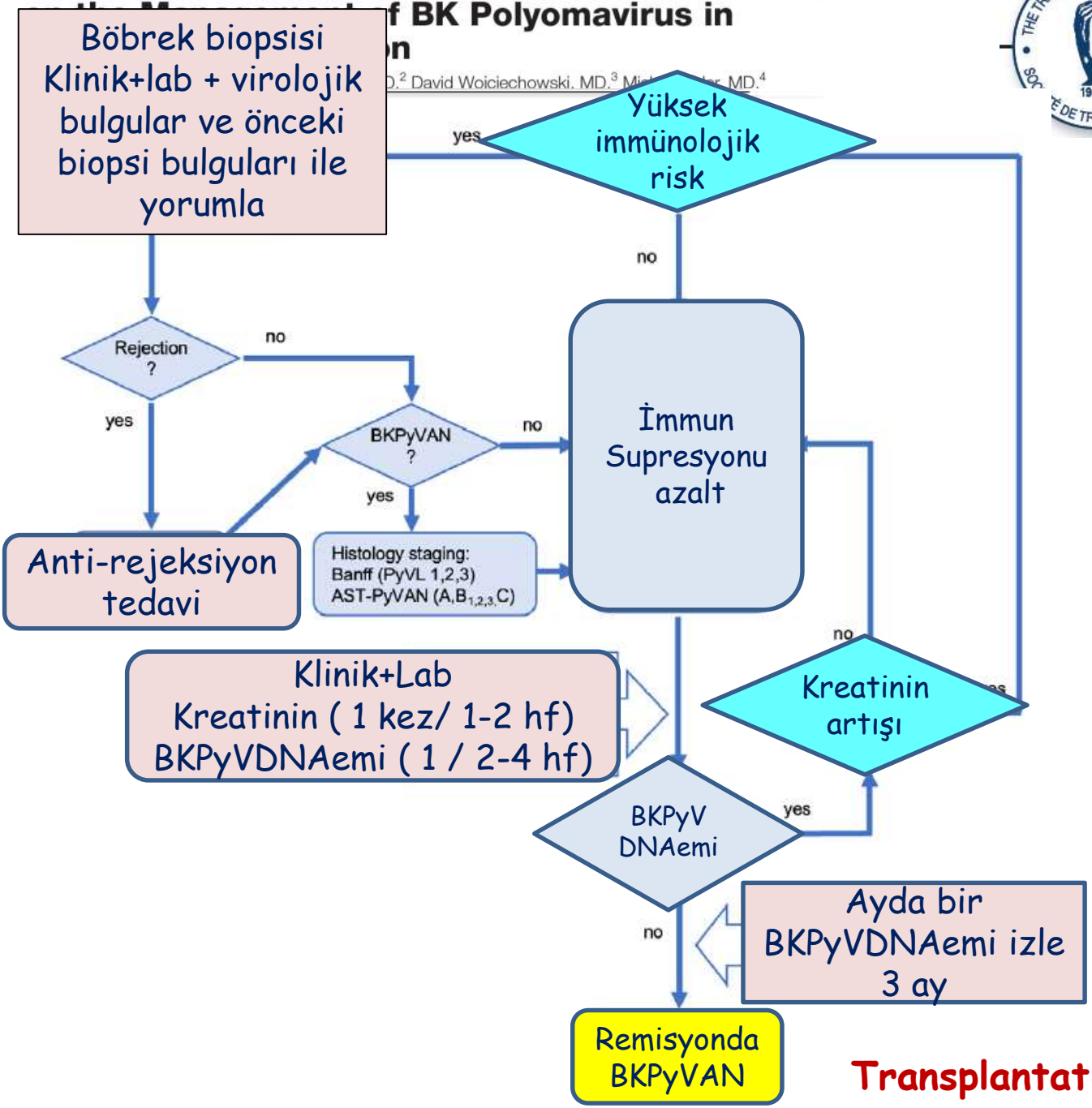

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Statement

- In the absence ... ply high-dose steroid ... or the next 3 to 6 m...
- Depending on t... decreasing immunos...

Akut rejeksiyon ??

Yüksek doz kortikosteroid uygulaması

Allograft renal fonksiyon takibi

Aylık BKPyVDNAemi izlemi (3-6 ay)

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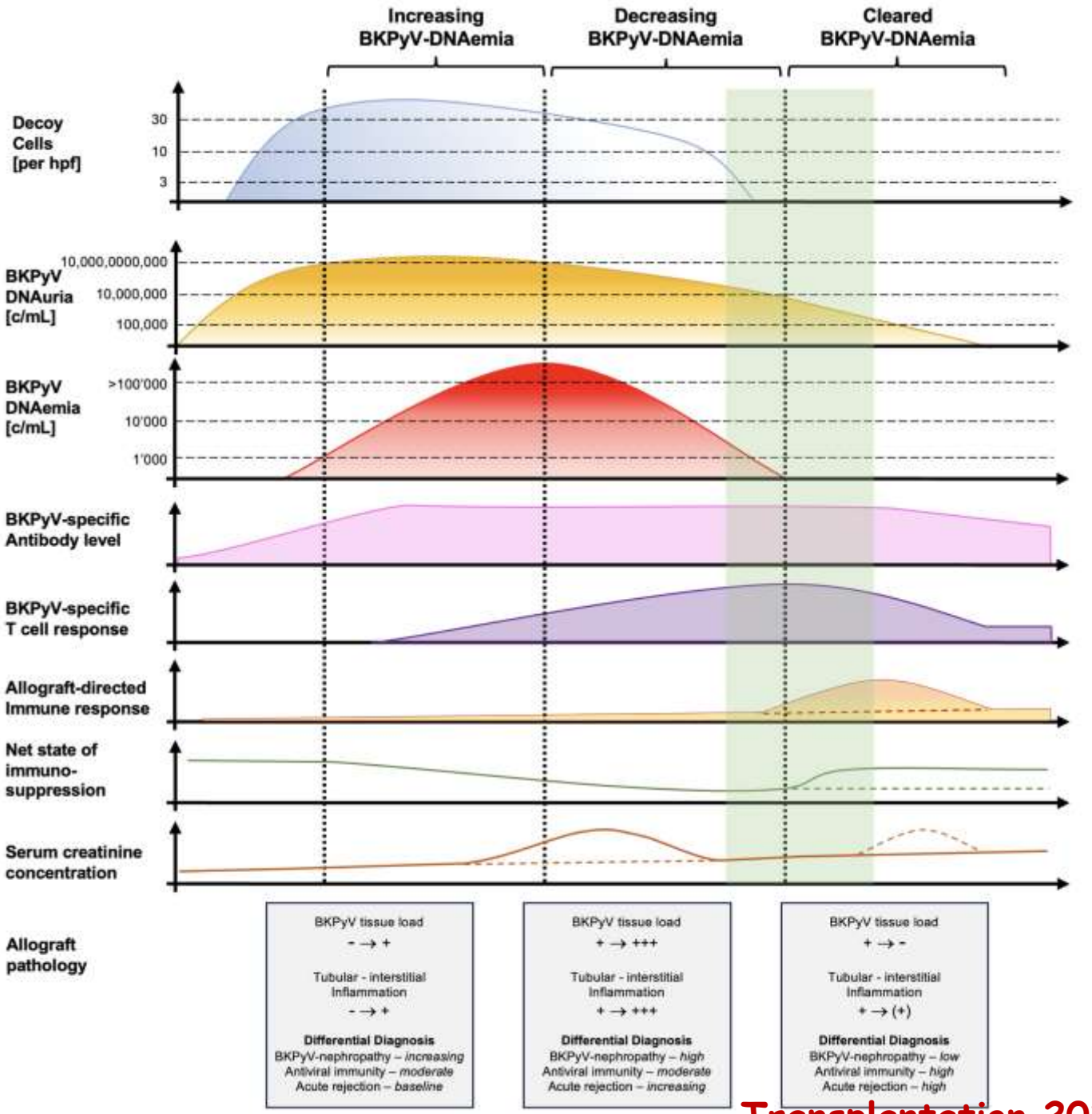

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Merkeze, immunsupresyona, kullanılan yönteme göre farklılık

Decoy h % 17 -73

BK viremi % 3- 62

Histopatoloji < 1 – 10

Graft kaybı < 1 - 1

Study author(s), yr (refer				iopsy-confirmed KVAN	Graft loss due to BKVAN	No. of recipients
Hirsch et al., 2002 (121)					Nil	78
Brennan et al., 2005 (129,				il	Nil	200
Bessollette-Bodin et al., 2(				il	Nil	104
Drachenberg et al., 2007					Nil	103
Dadhania et al., 2008 (23					Nil	120
Almeras et al., 2011 (159)				1	<1	119
Chakera et al., 2011 (134)					Nil	313
Sood et al., 2012 (238)					Nil	240
Barbosa et al., 2013 (239)					<1	187
					<1	284
Borni-Duval et al., 2013 (1					NR	240
Hirsch et al., 2013 (94)				R	NR	629
Schaub et al., 2010 (162)					Nil	203
Theodoropoulos et al., 2013 (152)	AZM/IL-2, T, M, ±P	38	12	5	1	666
Knoll et al., 2014 (194)	IL-2/ATG, T/C, M, P	NR	31	Nil	Nil	154
3C Study Collaborative Group et al.,	AZM, T, M	NR	7	1	Nil	426
2014 (151)	IL-2, T, M, P	NR	3	2	Nil	426
Schwarz et al., 2016 (240)		40	29	10	1	214
Sawinksi et al., 2015 (241)	ATG, T, M, P	NR	17	2	Nil	785
Wunderink et al., 2017 (142)	AZM/IL-2, T/C, M, P	NR	27	3	Nil	407

[a]T, tacrolimus; C, cyclosporine; A, azathioprine; M, mycophenolate; S, sirolimus; P, prednisolone; AZM, alemtuzumab; ATG, thymoglobulin; IL-2, basiliximab/daclizumab; R, rituximab; IVIG, intravenous immunoglobulin; NR, not reported.

Ambalathingal et al. Clin Microbiol Rev 2017; 30:503-528

TABLE 1 Diagnostic testing and prognostic values for BKV infection and disease

Diagnostic method	Sensitivity for detection of BKV infection (%)	Specificity for detection of BKV infection (%)	Positive predictive value (PPV) for diagnosis of BKVAN (%)	Negative predictive value (NPV) for diagnosis of BKVAN (%)	Comment(s)
Urine cytology for decoy cells	>80	70–84	20–35	>95	Useful for determining BKV reactivation but low PPV for BKVAN
Urine PCR	>98	78	30–40	>95	Effective at detecting possible BKVAN with BKV loads of $>1 \times 10^7$ copies/m
Serum PCR	90–100	83–96	50–80	>95	Highly specific and sensitive for detectin BKV reactivation; PPV for BKVAN increases with a higher BKV load; a cutoff of 1×10^4 copies/ml has been suggested as a threshold for biopsy specimens to exclude BKVAN
Haufen detection (electron microscopy)	100	>95	>95	100	Higher reported PPV than that for any other method, but the method is expensive
Histopathology			>98	100	Kidney biopsy is the gold standard for determining disease progression Stage/class A: infection/cytopathic changes, <25%; interstitial inflammation/tubular atrophy/fibrosis, <10% Stage/class B: infection/cytopathic changes, 11–50%; interstitial inflammation/tubular atrophy/fibrosis, <50% Stage/class C: infection/cytopathic changes, >50%; interstitial inflammation/tubular atrophy/fibrosis, >50

Tanı yöntemlerinde
NEGATİFLİK DAHA DEĞERLİ

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Karaciğer transplantasyonunda BKV tanı

Table 3. Specificity and Sensitivity Rates and Negative and Positive Predictive Values of the Methods According to Viremia

Test		Blood PCR +	Blood PCR –	Blood PCR T	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
	+	2	9	11				
Urine	–	3	25	28	40%	73.5%	18.1%	89.2%
PCR	T	5	34	39				
	+	2	11	13				
Decoy	–	3	23	26	40%	67.6%	15.3%	88.4%
	T	5	34	39				

NEGATİFLİK DAHA DEĞERLİ

Demir-Onder K, et al. Expert Clin Transpl. 2014;%;429-36

BKV -İzlem

- Decoy hücresi transplantasyon sonrası ;
  - İlk 3 ay için iki haftada bir
  - 6. aya kadar ayda bir kez
  - İlk 2 yıl süresince her 3 ayda bir

- Viremi izlenecekse transplantasyon sonrası;
  - İlk 9 ay, ayda bir
  - 2 yıl süresince her 3 ayda bir

BKV-Tedavi

İmmunsupresyonu AZALT

İlaç	Çukur Düzeyi	Öneri
Takrolimus	< 6 ng/mL	Güçlü, orta
Siklosporin	< 150 ng/mL	Güçlü, orta
Mikofenolat mofetil	Günlük dozun yarısı veya azı	Güçlü, orta
Sirolimus	< 6 ng/mL	Zayıf, düşük

Hirsh HH,et al. Clin Transplantation 2019; 33:e13528

Ek öneriler- değişim

Takrolimus	Düşük doz Siklosporin A
Kalsinörin inhibitörleri	Sirolimus
Mikofenolik mofelat	Leflunamid

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Camille
Helmut
Helio Te
Lars Pa
Germai
Society

mTOR inhibitörü ve CNI kombinasyonu veya belatacept temelli tedavi alırken BKPyVDNAemi ve biopsi ile kanıtlı nefropati gelişen nakil alıcılarında ;

immunsupresyonun azaltılmasına rehberlik edecek veri YOK.

Bela

- For kidney transplant recipients developing BKPyV-DNAemia or biopsy-proven BKPyV-nephropathy while receiving a belatacept-based regimen, there is insufficient data to guide the reduction of immunosuppression.

Possible approaches include

-to first reduce or discontinue the antimetabolite (**expert opinion**)

-to increase the interval of belatacept administration to every 6–8 wk (**expert opinion**)

-to switch to a low-level calcineurin-based or mTOR inhibitor–based immunosuppressive regimen (**expert opinion**)

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Society International BK Polyomavirus Consensus Group*

Cidofovir (B)

Leflunomide (B)

Florokinolon (A)

Statinler (A)

IVIG değerlendirilebilir

Adjunctive therapies

- *We suggest* consideration of intravenous immunoglobulin administration as *adjuvant therapy* ponse to reduced immunosuppression to facilitate viral clearance **(weak, D)**
- *We suggest* consideration of IVIG administration as *adjuvant therapy* to prevent acute rejectio immunosuppression reduction is necessary to facilitate viral clearance (**weak, D**)
- *We recommend* to not use *cidofovir* to treat BKPyV-DNAemia/-nephropathy in kidney transplant recipients (**strong, B**)
- *We recommend* to not use *leflunomide* to treat BKPyV-DNAemia/-nephropathy **(strong, B)**
- *We recommend* to not use *fluoroquinolones* to prevent or treat BKPyV-DNAemia or BKPyV-nephropathy in kidney transplant recipients (**strong, A**)
- *We recommend* to not use *statins* to prevent or treat BKPyV-DNAemia or BKPyV-nephropathy in kidney transplant recipients (**strong, A**)

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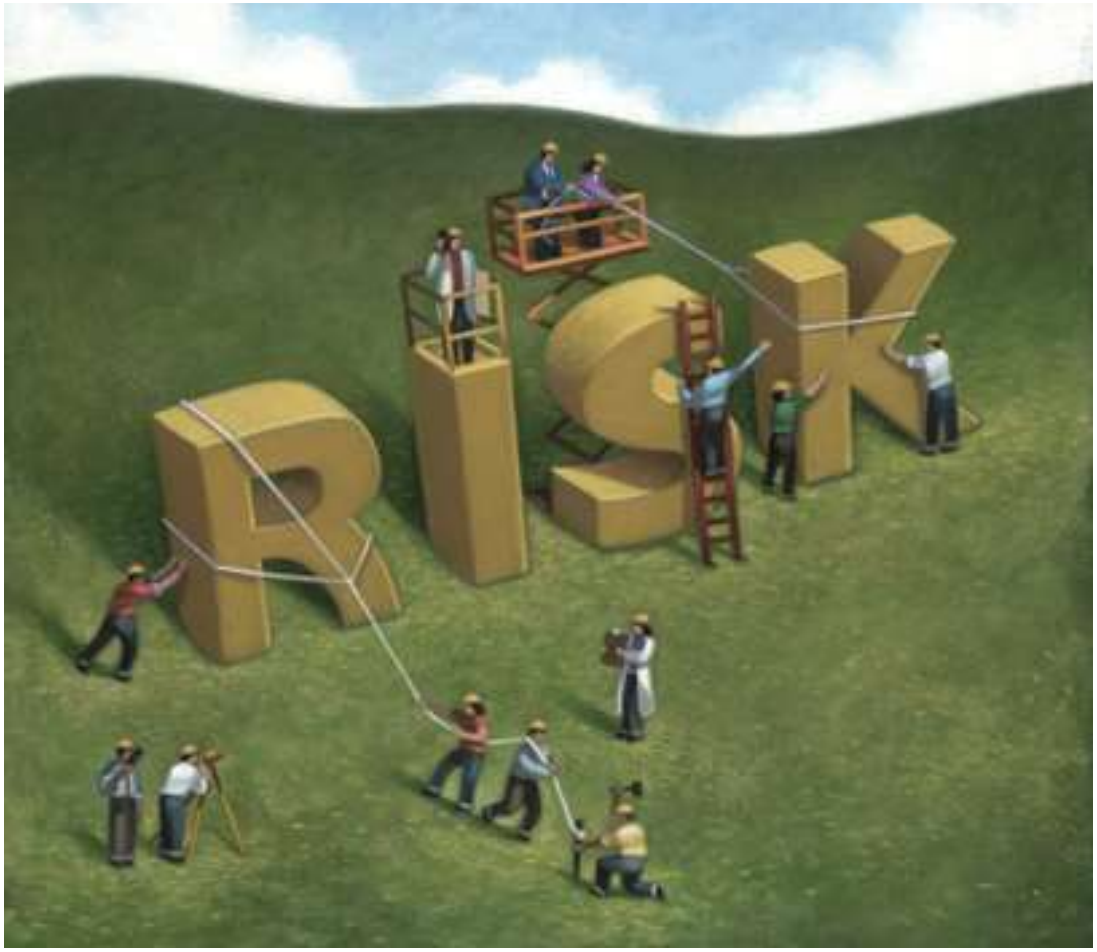
SONUÇ

- Transplante edilen organ ? BT, HSCT önemli
- İnfeksiyon kliniği değişken
- Nakil öncesi tarama rutin değil, sonrası **İzlem** (+)
- Tanıda moleküler yöntemler bir adım önde
- Tedavide - İmmunsupresyon AZALTILMALI
  Her merkez kendi protokolünü belirlemeli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