



II. Viral Enfeksiyonlar ve Başıřıklama Sempozyumu

BKV: Nefropatiden Greft Kaybına

Dr. Ebru ORUÇ

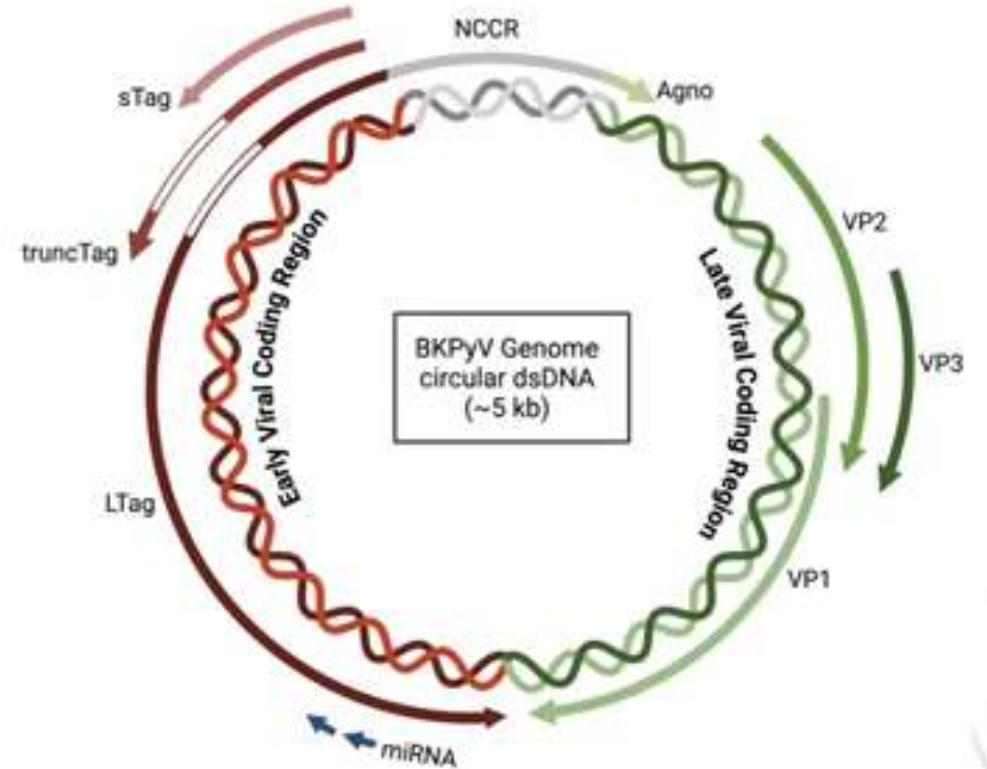
Saęlık Bilimleri Üniversitesi Etlik Şehir Hastanesi

Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji AD

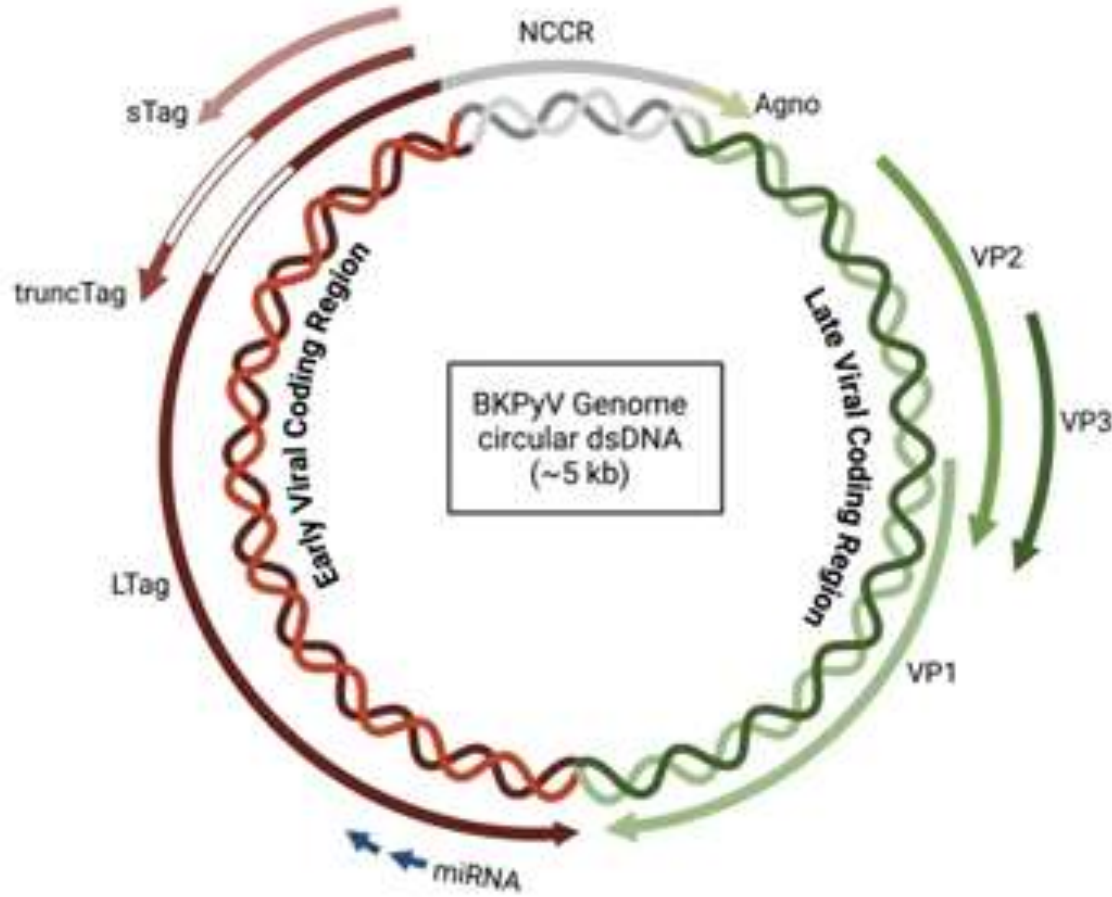
20.09.2025

BK Polyomavirus (BKPyV)

- 1971 yılında üreteral darlığı olan böbrek nakil hastasının idrarından izole edilmiştir.
- Polyomaviridae ailesinden
- Çift sarmallı
- Zarfsız, ikozahedral
- DNA virüsü
- Tür spesifik
- 14 adet insan polyoma virüs

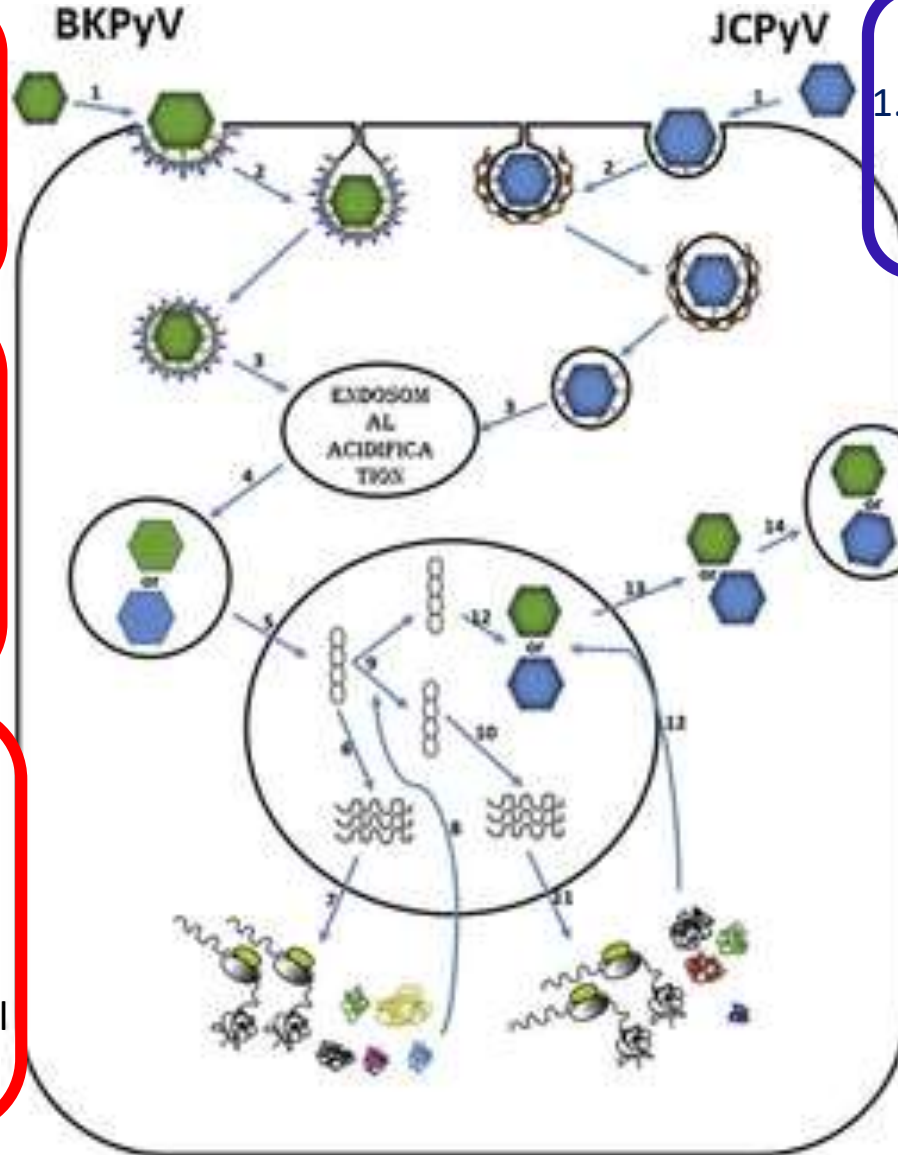


BKPyV Genom



- **Erken viral gen bölgesi (EVGR)**
 - TAG ve tAg kodlayan, viral transformasyon ve gen ifadesinin düzenlenmesinden sorumlu düzenleyici proteinleri içeren bölgedir.
- **Geç viral gen bölgesi (LVGR)**
 - VP1, VP2 ve VP3'ü ve yapısal olmayan ancak çoklu düzenleyici özellikleri olan agnoproteini kodlar.
- **Kodlama yapmayan kontrol bölgesi (NCCR)**
 - Viral erken ve geç genlerin ekspresyonunu, konakçı hücrenin farklılaşması ve aktivasyonu ile uyumu düzenler.

BKPyV Yaşam Döngüsü



1.A-(2,3) sialik asit veya gangliosidlere bağlanma

2. Caveolae aracılı endositozla giriş

3. BKV/JCV endozomal asitletme ve ER ile füzyondan geçiş.

4. ER'de kısmen zarsız virüs haline gelir.

5. Kısmen zarfsız virüs çekirdeğe girer.

6 & 7. EVGR çekirdekte transkripsiyonlanır ve sitozolde translasyonlanır.

8 & 9. EVGR proteini çekirdeğe girer ve viral genom replikasyonunu başlatır.

1.A-(2,6) bağlı sialik aside bağlanma

2. Clathrin bağımlı endositoz yoluyla giriş

15 BKV/JCV enfekte hücreden salınır.

13 & 14. Virion BKV/JCV çekirdekten ve plazma membranından dışarı çıkar.

12. Replik viral genom, LGVR bir araya gelir.

10 & 11. LVGR çekirdekte transkripsiyonlanır ve sitozolde translasyonlanır.

BKPyV-Epidemiyoloji

Seropozitiflik coğrafik bölgeye göre - % 40-100

Countries	BK-seroprevalence (%)
England	83–91
Finland	60
Italy	83
Germany	71
Switzerland	82
Czech Republic	69
Maryland, United States	69–100
Australia	97
China	45
Japan	80.8
Iran	41.8

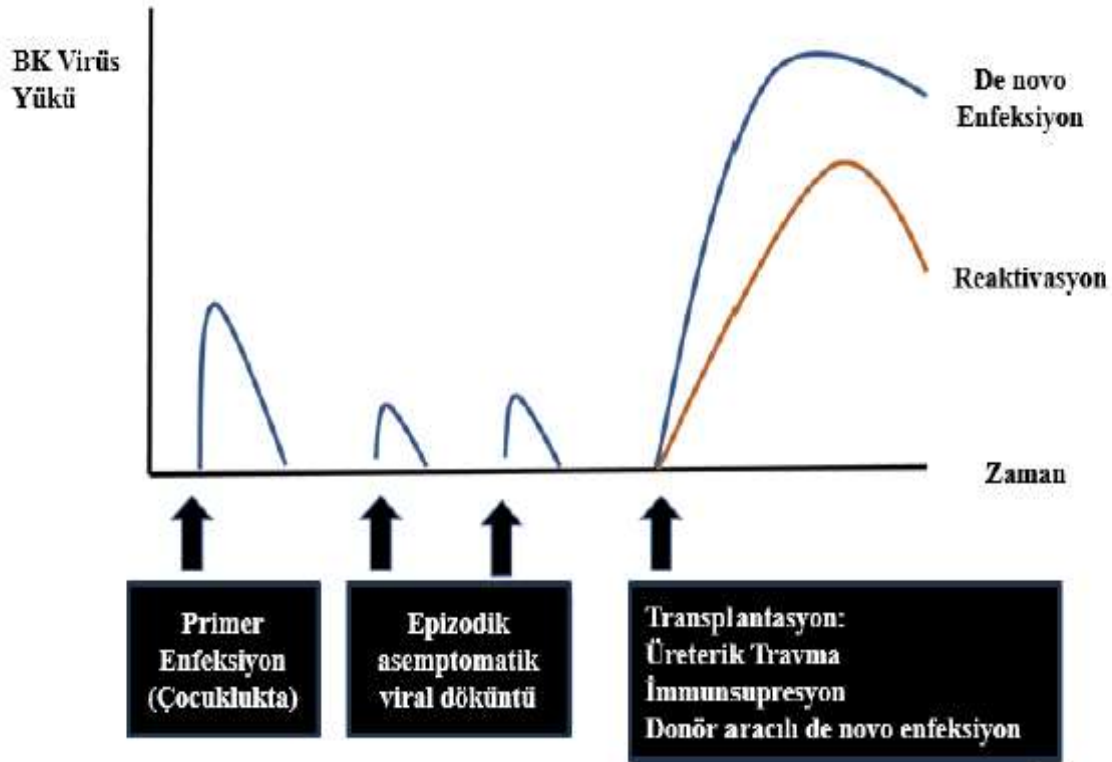
Ülkemizde % 78.5
(11-17 yaş grubunda % 89)

Us D, et al. Mikrobiyol Bul. 1991;25(2):173-177.

Us D. Enfeksiyon Hast ve Mikr. 2017:151

Fakhriya A, et al.JONEST 2020;20:127-150.

BKPyV Prevalans



- ✓ Sağlıklı gebelerin %3,2'sinde 2. trimestır sonu ve 3. trimestır başında
- ✓ İmmükompetan bireylerin %0 -20'sinde
- ✓ İmmüsupresyonlu bireylerde %10-60

Coleman, D.V. *J Infect Dis*, 1980;42(1):1-8.

Knowles, W.A. *Adv Exp Med Biol*, 2006;577:19-45.

Nickeleit, V. *N Engl J Med*, 2000;342(18):1309-15.

Bulařma Yolu

- ✓ Solunum yolu
 - Üst solunum yolu, tonsiller, valdeyer halkası
- ✓ Oral-fekal - Kanalizasyon bulaşı
- ✓ Kan transfüzyonu – Lökositler
- ✓ Transplasental -Fetus



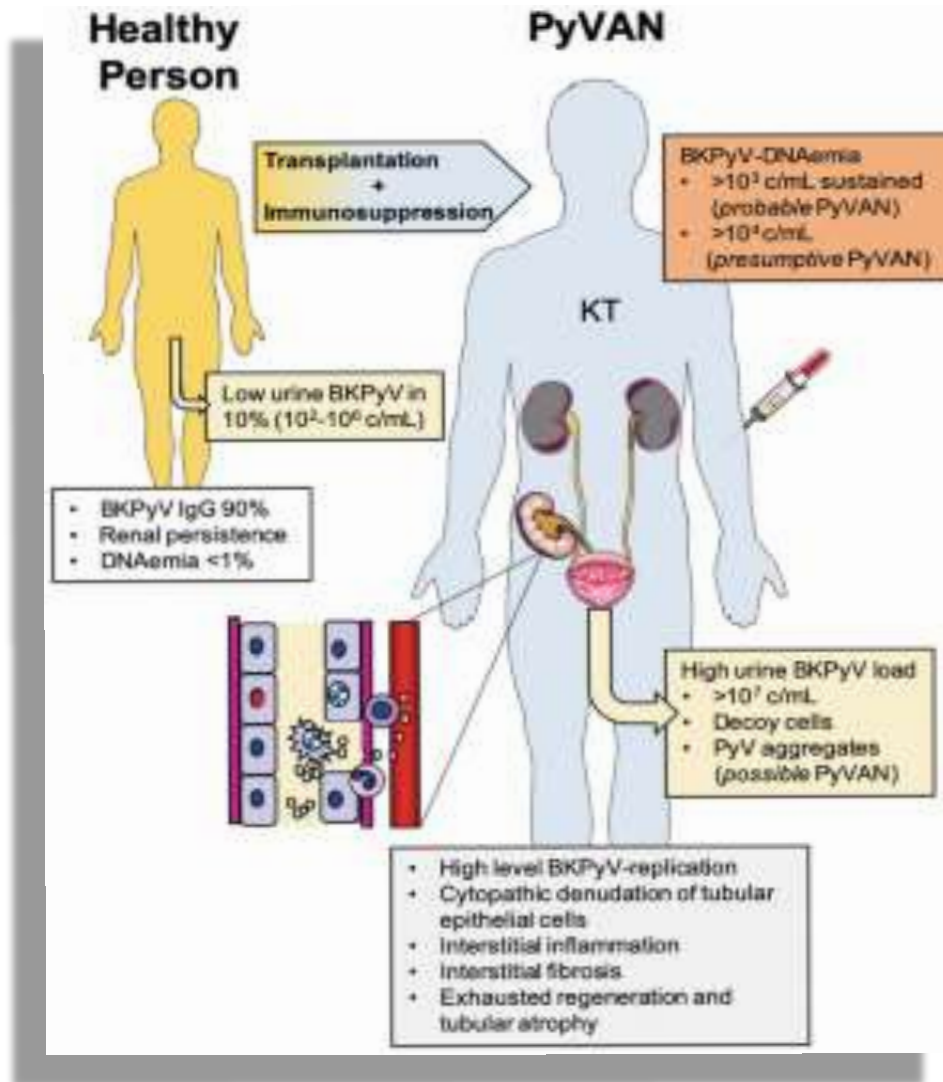
BKPyV-Klinik

- **Böbrek transplant alıcılarında**
 - Asemptomatik hematüri, kreatinin yüksekliği
 - Nefropati (% 1-10)
 - Uretral stenoz
- **Allojenik hemapoietik kök hücre alıcıları (HKHN)**
 - Hemorajik sistit (% 5-15)



intertisyel pnömoni
Meningoensefalit
Retinit
Hepatit
Vaskülopatii
Üroepitelyal kanser

Böbrek Nakli (BN)-BKPyV



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

Hemapoietik Kök Hücre Nakli-BKPyV

Phase I

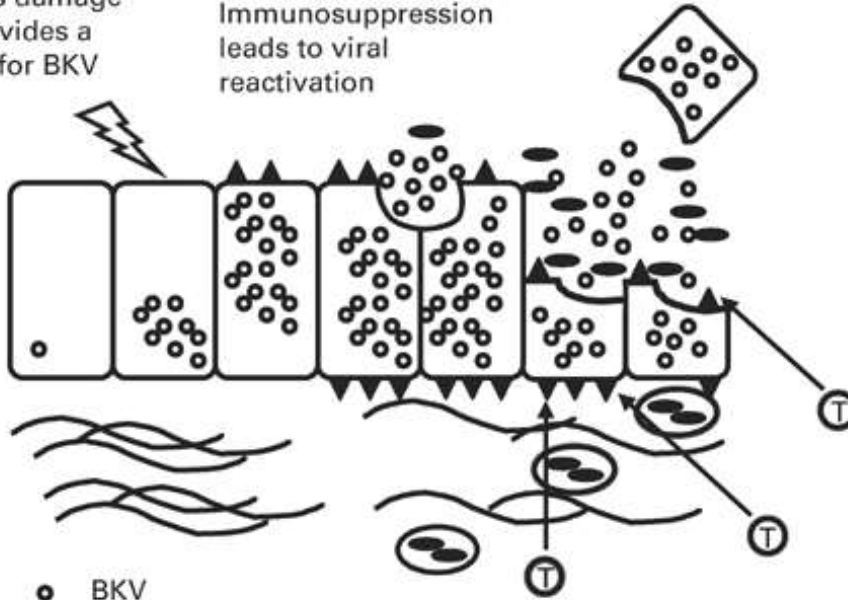
Chemo-irradiation causes damage to uroepithelium and provides a permissive environment for BKV replication

Phase 2

Immunosuppression leads to viral reactivation

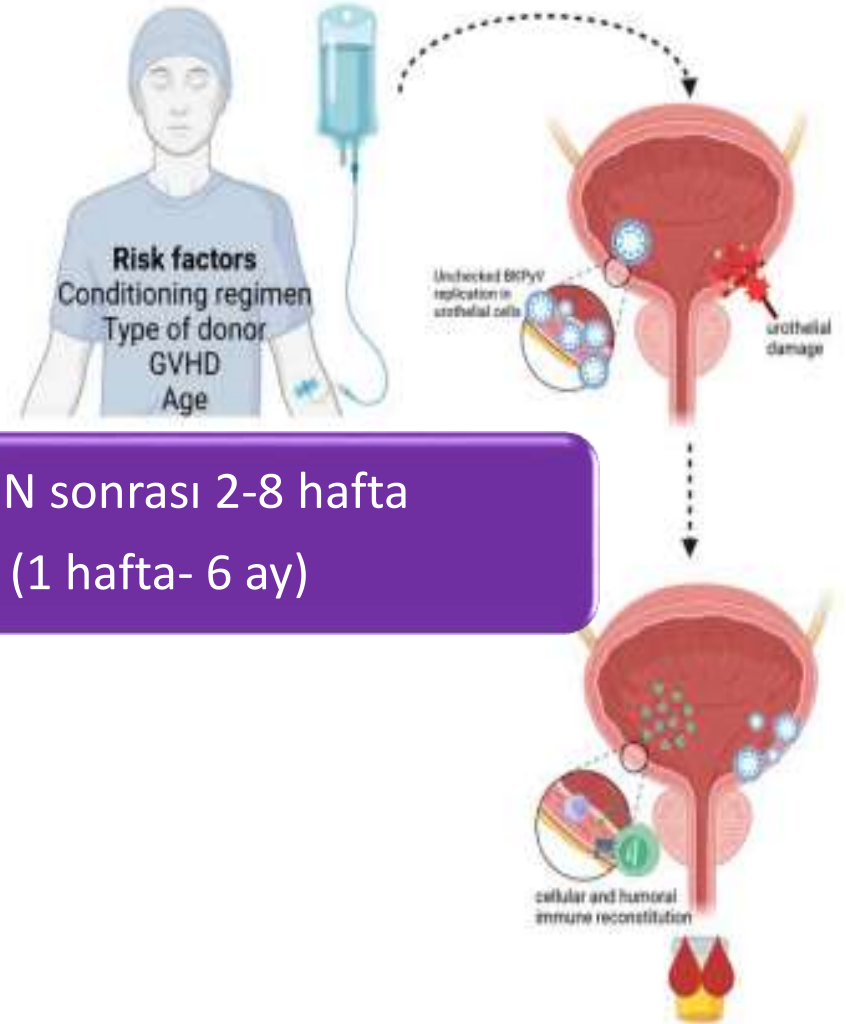
Transitional Epithelium

Submucosa



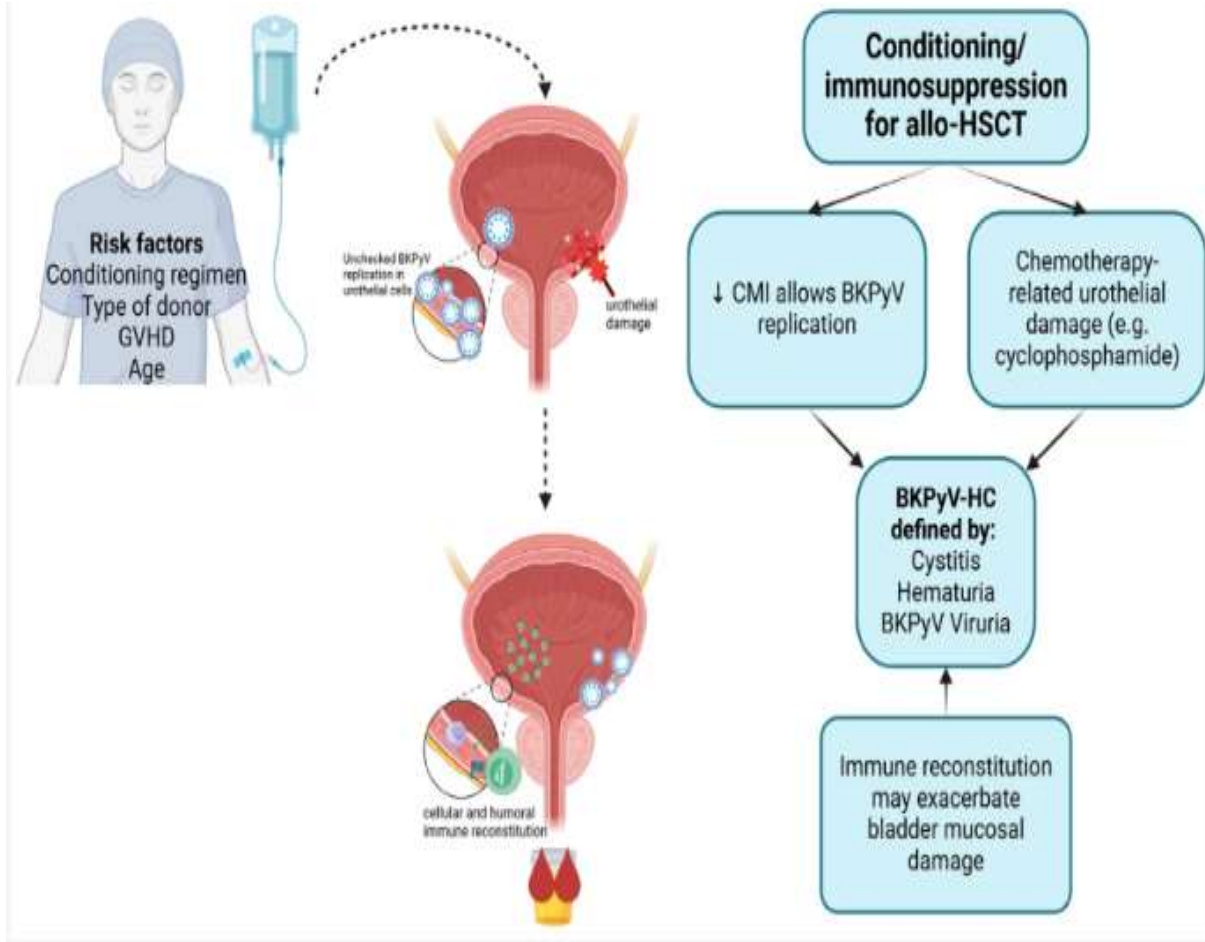
Phase 3

Allo-immune attack by donor lymphoid cells against BK viral antigens perpetuates mucosal damage



Hemorajik Sistit

Hemapoietik Kök Hücre Nakli-BKPyV-HC



%5-15 oranında

ECIL-6 asemptomatik hastada rutin tarama önermiyor.

Klinik seyri akut ve kendini sınırlar, şiddeti değişkenlik gösterir.

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

Simone Cesaro^{1*†}, Tina Dalianis², Christine Hanssen Rinaldo^{3,4}, Minna Koskenvuo⁵, Anna Pegoraro¹, Hermann Einsele⁶, Catherine Cordonnier⁷ and Hans H. Hirsch^{8,9†} on behalf of the 6th European Conference on

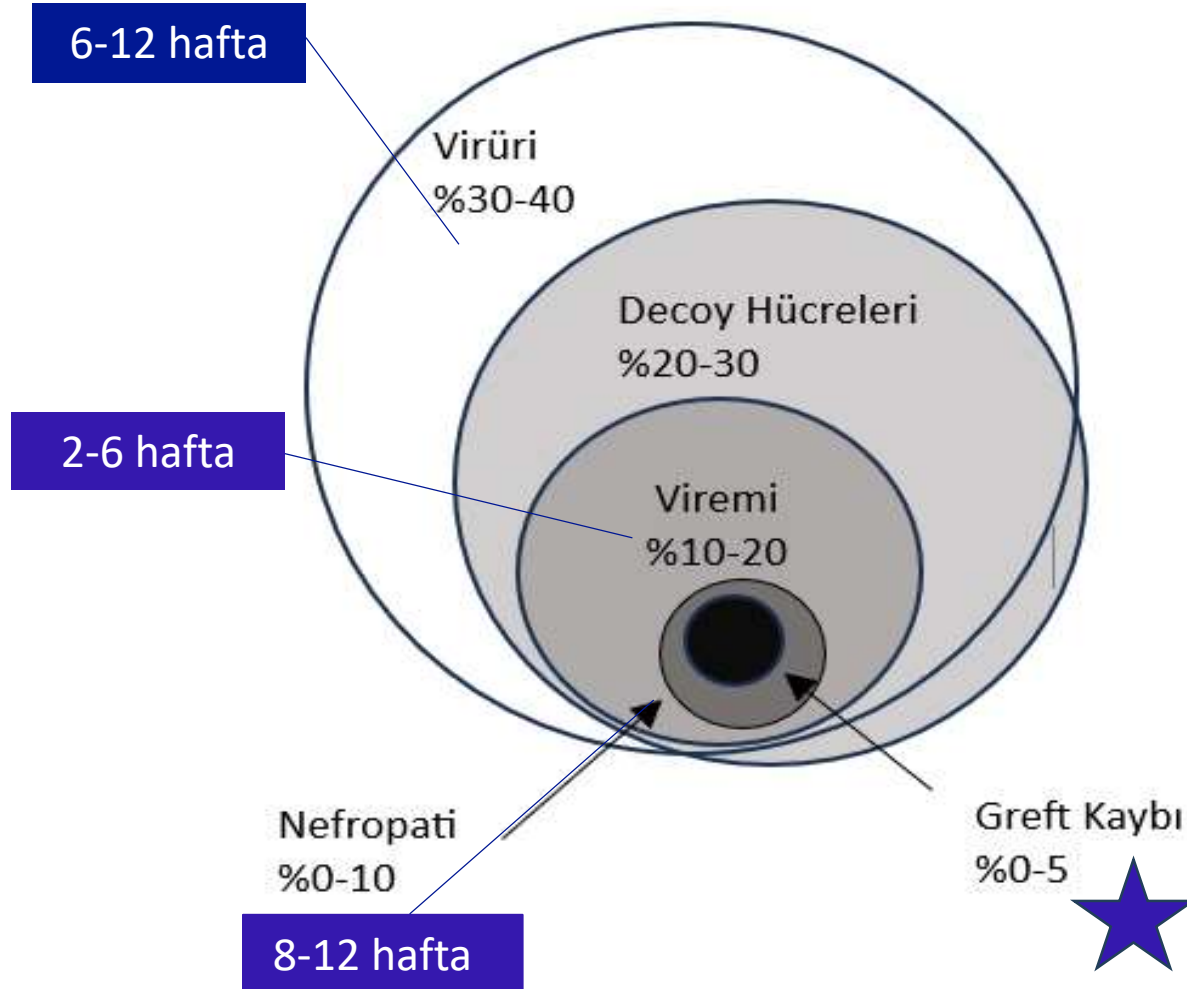
BKPyV-HC

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

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

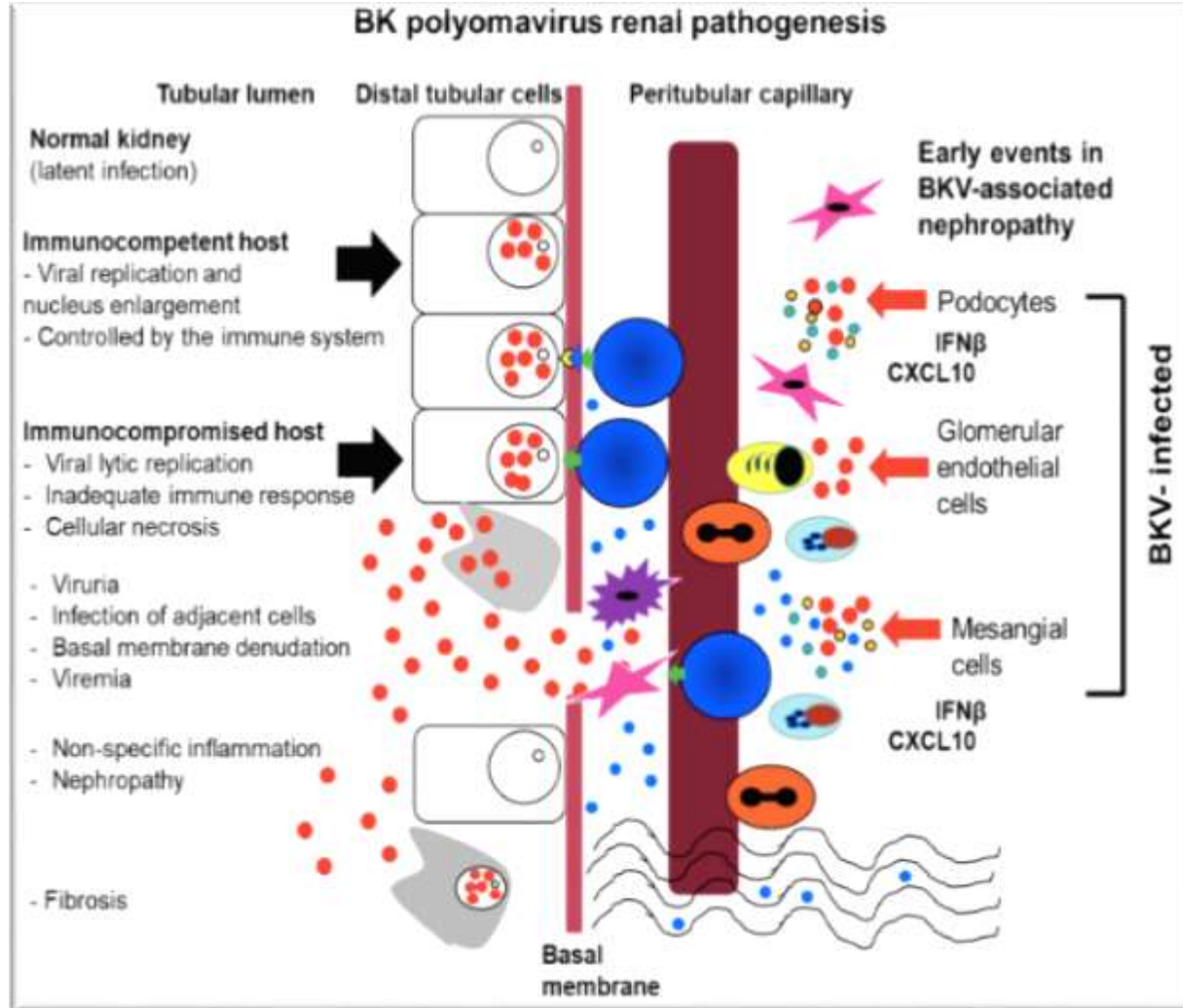
Böbrek Nakli-BKPyVAN



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
		BKPyV genome rearranged <i>NCCR</i>	Low, C
ABOi kidney transplantation	Low, C		

RISK FACTORS

Patogenez



Sessiz viral
replikasyon

Akut tübüler nekroz

Viral tubulointertisyel
nefrit

Kronik allograft
nefropatisi

Diğer Organ Nakilleri ve BKPyV

Brief Communication

BK DNAemia and native kidney polyomavirus nephropathy following lung transplantation

Geoffrey K. Dube^{a,*} , Ibrahim Batal^b , Lori Shah^c, Hilary Robbins^c, Selim M. Arcasoy^c ,
Syed Ali Husain^a 



2016 Liver Transplantation: Global view

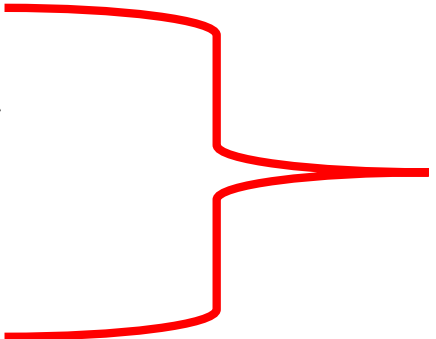
Different behaviour of BK-virus infection in liver transplant recipients

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

Thomas Crowhurst^{1,2*} , James Nolan³, Randall Faull^{1,4}, Mark Holmes^{1,2} and Chien-Li Holmes-Liew^{1,2}

Tanı

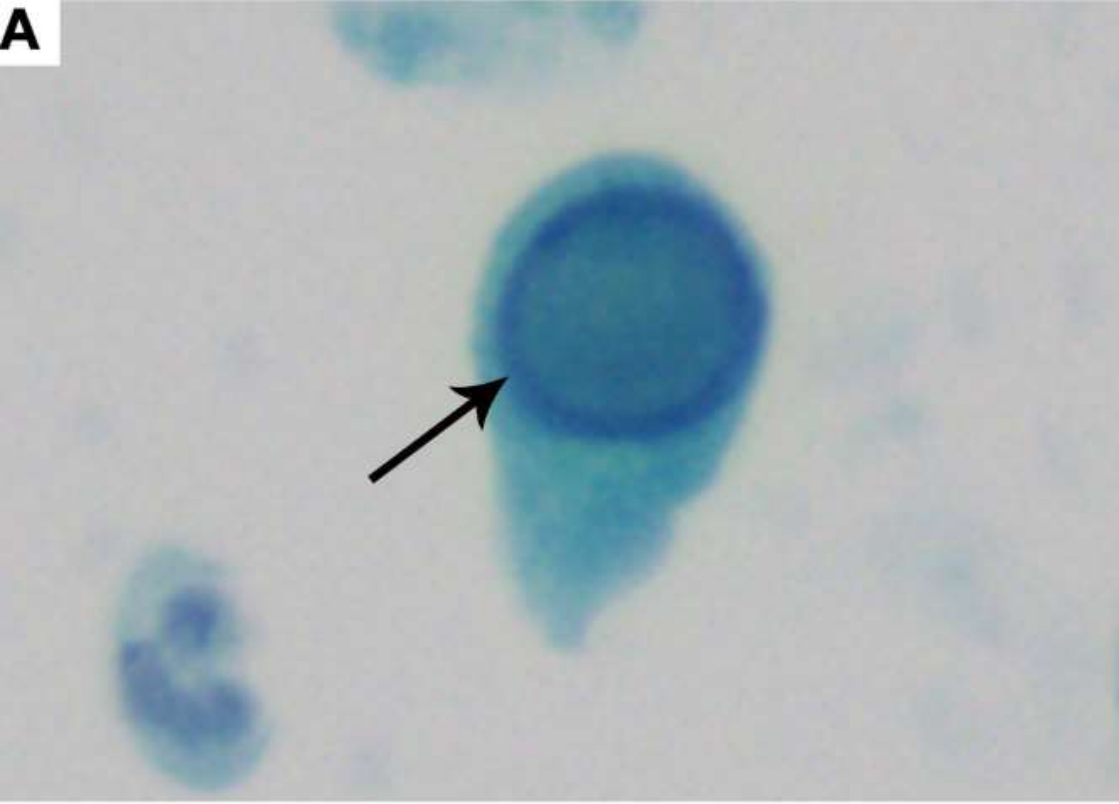
- İdrarda decoy hücresi
- Haufen yöntemi
- İdrarda PZR
- Kanda PZR
- Histopatoloji



Kantitatif viral yük ölçümü BKPyV enfeksiyonu için kabul edilen tarama aracıdır

Decoy Hücresi

A



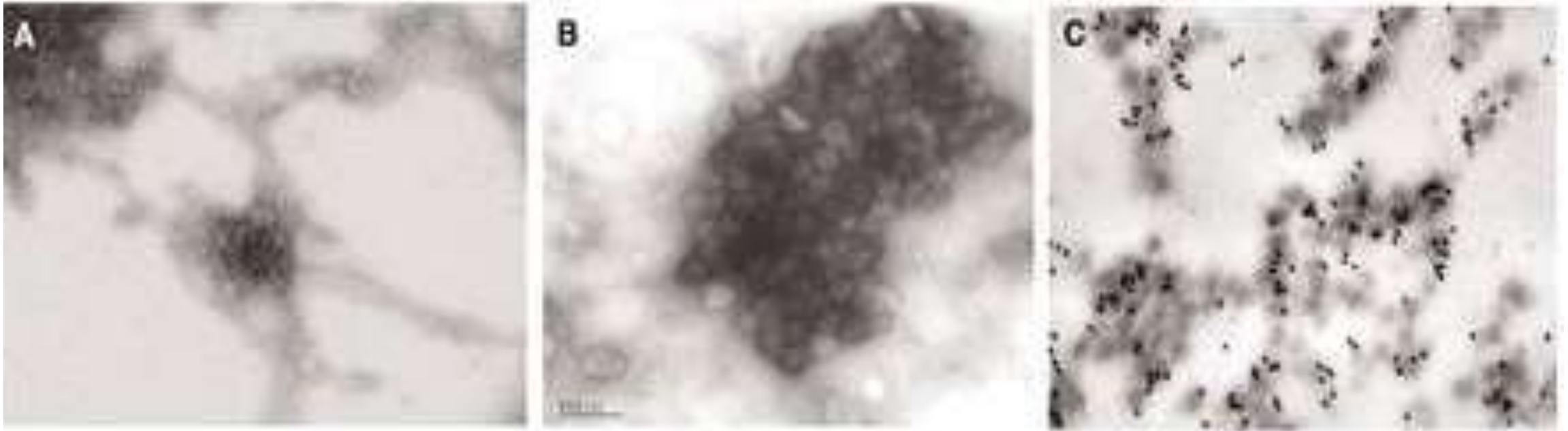
Papanicolaou Boyası

B



Hematoksilen-Eozin Boyası

Haufen Görüntüsü



Tanı

Tanı yöntemlerinde
NEGATİFLİK DAHA DEĞERLİ

Screening technique	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Advantages and limitation	References
Decoy cells	25	84	29	100	Widely available, useful marker in identification of BKV infection, but a poor diagnostic tool in predicting BKN. Not useful for monitoring decline in viral load	[175]
Haufen	100	99	97	100	Highly predictive for BKN, but not practical for routine practice as it requires electron microscopy with interpretation from a pathologist	[176]
Urinary BK-PCR	100	78	40	100	Measurement variations between laboratories limit its use	[175]
Urinary BK-mRNA	100	97	86	100	Still under assessment and requires further validation	[177,178]
Plasma BK-PCR	100	88	50–60	100	Broadly available but costly. Has good sensitivity and specificity but low PPV for BKN	[95,175]

Tanı-Patoloji

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

Consensus recommendations: pathology

- We recommend that in the context of detectable BKPyV-DNAemia, a kidney biopsy be performed as clinically indicated (eg, rise in serum creatinine, proteinuria, hematuria; **strong, A**)
- We suggest immunohistochemistry (clone PAb 416 against SV40 large T-antigen) for confirming the diagnosis of biopsy-proven PyVAN (**strong, A**)
- We suggest routine SV40 (LTag) immunohistology in patients with detectable BKPyV-DNAemia (**strong, B**)
- We suggest to use SV40 (LTag) immunohistology in patients with unknown BKPyV-DNAemia status with inflammatory changes in the biopsy (**weak, D**)
- We suggest to not use routine SV40 (LTag) immunohistology staining in patients with undetectable BKPyV-DNAemia (**weak, C**)
- We suggest to not perform an allograft biopsy during the course or resolution of BKPyV-DNAemia/-nephropathy unless rejection or another renal disease is a matter of concern and its detection will alter management (**weak, D**)

Tanı

Patoloji

Fokal tutulum (%10-30 negatif)

Medüller doku da dahil olmak üzere en az 2 kor örnek

SV40 büyük T antijenine yönelik immünohistokimyasal boyama (PAb416 klon SVO LTA_g)

BKPyV Nefropati- Akut Rejeksiyon Histopatolojik Özellikler

Feature	BK virus nephropathy	Cell-mediated rejection	Antibody-mediated rejection
Interstitial inflammation	<u>More CD20+ cells, plasma cells, neutrophils</u> Clusters of CD68+ cells	More T cells, eosinophils	No
Kidney localization	<u>Medullary > cortical</u> Geographic involvement	Cortical	Cortical
Tubulitis	Predominantly in infected tubules	Distant from infected tubules, more severe	No
Vascular inflammation	No	Yes	Yes
Glomerulitis	No	No	Yes
Transplant glomerulopathy	No	No	Yes
C4d+ PTCs	No	No	Yes



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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)*

- 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



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Screening

- We recommend regular screening of kidney transplant recipients for BKPyV replication to i biopsy-proven BKPyV-nephropathy (**strong, A**)
- We recommend screening kidney transplant recipients for plasma BKPyV loads *monthly* ur (**strong, B**; Figure 1)

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

DNAemia for the next 3 mo (**weak, D**)

- In resource-limited settings, we recommend using urine cytology for decoy cells as the minimal screening approach (**strong, B**) at similar time points to the above (**weak, D**)
- 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**)

Nakil sonrası

İlk 9 ay – Ayda bir kez

9 ay- 2yıl –Üç ayda bir

Greft fonksiyon bozukluğu ? Biyopsi ?

Diğer Kılavuzlar



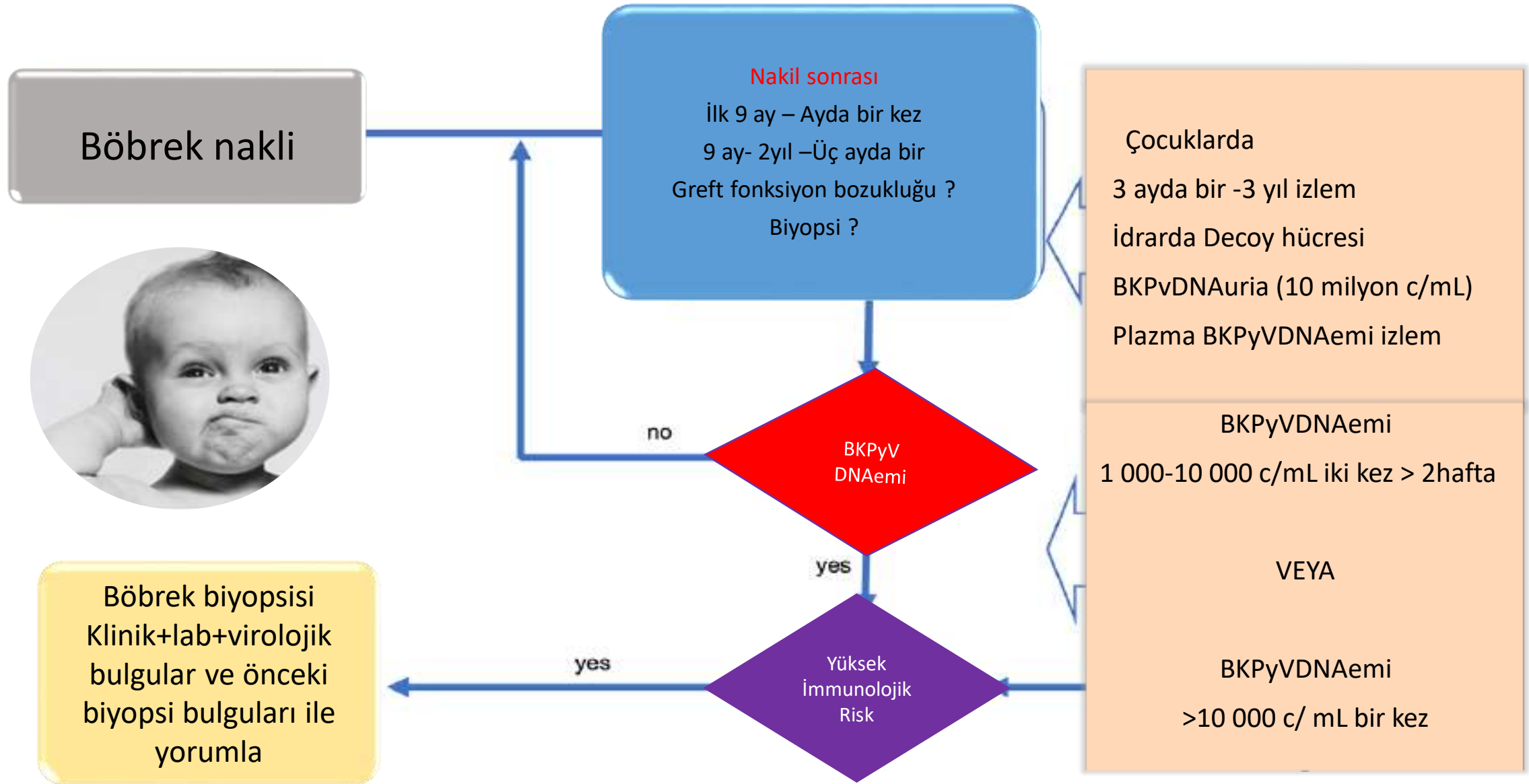
Nakil sonrası ilk 3-6 ay boyunca her ay ve daha sonra nakil sonrası ilk yılın sonuna kadar 3 ayda bir

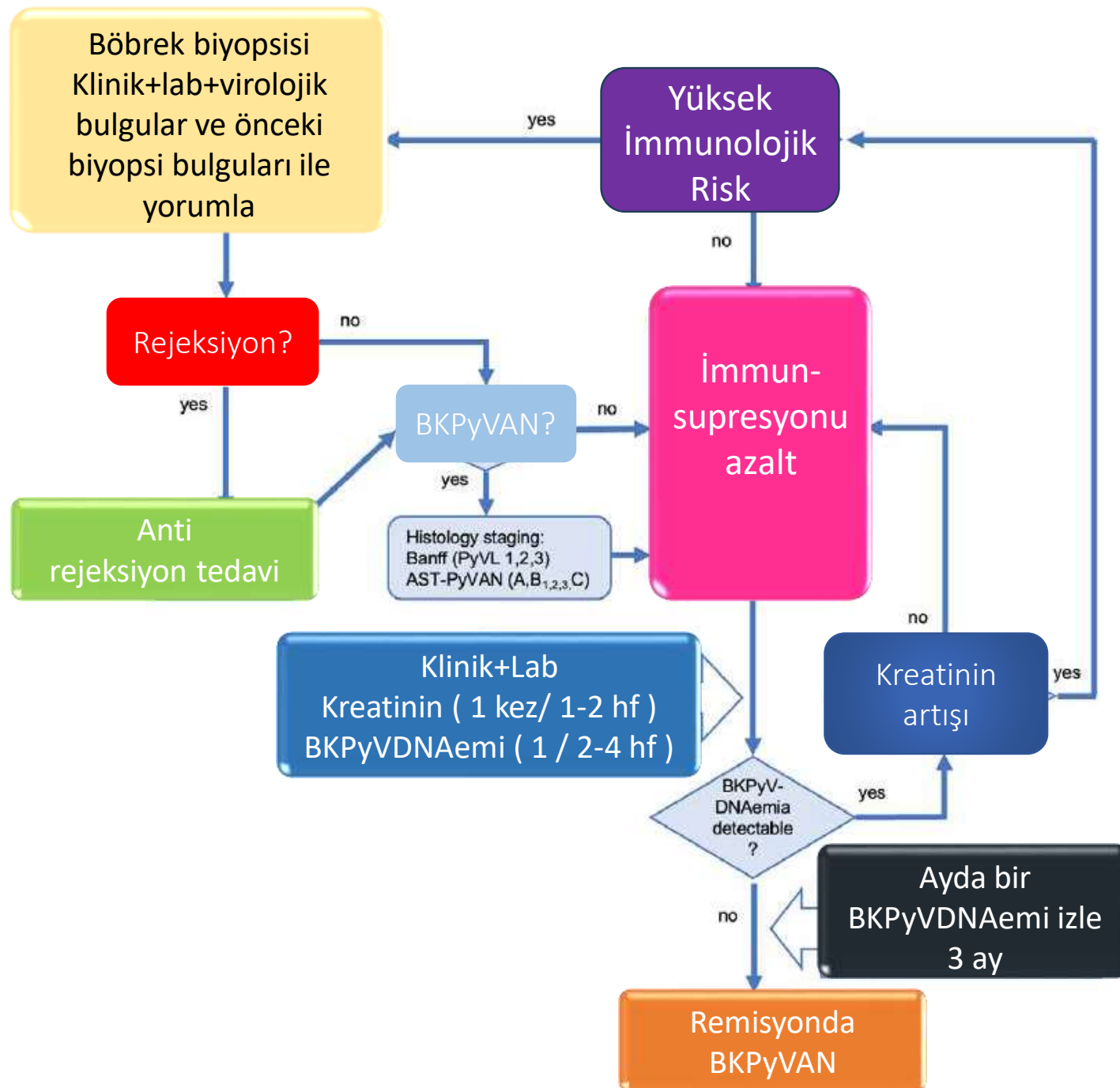


Nakil sonrası ilk 2 yıl 3 ayda bir, 3-5. yıllarda ise yılda 1 kez



Nakil sonrası 9. aya kadar her ay, nakil sonrası 2. yıla kadar 3 ayda bir







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Genel Tedavi Yönetim Yaklaşımı

- Merkez protokolüne göre (ilaç dozları ve doz konsantrasyonları)
- BKPyV-DNA-emi temizlenene ya da stabil ($<1000\text{c/mL}$) kalana kadar 2-4 hafta bir takip
- En düşük kabul edilebilir immünosupresyon tedavisi gören ve BKPyV-DNAemi seviyesi $<1000\text{ c/mL}$ 'nin nadir hastalar için;
 - BKPyV-DNAemi ve serum kreatinin her 3 ayda bir



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İmmunsupresyonu AZALT

Strategy 1: Antimetabolite is reduced first

I. Reduction of the dose of antimetabolite by at least 50%

- **When BKPyV-DNAemi is detected:**
 - Antimetabolit dozu % 50 azaltılması,
- II. **When BKPyV-DNAemi is not detected:**
 - BKPv-DNAemi 4 hafta içinde 10 kat veya tespit sınırının altına düşmezse antimetabolit kesilir,
- **When BKPyV-DNAemi is not detected and CNIs are used:**
 - Almıyorsa CNI yanına prednizon ekle ,alıyorsa dozu 5-10mg/gün olarak azaltılır.
- III. **If BKPyV-DNAemi is not detected and CNIs are not used:**
 - İS'nun daha da azaltılması gerekiyorsa, CNI dozunun kademeli azaltılır.
 - İlaç hedef konsantrasyonları tanımlanmamıştır ve bireyselleştirilmesi gerekir.
- The target concentrations for further reduction are not well defined and need to be individualized. Expert opinion and case reports discuss tacrolimus target trough concentrations of 3 ng/mL and cyclosporine target trough concentrations 75 ng/mL followed by tacrolimus target trough of 1.5 ng/mL; cyclosporine target trough of 50 ng/mL (no recommendation—statement only)



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Strategy 2: CNIs are reduced first

I. Reduction of the dose of CNI by 25%–50% in 1 or 2 steps to target trough concentrations of tacrolimus of 3–5 ng/mL and cyclosporine trough concentrations of 75–125 ng/mL

- We suggest:
 - ✓ CNI dozunu kademeli azaltılmalı,
 - ✓ 4 hafta içinde yanıt yok antimetabolit %50 azaltılmalı ve prednizon dozu 5-10mg/gün,
 - ✓ Antimetabolit kesilmeli,
 - ✓ ilaç hedef konsantrasyonları net tanımlanmamıştır ve bireyselleştirilmeli

• We suggest adding prednisone (or equivalent) 5–10 mg/d for patients who are not on corticosteroids to avoid CNI monotherapy (**weak, C**)

• The target concentrations of further reduction are not well defined and need to be individualized. Expert opinion and case reports discuss tacrolimus target trough concentrations of 3 ng/mL and cyclosporine target trough concentrations of 75 ng/mL followed by tacrolimus target trough of 1.5 ng/mL; cyclosporine target trough of 50 ng/mL (**no recommendation—statement only**)

Diğer Kılavuzlar



İS azaltılmasıyla viral klerens sağlanamazsa standart
İS alternatif bir ajana dönüştürülmesi

Takrolimus

Düşük doz
Siklosporin

CNI

mTORi

Mikofenolik asit

Sirolimus



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mTOR inhibitor regimens

- For kidney transplant recipients developing BKPyV-DNAemia or biopsy-proven BKPyV-nephropathy while receiving a combination of mTOR inhibitors and calcineurin inhibitors, there is insufficient data to guide the reduction of immunosuppression.

Possible approaches include mTOR inhibitörü ve CNİ kombinasyonu ya da Belatacept temelli tedavi alırken BKPyVDNAemi ve biyopsi ile kanıtlı nefropati gelişen nakil alıcılarında immunsüpresyonun azaltılması konusunda kılavuzluk yapacak yeterli veri bulunmamaktadır.

Belatacept regimens

- 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**)



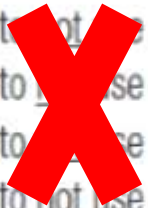
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IVIG ?

İS'un azaltılmasına yeterli yanıt vermeyen alıcılarda viral temizlenmeyi kolaylaştırmak için adjuvan tedavi olarak ve İS'un azaltılması sırasında yüksek immünolojik risk taşıyan alıcılarda akut reddi ve donör spesifik antikorların gelişmesini önlemek için kullanılabilir.

Adjunctive therapies

- We suggest consideration of IVIG administration as adjuvant therapy to prevent acute rejection in recipients with high immunological risk when immunosuppression reduction is necessary to facilitate viral clearance (**weak, D**)
- We recommend to not use **Sidofovir** to treat BKPyV-DNAemia/-nephropathy in kidney transplant recipients (**strong, B**)
- We recommend to use **Leflunomid** to treat BKPyV-DNAemia or BKPyV-nephropathy in kidney transplant recipients (**strong, A**)
- We recommend to use **Florokinonlar** to treat BKPyV-DNAemia or BKPyV-nephropathy in kidney transplant recipients (**strong, A**)
- We recommend to not use **Statinler**



Sidofovir

Leflunomid

Florokinonlar

Statinler



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Akut rejeksiyon??

- ✓ Yüksek doz kortikosteroid uygulaması
- ✓ Allograft renal fonksiyon takibi
- ✓ Aylık BKPyVDNAemi izlemi (3-6 ay)

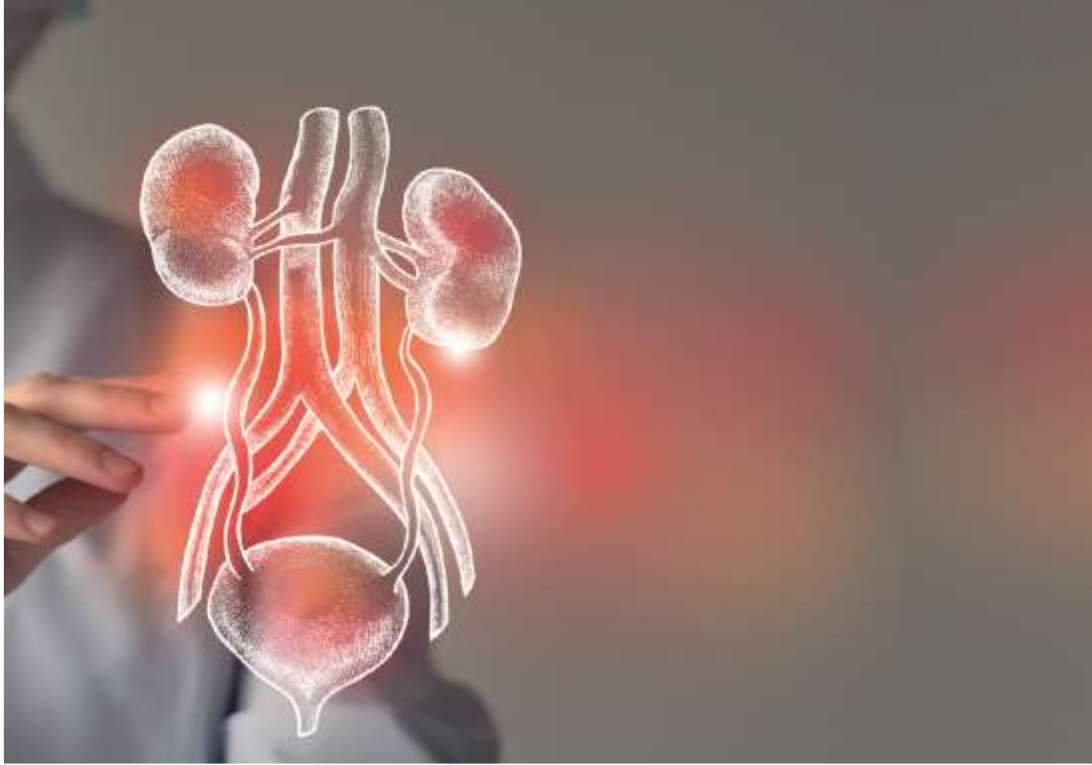
BKPyV Nefropati Sonrası Retransplantasyon?

BKPyV DNAemi tespit edilmeyen, kanıtlanmış
BKPyV nefropatisi nedeniyle allogreft
yetmezliđi sonrası retransplantasyonda
3 yıllık greft sađ kalımı %93



BKPyV Nefropati Sonrası Retransplantasyon?

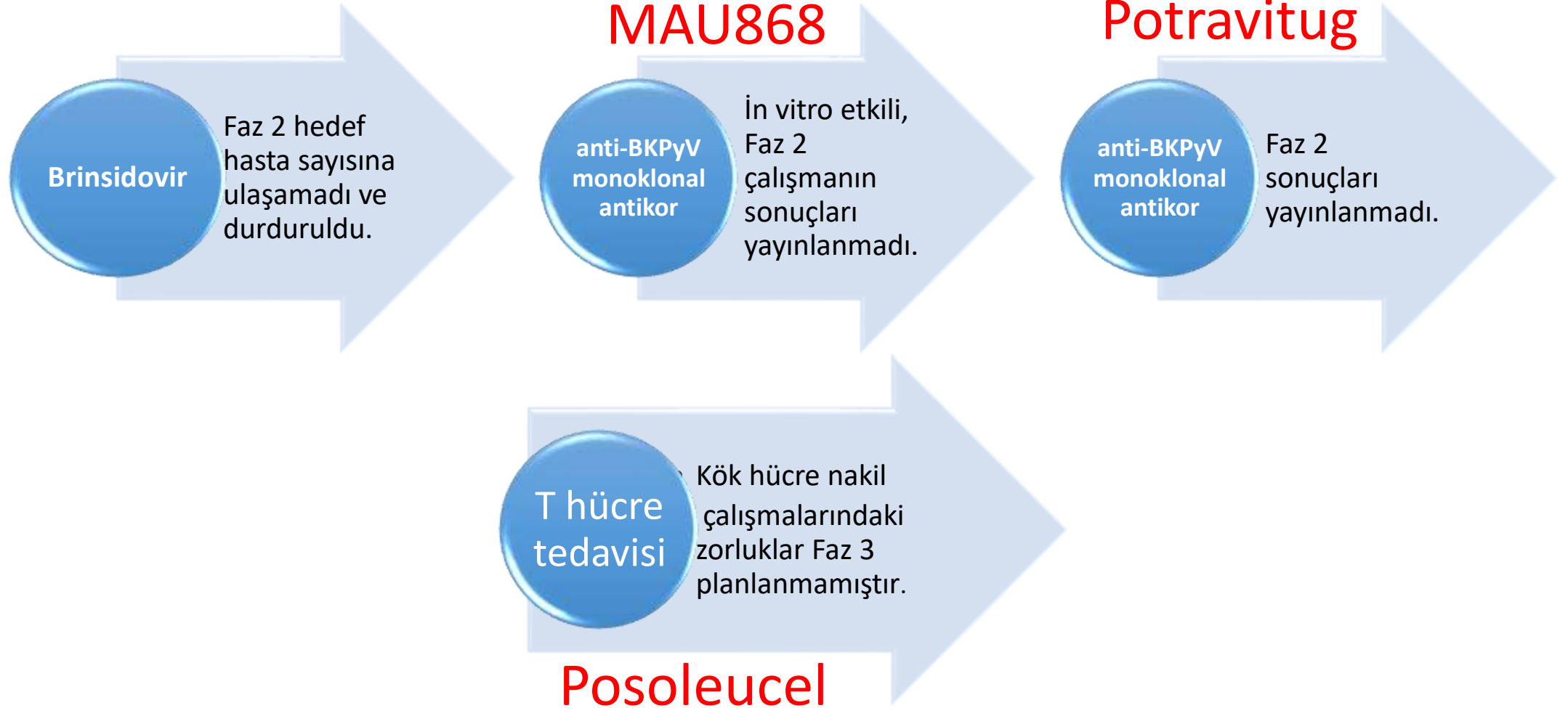
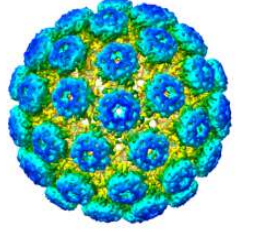
- We recommend retransplantation in otherwise eligible patients who lost their prior allograft from BKPyV-nephropathy (strong, B)
- We suggest that BKPyV-DNAemia be resolved before retransplantation (weak, C)
- We suggest not routinely performing graft nephrectomy before retransplantation in the **Rutin greft nefrektomi önerilmez** re subsequent to BKPyVnephropathy having undetectable BKPyV-DNAemia (weak, C)
- There is insufficient information to make recommendations on the choice of immunosuppression for **immünosupresyon seçimi?** isplant after a prior kidney transplant failed because of BKPyV-nephropathy (no recommendation—statement only)



Tekrar nakil ne zaman yapılmalıdır?

Bazı merkezler immünsüpresyona ara verildikten (örn. 6 ay) sonra BKPyVDNAemi saptanmaz ve düşük seviyede BKPyVüri durumunda izin vermektedir.

Geliştirilmekte Olan Tedaviler



Sonuç Olarak

- Merkezler;
 - ✓ Hastaların düzenli takipleri için standart tarama protokolü oluşturmalı,
 - ✓ Tanı için kurumsal algoritma düzenlemeli,
 - ✓ Tedavi için kılavuzlara dayalı protokoller hazırlamalı,
 - ✓ BKPyVAN remisyonu sonrasında hastaların bireysel özellikleri ve immünolojik riskleri göz önüne alınarak İS tedavilerini arttırmalıdır.

