Olgularla İmmünsüpresif Hastalarda Sorunlu Viral Enfeksiyonların Yönetimi:

BK, JC, HHV-6

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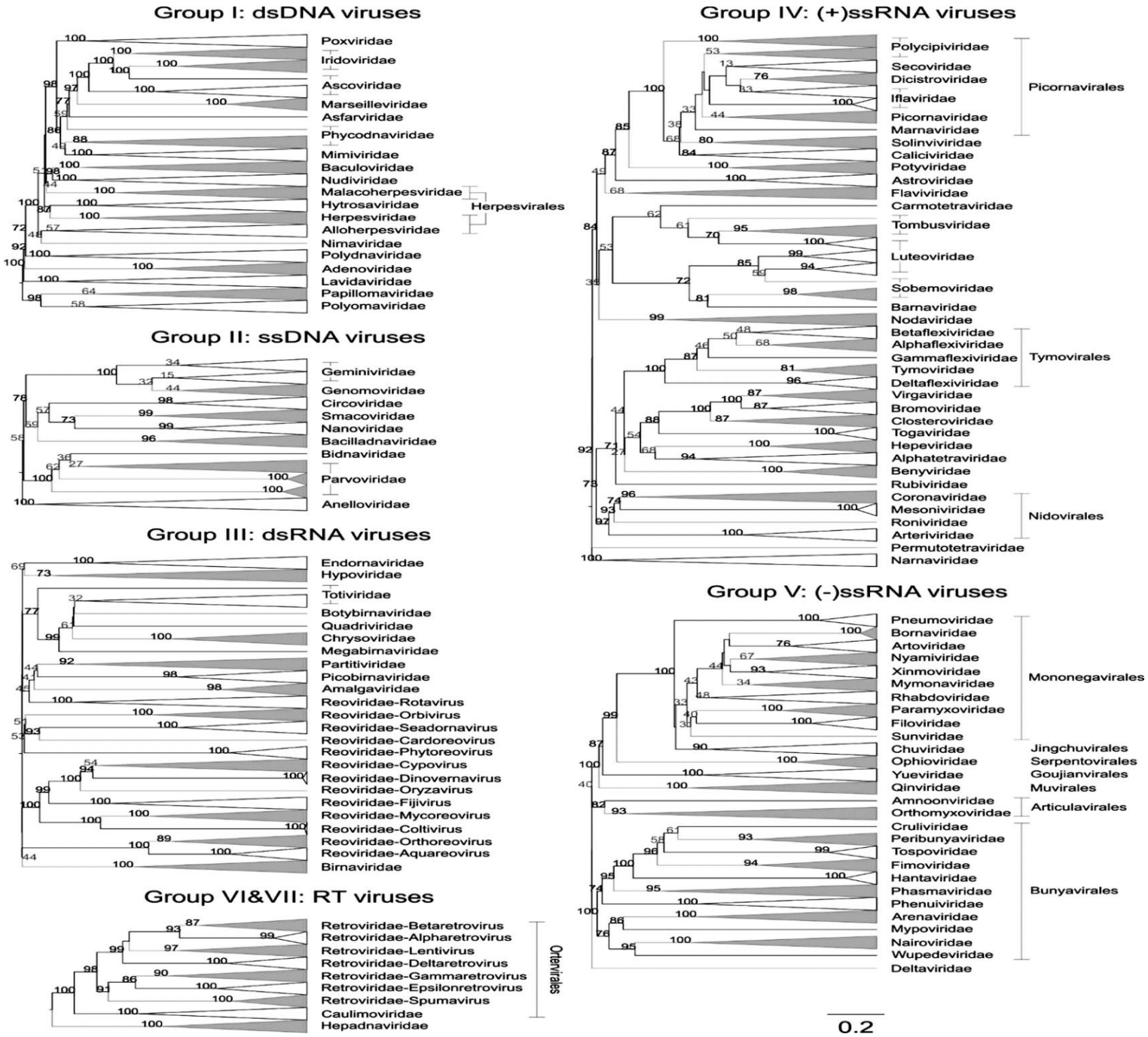
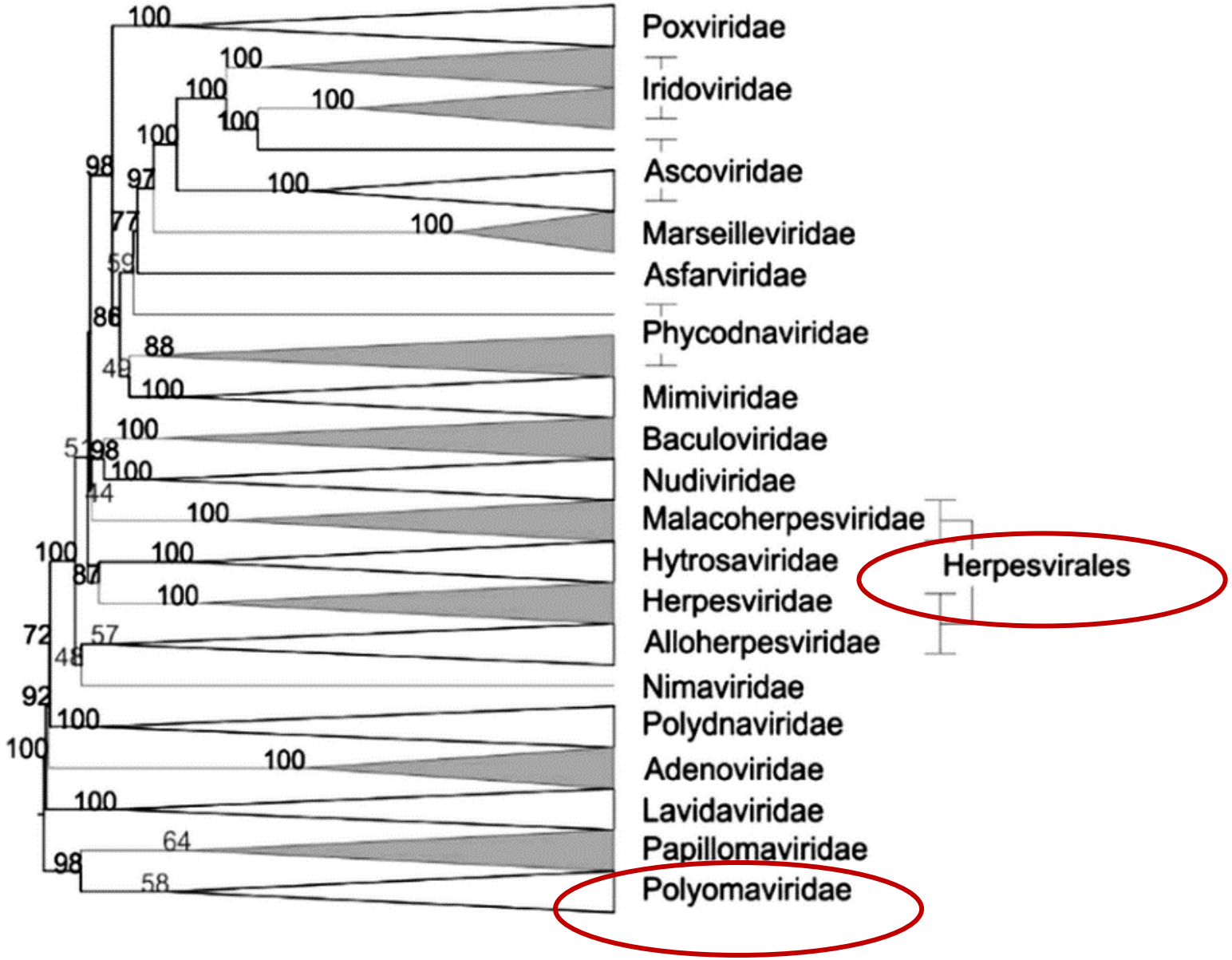
Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji ABD

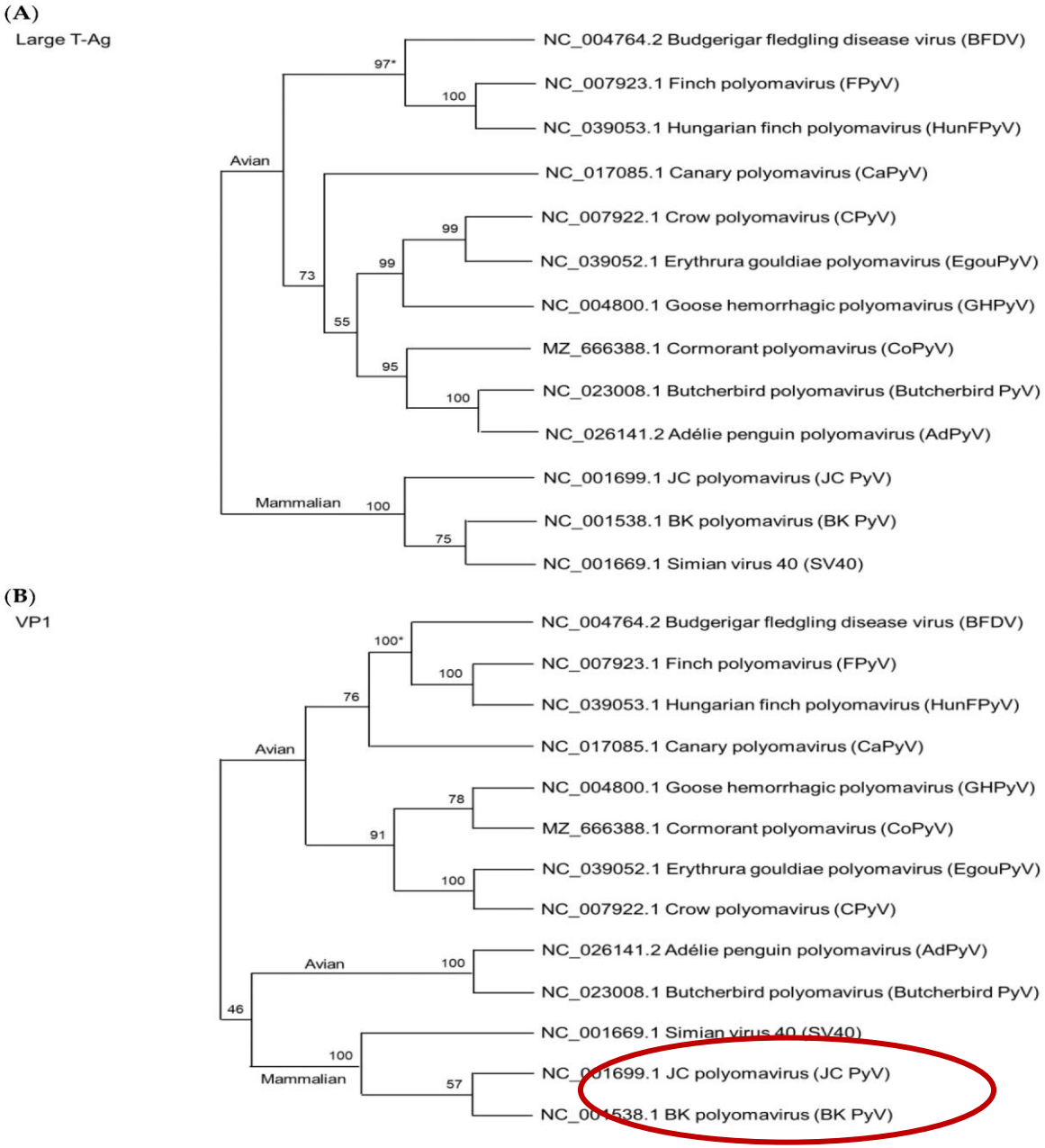
Sunum Planı:

- Kim Bunlar?
- Ne Yaparlar?
- Hangi immünsüpresyon?
- Olgularla Tanı & Tedavi…


Group I: dsDNA viruses
Poxviridae
Iridoviridae
Ascoviridae
Marseilleviridae
Asfarviridae
Phycodnaviridae
Mimiviridae
Baculoviridae
Nudiviridae
Malacoherpesviridae
Hytrosaviridae
Herpesviridae
Alloherpesviridae
Herpesvirales
Nimaviridae
Polydnaviridae
Adenoviridae
Lavidaviridae
Papillomaviridae
Polyomaviridae
Group II: ssDNA viruses
Geminiviridae
Genomoviridae
Circoviridae
Smacoviridae
Nanoviridae
Bacilladnaviridae
Bidnaviridae
Parvoviridae
Anelloviridae
Group III: dsRNA viruses
Endornaviridae
Hypoviridae
Totiviridae
Botybirnaviridae
Quadriviridae
Chrysoviridae
Megabirnaviridae
Partitiviridae
Picobirnaviridae
Amalgaviridae
Reoviridae-Rotavirus
Reoviridae-Orbivirus
Reoviridae-Seadornavirus
Reoviridae-Cardoreovirus
Reoviridae-Phytoreovirus
Reoviridae-Cypovirus
Reoviridae-Dinovernavirus
Reoviridae-Oryzavirus
Reoviridae-Fijivirus
Reoviridae-Mycoreovirus
Reoviridae-Coltivirus
Reoviridae-Orthoreovirus
Reoviridae-Aquareovirus
Birnaviridae
Group VI&VII: RT viruses
Retroviridae-Betaretrovirus
Retroviridae-Alpharetrovirus
Retroviridae-Lentivirus
Retroviridae-Deltaretrovirus
Retroviridae-Gammaretrovirus
Retroviridae-Epsilonretrovirus
Retroviridae-Spumavirus
Caulimoviridae
Hepadnaviridae
Ortervirales
Group IV: (+)ssRNA viruses
Polycipiviridae
Secoviridae
Dicistroviridae
Iflaviridae
Picornaviridae
Marnaviridae
Picornavirales
Solinviviridae
Caliciviridae
Potyviridae
Astroviridae
Flaviviridae
Carmotetraviridae
Tombusviridae
Luteoviridae
Sobemoviridae
Barnaviridae
Nodaviridae
Betaflexiviridae
Alphaflexiviridae
Gammaflexiviridae
Tymoviridae
Deltaflexiviridae
Tymovirales
Virgaviridae
Bromoviridae
Closteroviridae
Togaviridae
Hepeviridae
Alphatetraviridae
Benyviridae
Rubiviridae
Coronaviridae
Mesoniviridae
Roniviridae
Arteriviridae
Nidovirales
Permutotetraviridae
Narnaviridae
Group V: (-)ssRNA viruses
Pneumoviridae
Bornaviridae
Artoviridae
Nyamiviridae
Xinmoviridae
Mymonaviridae
Rhabdoviridae
Paramyxoviridae
Filoviridae
Sunviridae
Mononegavirales
Chuviridae
Ophioviridae
Yueviridae
Qinviridae
Jingchuvirales
Serpentovirales
Goujianvirales
Muvirales
Amnoonviridae
Orthomyxoviridae
Articulavirales
Cruliviridae
Peribunyaviridae
Tospoviridae
Fimoviridae
Hantaviridae
Phasmaviridae
Phenuiviridae
Arenaviridae
Mypoviridae
Nairoviridae
Wupedeviridae
Bunyavirales
Deltaviridae
0.2

Group I: dsDNA viruses




(A)
Large T-Ag
NC_004764.2 Budgerigar fledgling disease virus (BFDV)
NC_007923.1 Finch polyomavirus (FPyV)
NC_039053.1 Hungarian finch polyomavirus (HunFPyV)
NC_017085.1 Canary polyomavirus (CaPyV)
NC_007922.1 Crow polyomavirus (CPyV)
NC_039052.1 Erythrura gouldiae polyomavirus (EgouPyV)
NC_004800.1 Goose hemorrhagic polyomavirus (GHPyV)
MZ_666388.1 Cormorant polyomavirus (CoPyV)
NC_023008.1 Butcherbird polyomavirus (Butcherbird PyV)
NC_026141.2 Adélie penguin polyomavirus (AdPyV)
NC_001699.1 JC polyomavirus (JC PyV)
NC_001538.1 BK polyomavirus (BK PyV)
NC_001669.1 Simian virus 40 (SV40)
Avian
Mammalian
97*
100
73
99
55
99
95
100
100
75
(B)
VP1
NC_004764.2 Budgerigar fledgling disease virus (BFDV)
NC_007923.1 Finch polyomavirus (FPyV)
NC_039053.1 Hungarian finch polyomavirus (HunFPyV)
NC_017085.1 Canary polyomavirus (CaPyV)
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NC_023008.1 Butcherbird polyomavirus (Butcherbird PyV)
NC_001669.1 Simian virus 40 (SV40)
NC_001699.1 JC polyomavirus (JC PyV)
NC_001538.1 BK polyomavirus (BK PyV)
Avian
Avian
Mammalian
100*
100
76
78
91
100
100
46
100
57

Subfamily	Taxonomic name	Common name
Alpha-herpesvirinae	HHV-1	Herpes simplex virus 1 (HSV-1)
	HHV-2	Herpes simplex virus 2 (HSV-2)
	HHV-3	Varicella-zoster virus (VZV)
Beta-herpesvirinae	HHV-5	Human cytomegalovirus (HCMV)
	HHV-6	HHV-6 vairant A or B
	HHV-7	HHV-7
Gamma-herpesvirinae	HHV-4	Epstein-Barr virus (EBV)
	HHV-8	Kaposi's sarcoma-associated herpesvirus (KSHV)

HHV, human herpesvirus.

İmmünsüpresyon

- Yabancı antijenlere karşı bağışık yanıtın baskılanması;
- Organ nakli hastalarında nakledilen organ veya greftin reddinin önlenmesi,

alerji, otoimmün hastalıklar...

Yüksek düzeyde immünsüpresyon

- Kombine primer immün yetmezlik
- Kanser kemoterapisi
- SOT sonrası 2 ay
- HIV infeksiyonu
  - –CD4
    - <200 (erişkin, adolesan)
    - <%15 (süt çocuğu, çocuk)
- Her gün verilen kortikosteroid tedavisi
- ≥20 mg (veya 10 kg altında >2 mg/kg/gün) prednizon veya eşdeğeri >14 gün

Yüksek düzeyde immünsüpresyon:

- Bazı biyolojik immünmodulatörler
  - –TNF alfa blokeri
  - –Rituximab (monoklonal Ab > CD20)

- HSCT sonrası yüksek düzeyde immünsüpresyon
  - -Süresi değişken
  - -TX tipi (allojenik>otolog)
  - -GVHD gibi transplant sonrası komplikasyonlar ve tedavileri

Düşük düzeyde immünsüpresyon :

- Asemptomatik HIV infeksiyonu
  - –CD4
  - 200-499 hücre/mm3, erişkin ve adolesan
  - %15-24 süt çocuğu ve çocuk
- Kortikosteroid
  - –Yüksek düzeyden daha düşük dozda, >14 gün
  - –Günaşırı kortikosteroid tedavisi
- Metotreksat < 0.4 mg/kg/hafta
- Azatiyoprin < 3 mg/kg/gün
- 6-merkaptopürin < 1.5 mg/kg/gün

1) İmmünsüpresyonun nedenine göre (altta yatan hastalık)

SOT, HSCT, AIDS,…

2)Hedef patojene göre

HBV, HCV, VZV…

3) Kullanılan immünsüpresif ajana göre

Rituximab, AZT, MMF, Glukokotrikoidler…

???


EVERYTHING,
BUT LITTLE LITTLE
made on imgur

Olgu-1

- 49 yaşında erkek hasta
- Bilinen ek hastalık yok
- 4-5 aydır devam eden kilo kaybı,ateş ,gece terlemesi şikayetleri mevcut olan hasta bilinçte bozulma ile dış merkeze başvuru
- Dış merkez tetkiklerinde Anti-HIV pozitif saptanan hasta kliniğimize devir

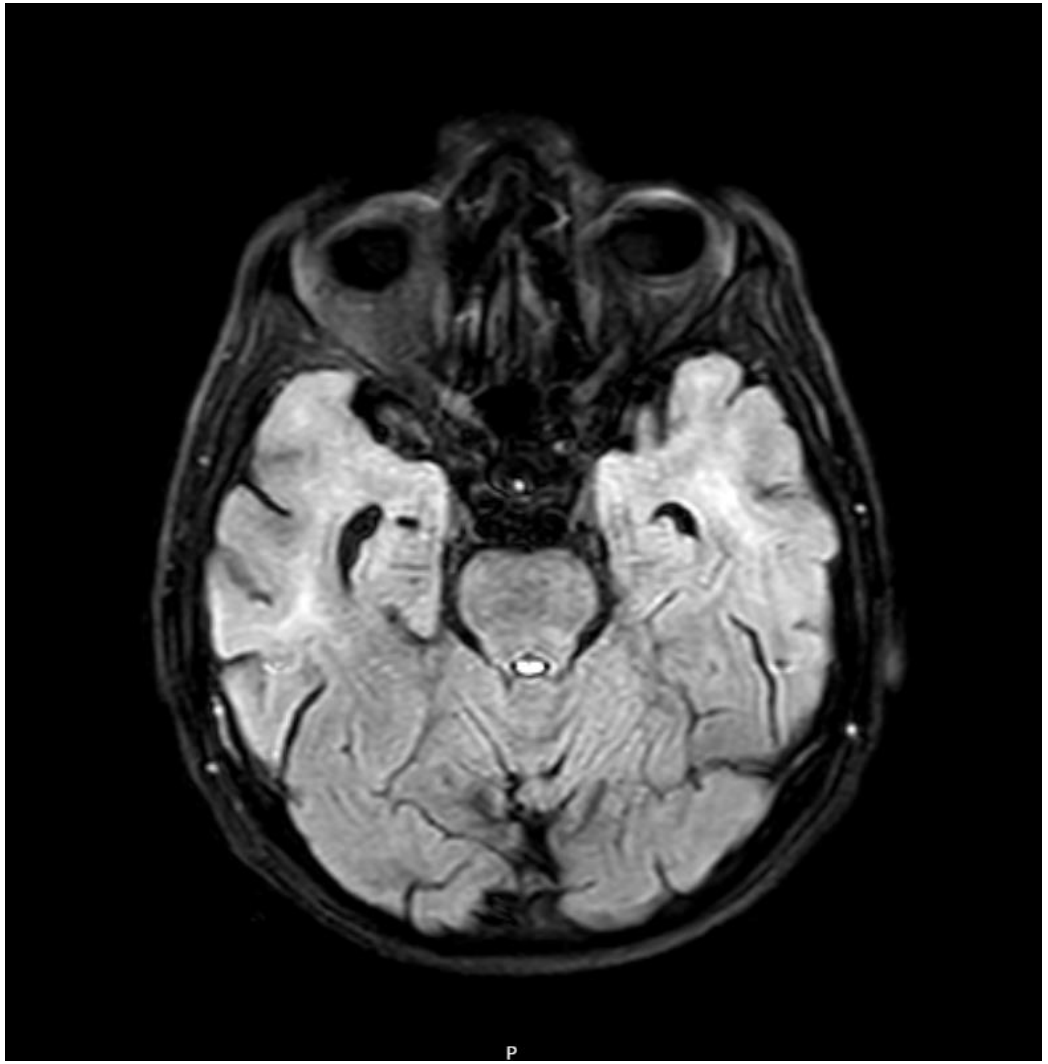
- Yapılan tetkiklerinde CD4 %19 (161) , HIV RNA : 5,47 milyon copy/ml saptandı.

- Öksürük balgam şikayeleri de olan hastanın çekilen toraks bilgisayarlı tomogafisinde tomurcuklanan ağaç manzarası ve yaygın buzlu cam görüntüsü mevcuttu.

- Hastaya göğüs hastalıkları tarafından bronkoskopi yapıldı ve balgam ARB tahlili pozitif olarak sonuçlandı.

- TMP-SMX profilaksisi
- Hastaya 4lü antitüberküloz (Rifampisin, izoniazid , etambutol ,pirazinamid) tedavisi başlandı.
- 1 hafta sonra hastada bilinç bulanıklığı olması üzerine tüberkülom ? Açısından lomber ponksiyon planlandı fakat hasta yakınları kabul etmedi.
- Hastaya beyin MR çekildi.
  - Bilateral serebral hemisferlerde beyaz cevherde yaygın T1 A'da hipointens sinyal değişikliği izlenmiştir.
  - Hastanın klinik muayene ve laboratuvar bulguları ile birlikte değerlendirilmesi ve kontrastlı incelemenin tekrarı önerilir

  - Gansiklovir IV (2 hafta)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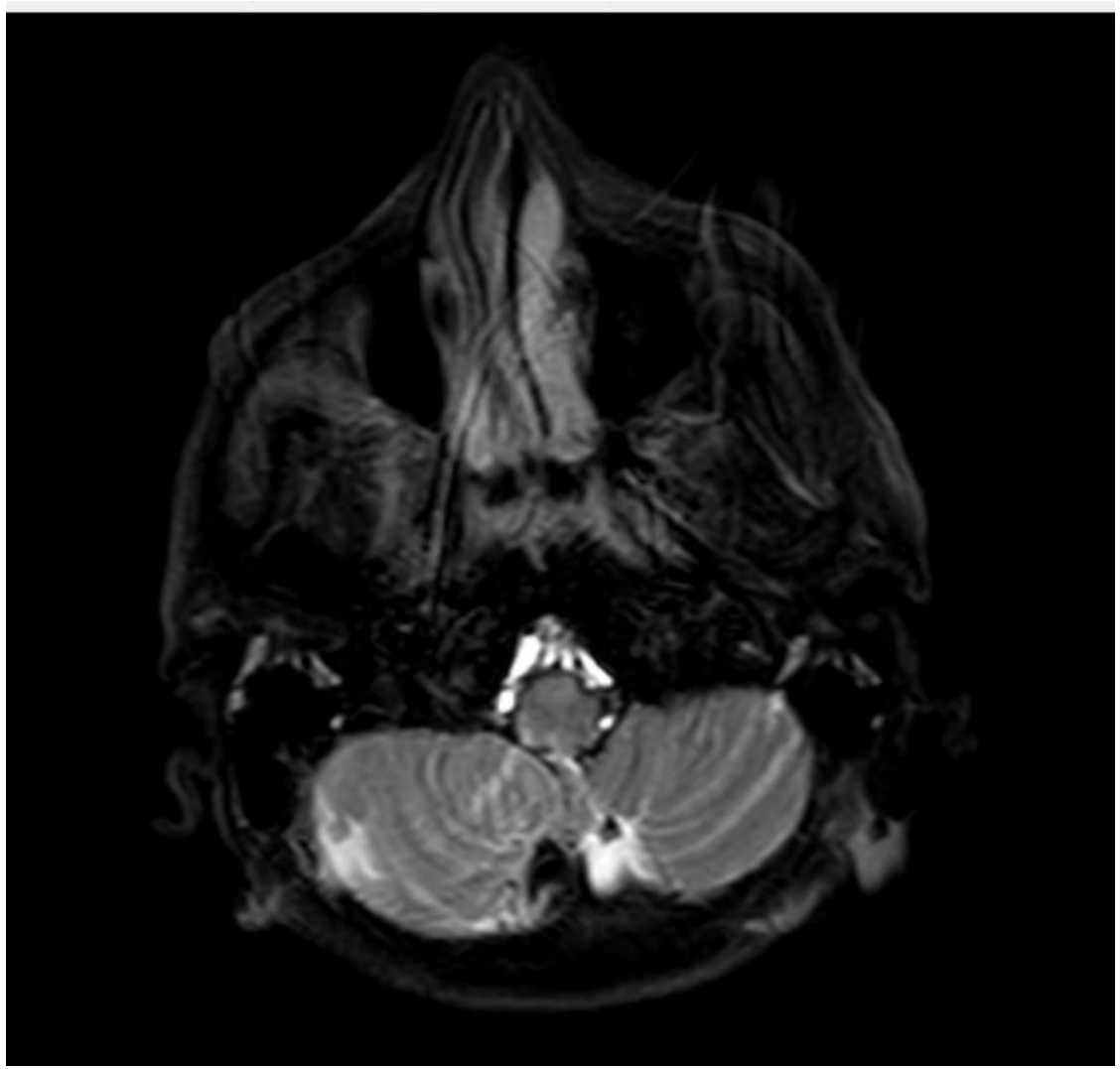


- Anti TBC’nin 2. haftasından sonra ART (DTG+TDF+FTC)

- 3. ay HIV RNA: <40 copy/ml
- CD4 95(%17)

MRG istenmiş…. Hasta yok…

7 ay sonra klinik progresyon, acil başvurusu:

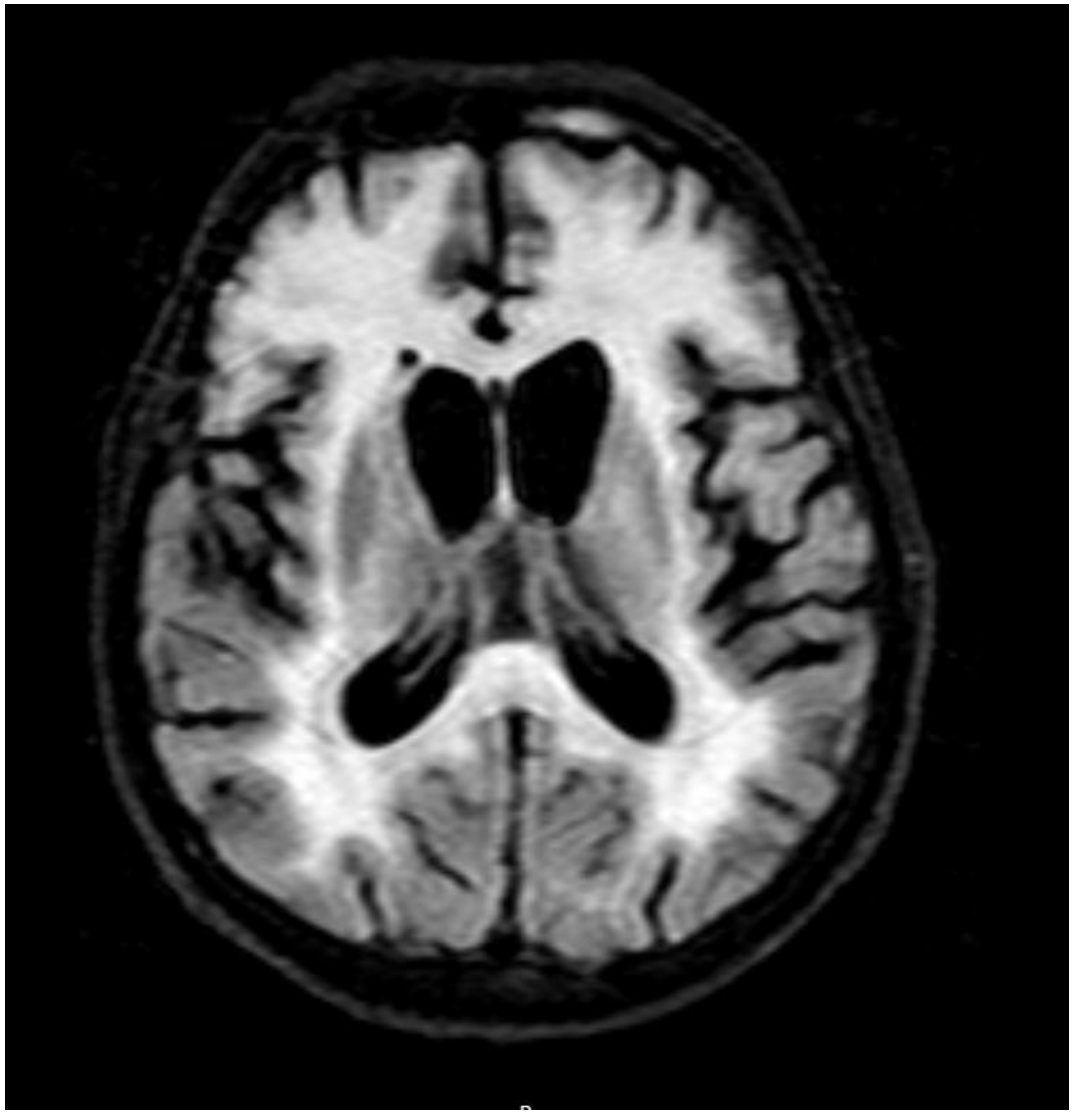
HIV RNA <40 copy/ml ; CD4:76 (%16)

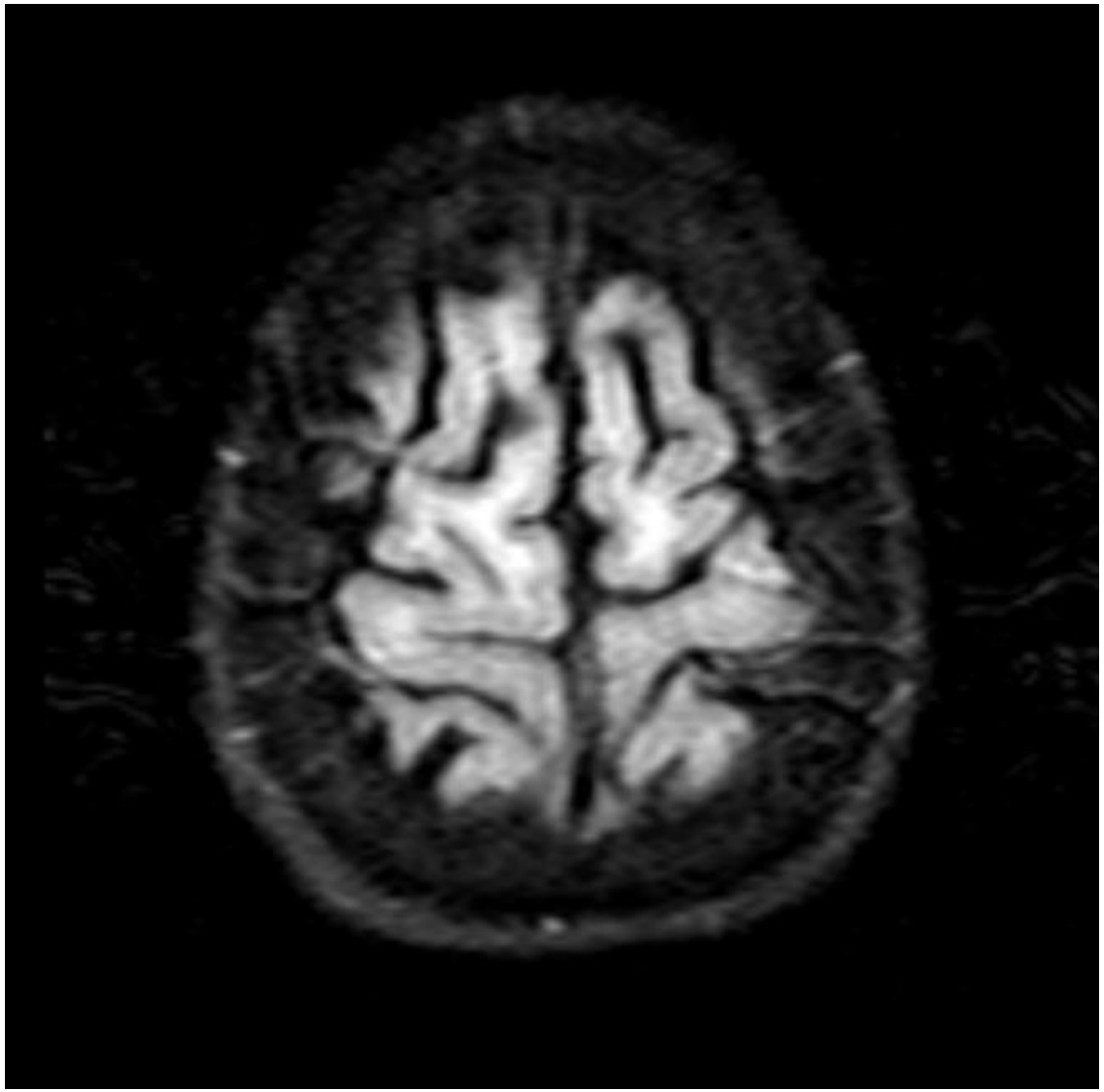
DİFÜZYON MRG

- İnceleme Diffüzyon A aksiyal ve ADC haritalama ile kraniyal bölgeye yönelik yapılmıştır.
- Bilateral frontal loblarda periventriküler alanlarda belirginleşen ADC'de karşılığı izlenen difüzyon kısıtlamasına uyan alanlar dikkati çekmiştir. Hastanın klinik muayene bulgularıyla birlikte değerlendirilmesi önerilir.

Kontrastlı Kraniyal MRG

Progresyon…





- Hasta toplamda 9 ay antitüberküloz tedavisi almış olup göğüs hastalıkları tarafından 9. ayın sonunda kesildi.
- Yer olmadığından dış merkeze
- Metilprednizolon (IRIS?)
    - CD4 artmamış ???
- Hastanın ataksik yürüyüşü, kognitif disfonksiyonu progrese olmaktadır.
- Hasta 15 gündür dış merkez YBÜ'de

Progresif Multifokal Lökoensefalopati

- JCV
- İmmünsüpresyon
- Progresif beyaz cevherde demiyelinizasyon
  - Kognitif bozukluk, desoryantasyon
  - Yürüme ve koordinasyon anormallikleri
  - Uzuvlarda parezi
  - Nöbet

Enfeksiyon hastalıklarında
T1 Kontrastlı seri eğilimii

Pinto M. Et al. Journal of Infection (2014) 68

- Virus ile karşılama çocukluk…
- Genelde serokonversiyon 10-15 yaş
- Erişkinlerde %80

Tanı:

- MRI
  - T2-weighted, FLAIR sekanslar: Hiperintens ; T1 sekanslarda: Hipointens
- BOS İnceleme
  - JCV PCR
  - Mikroskopi +biyokimya
- Beyin biyopsisi (Gold standard): Duyarlılık 64-96% and Özgünlük 100%.

Histopatoloji:

- Demyelinizasyon, gliozis
- Anormal astrositler, makrofajlar

Progressive Multifocal Leukoencephalopathy/JC Virus Infection

Updated: October 19, 2022
Reviewed: January 10, 2024

Epidemiology

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS), caused by the human polyoma virus JC virus (JCV) and characterized by focal demyelination.[1,2] JCV has a worldwide distribution, and 20% to 70% of people exhibit serologic evidence of exposure by their late teens or as adults.[3-7] Primary JCV infection usually occurs asymptomatically in childhood resulting in a chronic carrier state in most individuals. Viral DNA is detected in the urine of 20% to 30% of healthy adults.[4,8-12]

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines

Recommendations for Treating and Monitoring PML

Treatment

The main approach to treatment is to preserve immune function and reverse HIV-associated immunosuppression with effective ART.

- In patients not on ART who are diagnosed with PML, ART should be (re)started immediately **(AII)**.
- In patients who are receiving ART but remain viremic because of inadequate adherence or drug resistance, ART should be optimized to achieve HIV suppression **(AIII)**.
- No role for ART intensification in patients with HIV viral suppression **(BII)**.
- ART regimens should be selected based on likelihood of achieving virologic suppression and not CPE score **(BII)**.
- No effective direct-acting antiviral therapy exists for preventing or treating JCV infections or PML.
- The following agents are **not recommended** for the treatment of PML: cytarabine **(AII)**, cidofovir **(AII)**, interferon-alpha **(BIII)**, interleukin-2 **(BIII)**, topotecan **(BIII)**, pembrolizumab **(BIII)**.
- The following agents are **not recommended** due to limited data: 5HT2a receptor antagonist (e.g., olanzapine, ziprasidone, mirtazapine, cyproheptadine, risperidone) **(BIII)**, mefloquine **(BIII)**. Expert consultation is recommended prior to initiation of these agents.
- PML-IRIS may require administration of corticosteroid therapy **(BIII)**. The optimal corticosteroid regimen has not been established but should be tailored to individual patients. ART should NOT be discontinued during PML-IRIS **(AIII)**.

Monitoring

- Timing of follow-up assessments (clinical, lumbar puncture, and MRI) should be guided by clinical progress **(BIII)**.
- In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation **(BIII)**.
- In patients who clinically worsen before or after this 6- to 8-week period, repeat MRI should be obtained as soon as worsening is recognized **(BIII)**.

Key: ART = antiretroviral therapy; CPE = Central Nervous System (CNS) Penetration Effectiveness; IRIS = immune reconstitution inflammatory syndrome; JCV = JC virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

Spesifik antiviral tedavi yok!!!

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EACS GUIDELINES

Version 12.0
October 2023

English

Progressive Multifocal Leukoencephalopathy (PML)

Diagnosis and treatment	
Definitive diagnosis: compatible clinical-radiological picture, with either evidence of JCV-DNA in CSF or typical histological findings with in situ evidence of JCV-DNA or antigen **Probable diagnosis:** compatible clinical-radiological picture if JCV-DNA in CSF negative or not performed. JCV-DNA in plasma may complement PML diagnosis, particularly if CSF not available. May also be a marker of disease progression	
Off-ART	Initiate ART immediately (following general guidelines for treatment, see Initial Combination Regimen for ART-naïve Adults, INSTI may reasonably be preferred, given the importance of rapid immune reconstitution in PML. Attention should be made to development of IRIS, see IRIS section
On-ART, HIV-VL failure	Optimise ART (following general guidelines for treatment, see Virological Failure), INSTI may reasonably be preferred, given the importance of rapid immune reconstitution in PML. Attention should be made to development of IRIS, see IRIS section
On-ART, treated for weeks- months or on effective ART	Continue current ART
	Note: There is no specific treatment for JCV infection that proved to be effective in PML outside of anecdotal case reports. There is no recommendation to use the following drugs which previously or occasionally were used in PML: alpha-IFN, cidofovir, cytarabine, mefloquine, mirtazapine, corticosteroids (except for treatment of IRIS-PML, see IRIS section), iv immunoglobulins. Newer immune-based approaches have shown some efficacy, including Interleukin-7, infusion of polyomavirus-specific HLA-matched T-cells, PD1 inhibitors (pembrolizumab, nivolumab). Results from large retrospective cohorts did not show a benefit of IL-7 or PD1 inhibitors on survival, but no data from clinical trials are currently supporting recommending for or against their clinical use. If used, participation in treatment protocols is strongly encouraged

Kesin tanı imkanı???

Muhtemel tanı!

SC/ 38 yaş /kadın

- Halsizlik , yorgunluk, depresyon? Psikiyatri başvurusu
- Organik ety araştırılırken
- Anti- HIV (+)
- HIV RNA:986.000 copy /ml
- CD4: 13 (%3)
- Kraniyal MRG:

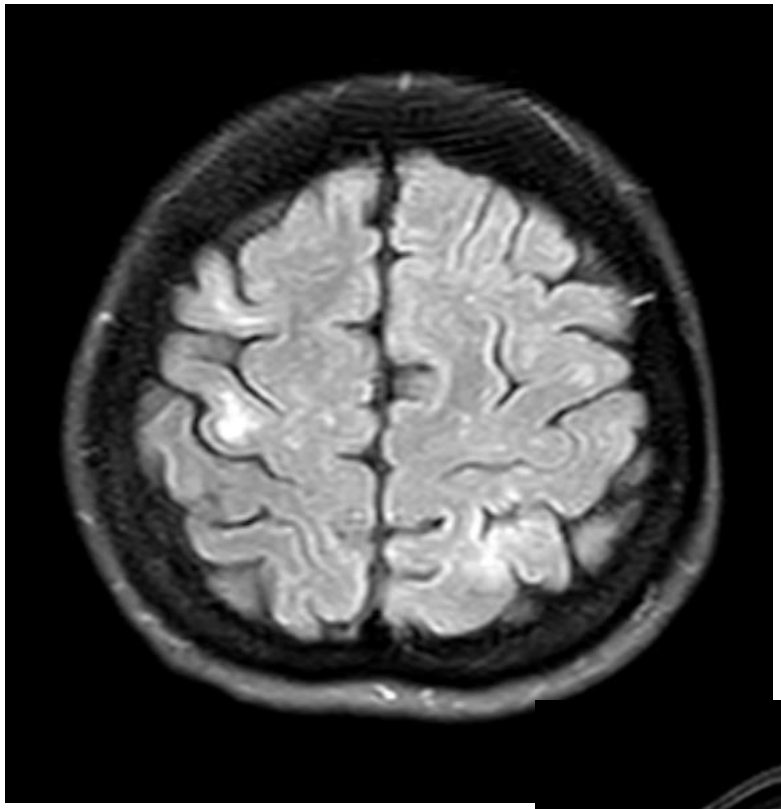
Serebral hemisferde , bilateral korona radiata ve sentrum semiovale düzeyinde daha belirgin olmak üzere, ayrıca sol serebellar hemisferde perivasküler space lehine değerlendirilen **yaygın T2 ve FLAİR A da hiperintens sinyal değişiklikleri** izlenmiştir. Yine verteks seviyesinde sağ frontalde ,bilateral bazal ganglia seviyesinde, ayrıca sağ posterior periventriküler alanlarda subkortikal derin beyaz cevher **içinde T2 ve FLAİR A da asimetrik hiperintens patolojik** sinyaller izlenmiştir. Görünümler demyelinizan hastalık lehine değerlendirildilmiş olup kontrastlı MRG korelasyonu önerilir.

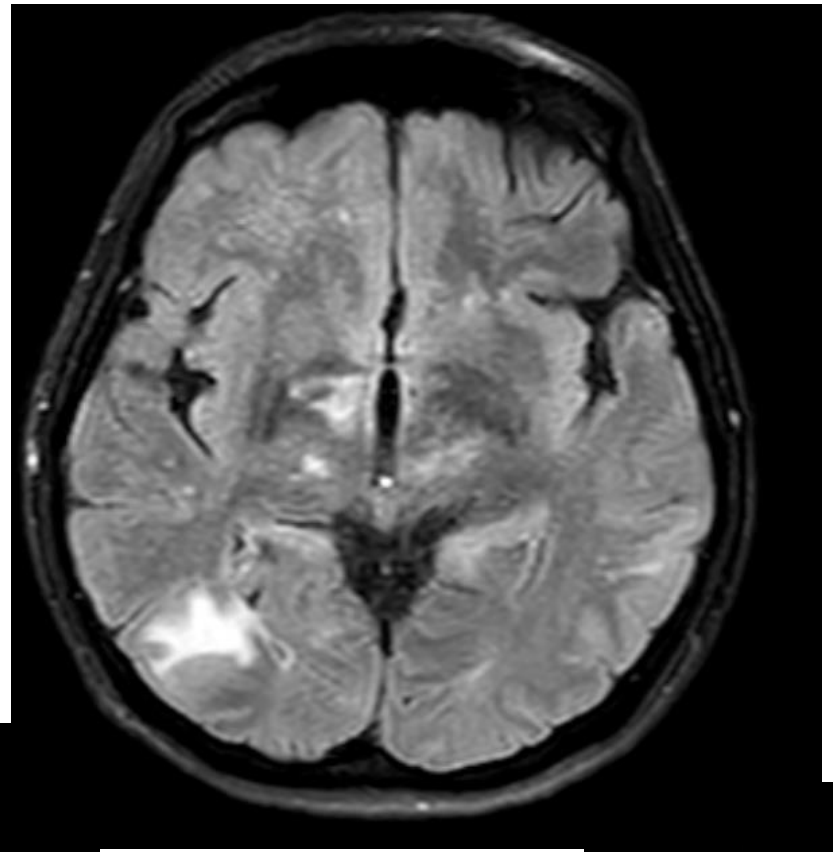
Kontrastlı MRG

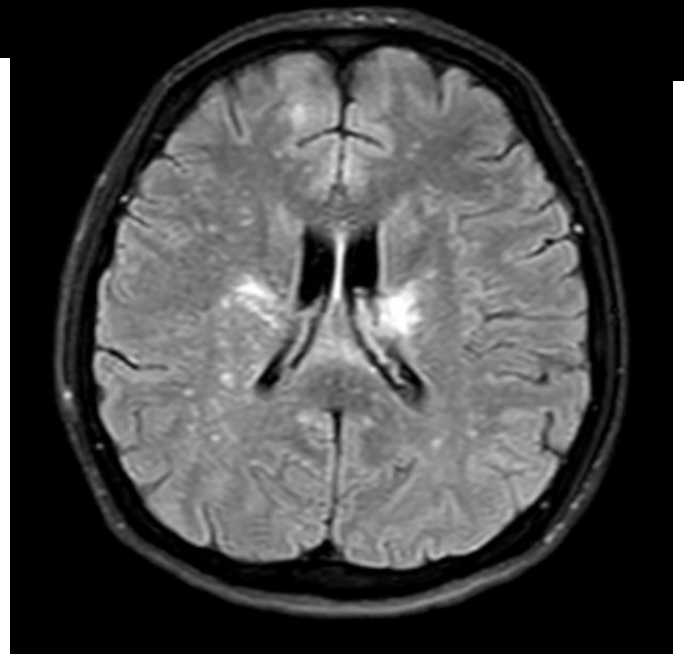
Supratentoriyal alanda bilateral serebral hemisferlerde bazal ganglialarda talamuslarda orta beyin yapılarında ve sol serebellar hemisfer ile sol serebellar pedinkülde **T2 ve FLAIR sekanslarda hiperintens T1'de hipointens** değişik boyutlarda IVKM E sonrası kontrastlanma göstermeyen multiple lezyon izlenmiştir. HİV pozitif öykülü hastada görünümler HİV'in santral sinir sistemi manifestasyonu açısından değerlendirilmesi klinik ve laboratuvar bulgularıyla birlikte değerlendirilmesi önerilir.

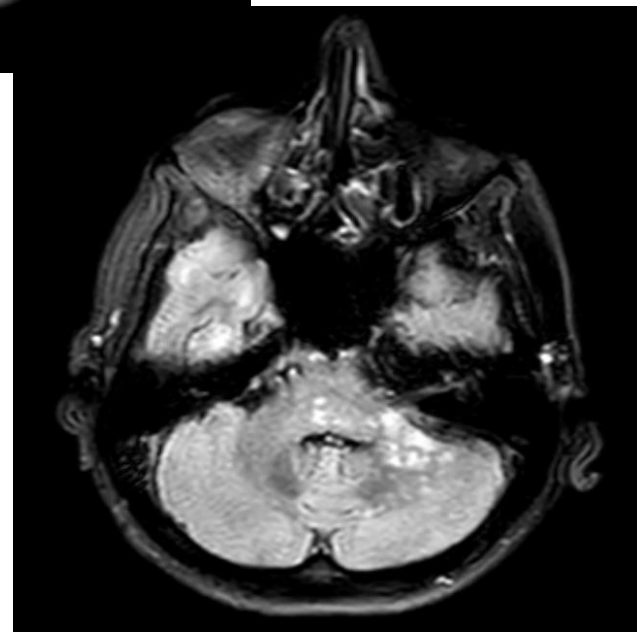
MRG Spektroskopi:

HIV ve bununla ilişkili santral sinir sistemi manifestasyon yönünden anlamlı olabilecek bulgular ile birlikte takip edilen hastanın sağ oksipital subkortikal alandaki lezyon alanından yapılan spektroskopik değerlendirmede NAA 'deki azalma ve Cho'deki artış nöronal kayıp ve hücresel proliferasyon yönünden anlamlı olarak değerlendirilmiştir. Primer santral sinir sistemi lenfoması açısından spektroskopik bulgular çok tipik olmamakla birlikte ayrıcı tanıda düşük gradeli glial neoplazik süreçler de geri planda düşünülmelidir.









Radyoloji!!!
Tedavi yanıtı-Survey

Olgu-2

- 44 yaş
- Erkek hasta
- 2017 yılında kardeşinden renal nakil (tam uyum)
- 2019 başlarına kadar işler yolunda
- 2019 ikinci yarısında kreatinin değeri önce dalgalanmaya sonra da progesif artış
  - İdrar BK:58.000
  - Kan BK: 5863

Kreatinin klirensi progresif artmakta

BKV DNA da artışta

BKVAN
-Renal biyosi önerdik ancak…
-Biyopsi iknası
-Ehil patolog

- İmmünsüpresyon dozunda azaltma (TK:7-8'den 4-5'e)
- Siprofloksasin başlanmış
- Fayda:?
- 2019 Sonund: Diyaliz

Received: 26 September 2018 | Revised: 18 January 2019 | Accepted: 6 February 2019
DOI: 10.1111/ajt.15328

BRIEF COMMUNICATION

AJT

Ciprofloxacin for BK viremia prophylaxis in kidney transplant recipients: Results of a prospective, double-blind, randomized, placebo-controlled trial

Samir J. Patel[1] | Richard J. Knight[2] | Samantha A. Kuten[1] | Edward A. Graviss[3]
Duc T. Nguyen[3] | Linda W. Moore[2] | William L. Musick[1] | Ahmed Osama Gaber[2]

BKVN daha az ama istatistiksel olarak???

Kinolon gurubunda anlamlı olarak kinolon direnci

Türkiye- TBC !!!

Review

Fluoroquinolones and BK Virus Nephropathy: A Myth or a Reality

Abstract
BK polyomavirus (BKV) is a challenging problem for the transplant nephrologist. Various strategies have been used to prevent or treat BK virus nephropathy (BKVN). These include reduction in immunosuppression, intravenous immune globulin, cidofovir, leflunomide, and the fluoroquinolone antibiotics. All these agents have their own toxicities. Great interest was shown to use fluoroquinolones to prevent BKVN after its useful experience was reported in bone marrow transplant. Fluoroquinolones being cheap and easily available, attracted nephrologists to use it, for prevention of BKVN. These agents have been shown *in vitro* studies to be effective. However, there are mixed results about their effectiveness in prevention of BKVN in clinical setting. This review will focus the evidence available for using fluoroquinolones in prevention of BKVN and its usefulness. Furthermore, a way forward to use these agents or not for prevention of BKVN will also be discussed.

Keywords: *BK polyomavirus, BK virus nephropathy, fluoroquinolones*

Nereden çıkardınız bunu?

Biol Blood Marrow Transplant 17: 1176-1181 (2011)

ASBMT American Society for Blood and Marrow Transplantation

Efficacy and Safety of Ciprofloxacin for Prophylaxis of Polyomavirus BK Virus–Associated Hemorrhagic Cystitis in Allogeneic Hematopoietic Stem Cell Transplantation Recipients

Ashley N. Miller,[1] Ashley Glode,[2] Kathy R. Hogan,[2] Christine Schaub,[1] Cindy Kramer,[3] Robert K. Stuart,[1] Luciano J. Costa[1]

Viral DNA Giraz inhibisyonu…

- 2019 sonunda yeniden rutin diyalize giren hastaya oğlundan ikinci kez nakil
- Bu sefer Kan ve İdrar BK sıkı takip
- 2020 ortası: Rejekt bulguları
  - BK kan:1362
  - İdrar:33.000
- 2020 Sonunda Diyaliz ihtiyacı
- 2021 eks

KDIGO CLINICAL PRACTICE GUIDELINE ON THE EVALUATION AND MANAGEMENT OF CANDIDATES FOR KIDNEY TRANSPLANTATION

PUBLIC REVIEW DRAFT
OCTOBER 2018

RESEARCH RECOMMENDATIONS

- Studies should determine the post-transplant infection rates, morbidity, and mortality of transplant candidates colonized with MDROs.

- Studies should determine newer strategies to increase the immunogenicity of vaccines in transplant candidates including influenza, shingles, pneumococcal, and hepatitis B vaccines. With newer high-dose influenza vaccines and adjuvanted influenza vaccines, comparative trials can be performed with immunogenicity or efficacy as an endpoint. Similarly, inactivated shingles vaccine should be evaluated in this population.

- Studies should examine whether pre-transplant vaccinations affect the incidence of post-transplant disease, specifically where the disease outcome is measurable (e.g., varicella zoster).

- Studies should examine whether it is ideal to treat HCV-positive transplant candidates pre- or post-transplant.

10.5.9 BK virus

10.5.9.1: We recommend not screening for BK virus infection in KTCs. *(1C)*

10.5.9.1.1: We recommend not excluding patients for repeat transplantation if a previous graft was lost due to BK nephropathy. *(1C)*

BK Virüs

- Polyomavirusler zarfsız, 30-45 nm çapında DNA virusleri
  - Polyomavirusler Papovaviridae ailesi
  - İnsan, maymun, tavşan, kemirici ve kuş
  - İnsanda enfeksiyon

–BK virus

–JC virus

–SV40

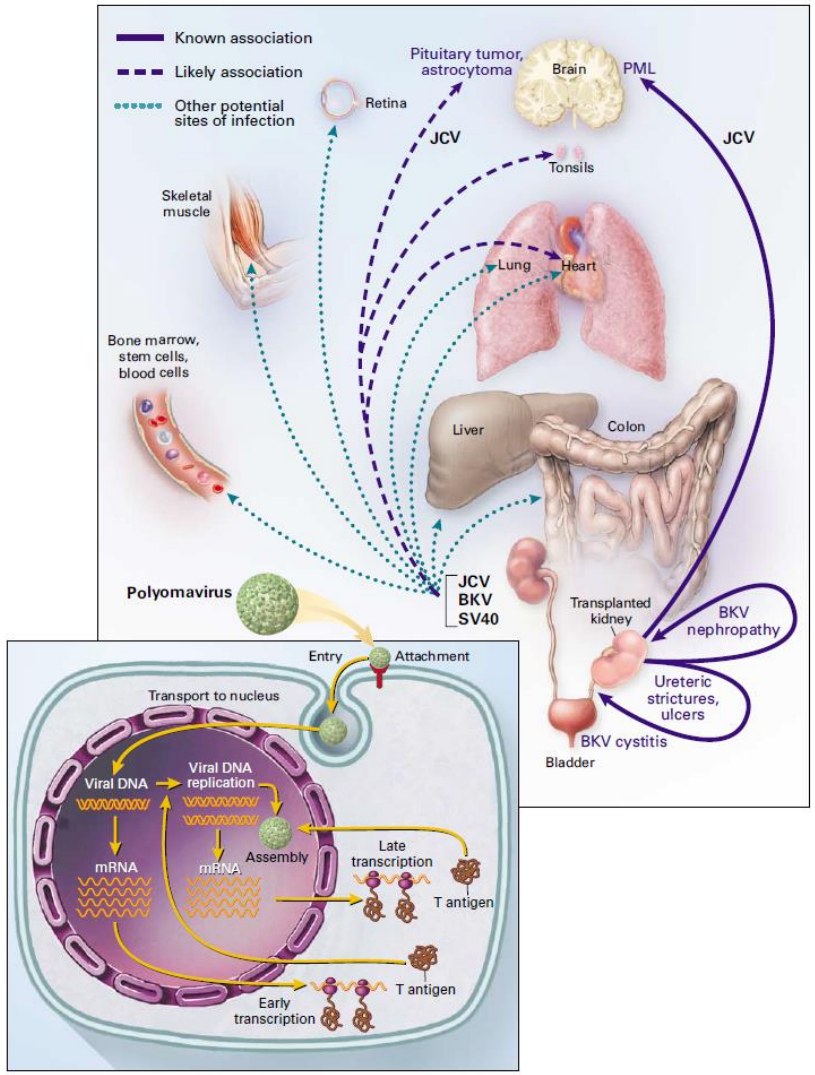
En sık

- Poliomavirus primer infeksiyon fekal-oral, solunum, transplasental/donör dokusu yoluyla

- Viremik faz boyunca hedef organları
(üroepitelyum, lenfoid doku, beyin)

- Latent/ılımlı litik infeksiyon

- BKV immunsupresyon döneminde çoğalır



Daniel L.Bohl, et al. Clin J Am Soc Nephrol 2:s36-S46,2007

BK Virus Replikasyonunda Risk:

Modifiye Edilemeyen Riskler

- >65 yaş
  - Alıcı
  - Verici
- Erkek Cinsiyet
- HLA Uyumsuzluğu
- Akut Rejekt
- Donör seropozitif
- Alıcı seronegatif
- Siyah ırk

Modifiye Edilebilen

- Takrolimus
- ATG
- Siklofosfamid

Tacrolimus-based regimen is a risk factor for BKV treatment

Retrospective analysis of scientific registry of transplant recipients data from 34,937 kidney transplant recipients 2004-2006

N-34,397	*Adjusted odds ratio for BKV treatment at month 12 post-transplant*	*95% confidence interval*
Tacrolimus as baseline immunosuppression[a]	*1.35*	*1.04, 1.74*
Thymoglobulin induction	*1.23*	*1.03, 1.45*
Male recipient	*1.62*	*1.40, 1.88*
Paediatric recipient (0-11 years of age)	*1.96*	*1.33, 2.89*
Donor > 65 years of age	*1.88*	*1.35, 2.61*
HLA mismatch	*1.36*	*1.07, 1.73*

A as compared to CsA modified as baseline immunosuppression
BKV, BK virus; HLA human leukocyte antigen;
CsA, cyclosporin

1.Schold JD et al Transpl Int 2009; 22:626-34

Olgu-3

- ST, 28 y
- Erkek hasta
- B-ALL 3yıl önce
- 3 yıl önce Haploidentik AKIT
- Kronik GVHD (1yıldır)
- Steroid ve MMF yanıtsız
- Ruksolitinib alıyor

Chemotherapy regimen: Hyper CVAD

Agents involved

Cycle A

• Cyclophosphamide	300 mg/m^2 IV in 250 mL of NS	Days 1 – 3
• Dexamethasone	40 mg IV/po	Days 1 – 4; Days 11 – 14
• Methotrexate	12 mg IT	Day 2
• Doxorubicin	50 mg/m^2 IV	Day 4
• Vincristine	2 mg IV in 50 mL of NS	Day 4, 11
• Cytarabine	70 mg IT	Days 11

Cycle B

• Methotrexate	1000 mg/m^2 IV in 1250 mL of NS	Day 1
• Cytarabine	3 g/m^2 in 250 mL of NS q12h If > 60 years old: reduce to 1.5 g/m^2/dose	Days 2 – 3

- 6 aydır süren İYE atakları
- Karın ağrısı ve sonra makroskopik olarak belirginleşen idrarda kan şikayeti mevcut
- BKV:
  - İdrar:10.000 copy/ml
  - Kan:3500 copy/ml
- Spesifik tedavi…
  - Grade 1,2,3,4?
  - Tedavi yaklaşımı?

- Cidofovir 5mg/kg +Probenesid (ilk hafta 2 doz ardından haftalık)

- 2. hafta sonunda şikayetleri

- 3. hafta sonunda bulguları düzeldi

J Antimicrob Chemother 2018; **73**: 12–21
doi:10.1093/jac/dkx324 Advance Access publication 8 September 2017

Journal of Antimicrobial Chemotherapy

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

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.

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

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

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

Aklımda deli sorular!!!

Table 7. Summary recommendations for BKPyV-HC

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

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

Olgu-4

- MZ, 54 yaş
- Kadın
- Over Ca tanılı hasta, 2020 yılında tanı almış
- Bilateral ooferektomi

- Diff MRG: Solda daha belirgin, medülla oblangata düzeyinde, her iki tarafta anteriorda fokal diffüzyon kısıtlanması gösteren milimetrik alanlar izlenmiştir

- Nörolojik muayene: Bilateral solda belirgin disdiadokokinezi, dizartri, destek ile mobilize

- Şubat 2024 DM Beyin MRG: Normal

- LP:

<u>BOS Bulguları:</u>

BOS Mikroskopi: Hücre yok

BOS MTP: 88 mg/dl

BOS Multiplex PCR: HHV-6

Tekrarı:HHV-6

Table 4. Human herpesvirus 6B reactivation after allogeneic hematopoietic stem cell transplantation: disease associations.

Epidemiological associations	Level of *in vitro* or *in vivo* support for causation
HHV-6B end-organ disease	
Encephalitis (predominantly limbic)	Strong
Non-encephalitic central nervous system dysfunction e.g. delirium, myelitis	Moderate
Myelosuppression, allograft failure	Moderate
Pneumonitis	Weak
Hepatitis	Weak
Other	
Fever and rash	Strong
Acute graft-*versus*-host disease	Moderate
CMV reactivation	Moderate
Increased all-cause mortality	Weak

HHV-6B: human herpesvirus 6B; CMV: cytomegalovirus. Adapted from Table 29.2 in Hill and Zerr.[98]

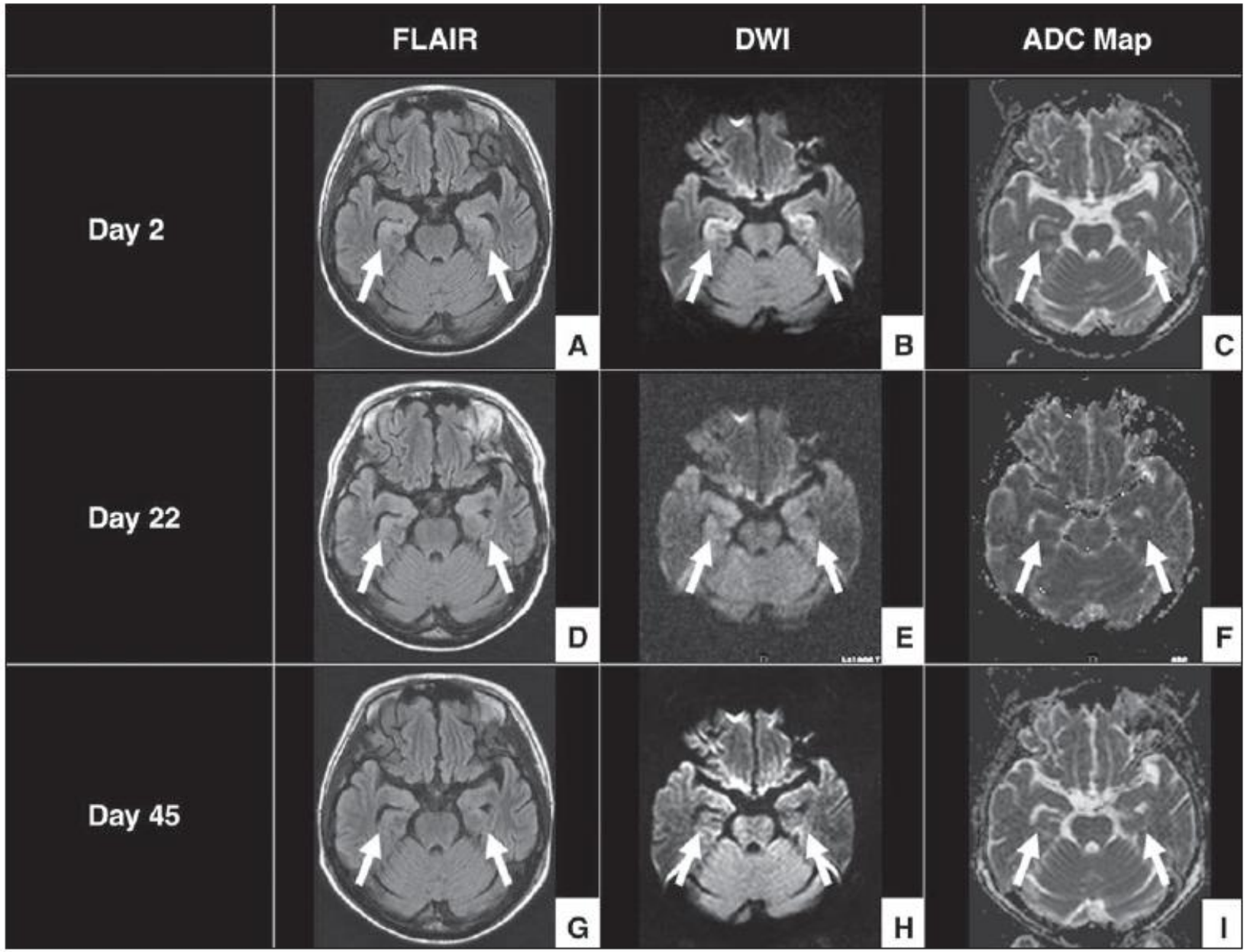
Klinik tanı???

Spesifik Tedavi???

Palyatif/ Konservatif tedavi

Gansiklovir IV
Destek tedavisi fayda(+)

CT and MRI of Human Herpesvirus 6 Encephalopathy



HHV-6

- Betaherpesvirüsler
- Çift sarmal DNA etrafında kapsid
- Çekirdekli hücreler (CD4 + T hücreler dahil)
- Nörotrop

- HHV-6A; HHV-6B (%90 genetik benzer)
- CIHHV-6
  - Telomer bölgesine entegre
  - 1/3 HHV-6A
  - 2/3 HHV-6B

HHV-6

- Bulaş yolu???

- Primer Enfeksiyon
  - <3 yaş
  - 6. hastalık; ekzantema subitum

Donör kaynaklı yeni enfeksiyon???

- Reaktivasyon
  - Genelde immünsüpresyon

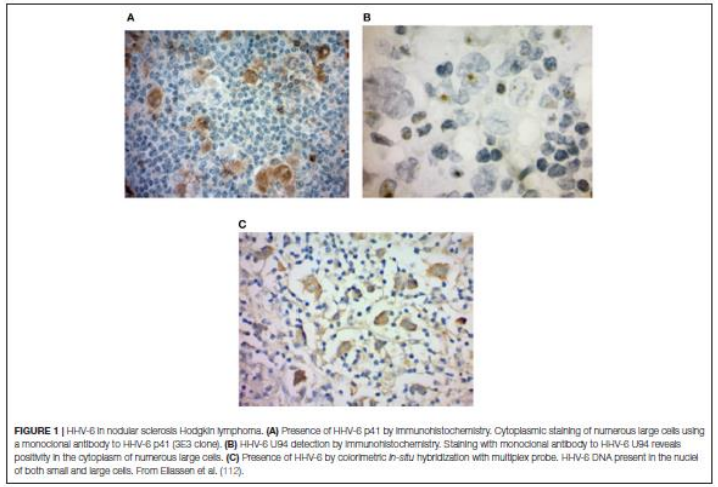


FIGURE 1 | HHV-6 in nodular sclerosis Hodgkin lymphoma. **(A)** Presence of HHV-6 p41 by immunohistochemistry. Cytoplasmic staining of numerous large cells using a monoclonal antibody to HHV-6 p41 (3E3 clone). **(B)** HHV-6 U94 detection by immunohistochemistry. Staining with monoclonal antibody to HHV-6 U94 reveals positivity in the cytoplasm of numerous large cells. **(C)** Presence of HHV-6 by colorimetric *in-situ* hybridization with multiplex probe. HHV-6 DNA present in the nuclei of both small and large cells. From Eliassen et al. (112).

Klinik:

- İmmünkompetan Hastalar:
  - Febril Nöbetler
  - Ensefalit
- İmmünsüprese Hastalar

Table 4. Human herpesvirus 6B reactivation after allogeneic hematopoietic stem cell transplantation: disease associations.

Epidemiological associations	Level of *in vitro* or *in vivo* support for causation
HHV-6B end-organ disease	
Encephalitis (predominantly limbic)	Strong
Non-encephalitic central nervous system dysfunction e.g. delirium, myelitis	Moderate
Myelosuppression, allograft failure	Moderate
Pneumonitis	Weak
Hepatitis	Weak
Other	
Fever and rash	Strong
Acute graft-*versus*-host disease	Moderate
CMV reactivation	Moderate
Increased all-cause mortality	Weak

HHV-6B: human herpesvirus 6B; CMV: cytomegalovirus. Adapted from Table 29.2 in Hill and Zerr.[98]

GUIDELINE ARTICLE

Guidelines from the 2017 European Conference on Infections in Leukaemia for management of HHV-6 infection in patients with hematologic malignancies and after hematopoietic stem cell transplantation

Katherine N Ward,[1] Joshua A Hill,[2] Petr Hubacek,[3] Rafael de la Camara,[4] Roberto Crocchiolo,[5] Hermann Einsele,[6] David Navarro,[7] Christine Robin,[8] Catherine Cordonnier,[8] and Per Ljungman;[9] for the 2017 European Conference on Infections in Leukaemia (ECIL)*

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Haematologica 2019
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Antikor testi HHV-6A / HHV-6B ayrımını yapamaz!

Çoğunlukla kullanılan PCR testleri Ayrımı yapamaz ancak yeni yöntemler…

Table 2. Human herpesvirus 6 (HHV-6) diagnostic tests.

Method	Use and limitations
Virus culture*	Diagnosis of infection: gold standard, specialized, labor-intensive
Viral antigen test (immunohistochemical staining)*	Diagnosis of infection: limited sensitivity, slow turn-around time
Detection of viral mRNA by reverse transcription PCR*	Late gene transcripts to confirm virus replication. No international standardization or specific thresholds for virus replication, especially for CIHHV-6
Quantitative viral DNA PCR	Longitudinal studies, comparison of HHV-6 DNA levels in blood *vs.* organs. Can discriminate between HHV-6A and HHV-6B*
Droplet digital PCR*	Precise method for DNA levels, identification of CIHHV-6
Fluorescence *in situ* hybridization*	Confirmation of CIHHV-6

*Not available to most diagnostic laboratories. PCR: polymerase chain reaction; CIHHV-6: chromosomally integrated HHV-6.

malignite…

frontiers in Oncology

REVIEW
published: 13 November 2018
doi: 10.3389/fonc.2018.00512

Human Herpesvirus 6 and Malignancy: A Review

Eva Eliassen[1], Emily Lum[1], Joshua Pritchett[2], Joseph Ongradi[3], Gerhard Krueger[4], John R. Crawford[5], Tuan L. Phan[1,6], Dharam Ablashi[1] and Stanley David Hudnall[7]*

Malignite Doku

ers.

HHV-6 positive patients/Total number of patients (%)	HHV-6 positive controls/Total number of controls (%)	Type of control tissue	Of typed samples: HHV-6A%, HHV-6B%, (HHV-6A/B Coinfection%); Coinfections with other viruses
16/99 **(16.2%)**	0/40 (0%)	20 matched, 20 unmatched ovarian tissues	63%, 37%
0/93 **(0%)**	NA	NA	NA
0/7 **(0%)**	NA	NA	NA
1/95 **(1%)**	0/5 (0%)	Adjacent normal tissue	NA
0/57 **(0%)**	NA	NA	NA
2/255 **(0.8%)**	1/208 (0.5%)	Adjacent normal tissue	NA
2/252 **(0.8%)**	NA	NA	NA
39/103 **(37.9%)**	9/66 (14%)	Normal CT	22/23 with high grade dysplasia had high-risk HPV
6/195 **(3.1%)**	1/125 (0.8%)	Normal CT	86% HPV+
7/187 **(3.7%)**	7/201 (3.5%)	CT, normal or inflamed	57% HPV+
1/51 **(2%)**	0/58 (0%)	CT, normal or inflamed	0%, 100%; HPV+
2/8 **(25%)**	NA	NA	50% 50%
6/72 **(18.8%)**	0/30 (0%)	CT, normal and cervicitis	66.7% HPV+
10/30 **(33.3%)**	0/7 (0%)	Normal oral, salivary gland tissues, CT	20%, 50%, (30%)
10/26 **(38.5%)**	1/8 (12.5%)	Normal CT	38.6%, 38.6%, (42.8%)

References	Cancer type	Detection method	HHV-6 positive patients/Total number of patients (%)	HHV-6 positive controls/Total number of controls (%)	Type of control tissue
Cantalupo et al. (30)	Head/neck squamous cell carcinoma	Pickaxe	11/517 **(2.1%)**	6/515 (1.2%)	Adjacent normal tissue
Cao et al. (29)	Head/neck squamous cell carcinoma	VirusScan	12/498 **(2.4%)**	NA	NA
Arivananthan et al. (78)	Laryngeal	ISH	4/4 **(100%)**	0/7 (0%)	Normal oral, cervical, salivary gland tissues
Arivananthan et al. (78)	Salivary gland	ISH	6/8 **(75%)**	0/7 (0%)	Normal oral, cervical, salivary gland tissues
Arivananthan et al. (78)	Oral SCC	ISH	16/21 **(76.2%)**	0/7 (0%)	Normal oral, cervical, salivary gland tissues
Yadav et al. (80)	Oral SCC	ISH	33/42 **(78.6%)**	12/30 (40%)	Normal mucosa, LP, leukoplakia
Yadav et al. (80)	Oral SCC	IHC	41/51 **(80.4%)**	15/25 (60%)	Normal mucosa, LP, leukoplakia
Yadav et al. (81)	Oral SCC	IHC	7/7 **(100%)**	0/3 (0%)	NPC
Saravani et al. (82)	Oral SCC	PCR	13/45 **(28.9%)**	NA	NA
Yadav et al. (80)	Oral SCC	PCR	19/24 **(79%)**	5/35 (14.3%)	Normal mucosa, LP, leukoplakia, breast cancer
Yadav et al. (81)	Oral SCC	PCR	11/16 **(68.8%)**	NA	NA
Shanehsazzadeh et al. (83)	Salivary gland cancer*	PCR	28/60 **(46.7%)**	NA	NA
Chen et al. (84)	NPC	PCR, ISH	13/42 **(30.9%)**	1*/48 (2.1%*)	Nasopharynx, precancerous and normal
Kositanont et al. (85)	NPC	PCR	5/34 **(14.7%)**	0/5 (0%)	Non-cancerous tissue

Malignite-Hasta

References	Cancer type	Detection methods	HHV-6 positive tissues	HHV-6 cellular localization	Antigen detection	HHV-6 variant	Disease course
Campioni et al. (86)	DLBCL	PCR, RT-PCR, FISH	Bone marrow, pleural effusion derived mesothelial cells, peripheral blood	17p chromosome region of a marker chromosome	U94 exhibited levels of transcription (100 ± 15 transcripts/1 μg RNA)	IciHHV-6A	An 82-years-old man with DLBCL died of respiratory insufficiency
Zhang et al. (87)	PEL-like lymphoma	PCR, FISH, ddPCR	Tumor tissue, peripheral blood	19q telomere absent from lymphoma cells despite retention of both copies of chromosome 19	NA	IciHHV-6A	A 73-years-old woman developed an HHV-8-unrelated PEL-like lymphoma that resolved following R-CHOP therapy, and she remained in remission for 9 years, eventually dying from complications of diabetes
Nakayama-Ichiyama et al. (88)	PCLBCL	IHC	Tumor tissue of the leg (HHV-8 coinfection)	Nucleoli of lymphoma cells	NA	NA	A 91-years-old woman developed PCLBCL, leg type. Lymphadenopathy disappeared and skin lesions showed improvement after R-CHOP therapy
Nakayama-Ichiyama et al. (89)	DLBCL	IHC	Tumor tissue of the leg (HHV-8 coinfection)	Nucleoli of lymphoma cells	NA	NA	A 69-years-old woman developed DLBCL, not otherwise specified (NOS), nongerminal center B-cell–like subtype, stage IIIA. Symptoms and lesions disappeared after treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone
Lohl et al. (90)	ALL	PCR	Blood	22q-tel chromosome region	NA	IciHHV-6	A 3.5-years old girl was diagnosed with ALL. High-copy numbers of HHV-6 were found during induction therapy
Hubacek et al. (91)	AML	PCR, FISH	Hair follicles, blood, all sampled tissues	Integrated on a marker chromosome of unknown origin	NA	IciHHV-6A	A 33-years old woman with AML was found to have high levels of HHV-6A DNA in blood during treatment. She died of CMV pneumonitis after HSCT
Hubacek et al. (91)	ALL	PCR, FISH	Hair follicles, blood, all sampled tissues	18p11.3 chromosome region	NA	IciHHV-6B	A 6-years old boy with ALL developed GvHD post-transplant and later died of CMV pneumonitis
Lin et al. (92)	TCL	Viral culture	Bone marrow	NA	NA	NA	A 48-years-old man developed gammadelta T-cell lymphoma 4 years after undergoing kidney transplantation. Long term remission was not achieved
Dalbata et al. (93)	Pre-B-cell ALL	PCR, SB, ISH, FISH	Liver, spleen, lungs, and brain, PBMC	1q44 chromosome region Nuclei of 80% of PBMCs and the majority of leukemic cells	NA	IciHHV-6B	An 83-years-old woman developed pre-B-cell ALL with a t(9;22)(q24; q11) chromosomal abnormality resulting in generation of Philadelphia (Ph1) chromosome

(Continued)

References	Cancer type	Detection methods	HHV-6 positive tissues	HHV-6 cellular localization	Antigen detection	HHV-6 variant	Disease course
Dalbata et al. (94)	AML and AILD	PCR	Lymph node, pericardial effusion, liver, BM, lungs, spleen, kidneys, heart	NA	NA	HHV-6B	A 47-years-old man with AML was diagnosed with AILD 4 months after induction of chemotherapy and died of fulminant hepatitis
Bandobashi et al. (95)	Burkitt's Lymphoma	PCR	Bone marrow	Lymphoma cells	NA	NA	A 58-years-old woman developed Burkitt's lymphoma. Chemotherapeutic response was minimal, the disease progressed into a leukemic phase, and she died of septicemia 6 weeks after admission
Maeda et al. (96)	NSHL	ISH, IHC, Serology	Lymph nodes	Macrophages and lymphocytes, predominantly in lymphoid follicles, but not in RS nor Hodgkin cells	Antigens detected in lymph nodes	NA	A 7-years-old boy showed changes developed HL of the NS-LD subtype. Chemotherapy resulted in complete remission
Stödberg et al. (97)	Diffuse leptomeningeal oligodendrogliomatosis	PCR	CSF, serum, and tumor tissue	NA	Limited attempts at antigen detection were unsuccessful	HHV-6A	A 2-years-old boy developed a leptomeningeal tumor. After chemotherapy and complementary antiviral therapy, the boy's clinical condition stabilized, and his predominant problem became a gradually more evident autistic disorder
Rantala et al. (98)	Pilocytic astrocytoma	PCR	CSF initially, tumor tissue	NA	NA	NA	A 14-months old girl developed a pilocytic astrocytoma in the cerebellum 11 months after a period of fever, exanthema, encephalitis, carditis, and intractable seizures, during which time HHV-6 was identified in the CSF. After removal of the tumor, she still had severe hypotonia, poor social contact, and up to 5 series of infantile spasms daily

HHV-6 Ensefaliti

- HSCT alıcılarında

- Tanı???
  - Trombositopeni
  - LP kontrendikasyonu
  - BOS PCR

- Prevalans???

GUIDELINE ARTICLE

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Katherine N Ward,[1] Joshua A Hill,[2] Petr Hubacek,[3] Rafael de la Camara,[4] Roberto Crocchiolo,[5] Hermann Einsele,[6] David Navarro,[7] Christine Robin,[8] Catherine Cordonnier,[8] and Per Ljungman;[9] for the 2017 European Conference on Infections in Leukaemia (ECIL)*

Ferrata Storti Foundation

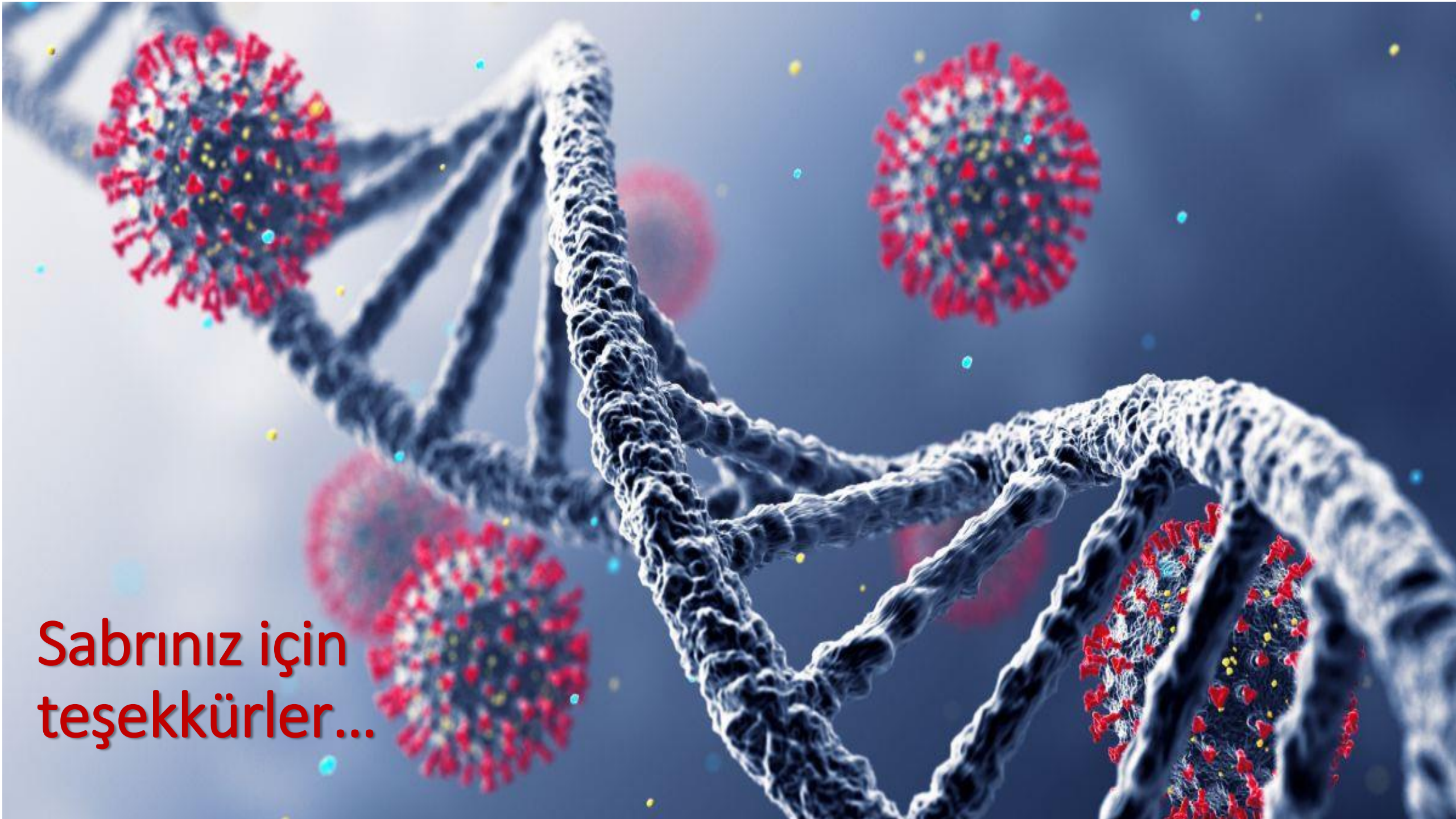
Haematologica 2019
Volume 104(11):2155-2163

- Intravenous foscarnet or ganciclovir are recommended for treatment of HHV-6B encephalitis. Drug selection should be dictated by the drug's side effects and the patient's comorbidities (AIIu).
- The recommended doses are 90 mg/kg b.d. for foscarnet and 5 mg/kg b.d. for ganciclovir (AIIu).
- Antiviral therapy should be for at least three weeks and until testing demonstrates clearance of HHV-6 DNA from blood and, if possible, CSF (CIII).
- Combined ganciclovir and foscarnet therapy can be considered (CIII).
- Immunosuppressive medications should be reduced if possible (BIII).
- There are insufficient data on the use of cidofovir to make a recommendation.

Treatment of human herpesvirus 6B associated end-organ diseases other than encephalitis

Since the strength of associations with other end-organ diseases is moderate or weak, there are insufficient data to guide a recommendation for antiviral treatment.

- No recommendation can be made.


Sabrınız için
teşekkürler...