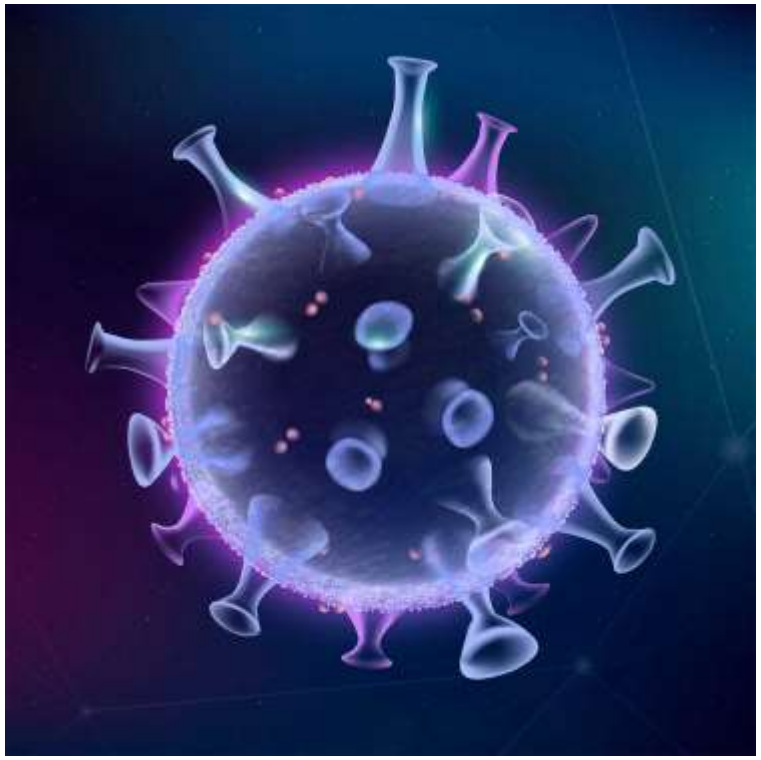
KLİMİK TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ 39.YIL

NİÇG



Nakli alıcılarında CMV yönetimi

Dr.Hande Arslan
Başkent ÜTF
Enfeksiyon Hastalıkları AD

10 OCAK 2026

Clinical Infectious Diseases

MAJOR ARTICLE

Consensus Definitions of Cytomegalovirus (CMV) Infection and Disease in Transplant Patients Including Resistant and Refractory CMV for Use in Clinical Trials: 2024 Update From the Transplant Associated Virus Infections Forum

Per Ljungman,[1,2] Roy F. Chemaly,[3] Fareed Khawaya,[3] Sophie Alain,[4] Robin Avery,[5] Cyrus Badshah,[6] Michael Boeckh,[7,8] Martha Fournier,[9] Aimee Hodowanec,[10] Takashi Komatsu,[10] Ajit P. Limaye,[11] Oriol Manuel,[12] Yoichiro Natori,[13] David Navarro,[14,15] Andreas Pikis,[10] Raymund R. Razonable,[16,17] Gabriel Westman,[18,19] Veronica Miller,[20] Paul D. Griffiths,[21] and Camille N. Kotton[22]; for the CMV Definitions Working Group of the Transplant Associated Virus Infections Forum

Special Feature

OPEN

The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation

Camille N. Kotton, MD,[1] Deepali Kumar, MD,[2] Oriol Manuel, MD,[3] Sunwen Chou, MD,[4] Randall T. Hayden, MD,[5] Lara Danziger-Isakov, MD, MPH,[6] Anders Asberg, PhD,[7] Helio Tedesco-Silva, MD,[8] and Atul Humar, MD[2]; on behalf of The Transplantation Society International CMV Consensus Group*

Table 1. Definitions of Cytomegalovirus Disease Not Changed From Previous Publication

Disease Entity	Proven	Probable
Pneumonia	Clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea combined with CMV documented in lung tissue by virus isolation, rapid culture, histopathology, immunohistochemistry, or DNA hybridization techniques	
GI disease	Proven disease requires upper and/or lower GI symptoms plus macroscopic mucosal lesions plus CMV documented in tissue by histopathology, virus isolation, rapid culture, immunohistochemistry, or in situ nucleic acid hybridization techniques; studies should give information regarding the presence or absence of gut GVHD in HCT recipients	This requires upper and/or lower GI symptoms and CMV documented in tissue by histopathology, virus isolation, rapid culture, immunohistochemistry, or in situ nucleic acid hybridization but without the requirement for macroscopic mucosal lesions; it should, however, be noted that this definition may increase the risk of false positives, lowering the statistical sensitivity to a therapeutic effect; studies should report the presence or absence of gut GVHD in hematopoietic cell transplant recipients
Hepatitis	Abnormal liver function tests *plus* CMV documented in tissue by histopathology, immunohistochemistry, virus isolation, rapid culture, or DNA hybridization techniques *plus* the absence of other documented cause of hepatitis	Not defined
Encephalitis and ventriculitis	CNS symptoms *plus* detection of CMV in CNS tissue by virus isolation, rapid culture, immunohistochemical analysis, in situ hybridization, or preferably quantitative polymerase chain reaction	CNS symptoms *plus* detection of CMV in cerebrospinal fluid without visible contamination of blood *plus* abnormal imaging results or evidence of encephalitis on electroencephalogram
Nephritis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a kidney allograft biopsy specimen obtained from a patient with renal dysfunction together with the identification of histologic features of CMV infection	Not defined
Cystitis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a bladder biopsy specimen obtained from a patient with cystitis together with the identification of conventional histologic features of CMV infection	Not defined
Myocarditis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a heart biopsy specimen obtained from a patient with myocarditis together with the identification of conventional histologic features of CMV infection	Not defined
Pancreatitis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a pancreatic biopsy specimen obtained from a patient with pancreatitis together with the identification of conventional histologic features of CMV infection	Not defined
Other end-organ disease	CMV can also cause disease in other organs, and the definitions of these additional disease categories include the presence of compatible symptoms and signs and documentation of CMV by biopsy by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization	Not defined

Abbreviations: CMV, cytomegalovirus; CNS, central nervous system; GI, gastrointestinal; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplant.

Table 2. DNA Levels in Bronchoalveolar Lavage Fluid (IU/mL) for Diagnosis of Probable or Unlikely Cytomegalovirus Pneumonia

Patient Category	Probable	Unlikely
Allogeneic HCT patients[a]	$> 10^3$ [a]	$< 5 \times 10^2$
Autologous HCT patients CAR T cell-treated patients	Cannot be defined	$< 5 \times 10^2$
Solid organ transplant patients except lung transplant patients isolated or combined	Cannot be defined	$< 5 \times 10^2$
Lung transplant patients	Cannot be defined	Cannot be defined

Abbreviation: CAR, Chimeric Antigen Receptor; HCT, hematopoietic cell transplant.

[a]Possible cytomegalovirus pneumonia is defined as the same viral load + presence of co-pathogens.

Table 3. Definitions of Cytomegalovirus Gastrointestinal Disease

Patient Category	Proven CMV Disease	Probable CMV Disease	Possible CMV Disease
Allogeneic HCT patients	Upper and/or lower GI symptoms *plus* macroscopic mucosal lesions *plus* CMV documented in tissue[a]	Upper and/or lower GI symptoms and CMV documented in tissue[a] (not by PCR) but without the requirement for macroscopic mucosal lesions	Upper and/or lower GI symptoms and CMV documented in tissue by PCR but without the requirement for macroscopic mucosal lesions;
Solid organ transplant patients except small bowel transplant patients	Upper and/or lower GI symptoms *plus* macroscopic mucosal lesions *plus* CMV documented in tissue[a]	Upper and/or lower GI symptoms and CMV documented in tissue (not by PCR) but without the requirement for macroscopic mucosal lesions	diarrhea rated at least National Cancer Institute, Common Terminology Criteria for Adverse Events (version 4.0), grade 2 and CMV documented in blood and exclusion of other likely causes of diarrhea
Small bowel transplant patients	Upper and/or lower GI symptoms *plus* macroscopic mucosal lesions *plus* CMV documented in tissue[a]	Not applicable	
Autologous HCT and CAR T cell–treated patients	Upper and/or lower GI symptoms *plus* macroscopic mucosal lesions *plus* CMV documented in tissue[a]	Upper and/or lower GI symptoms and CMV documented in tissue (not by PCR) but without the requirement for macroscopic mucosal lesions	

Abbreviations: CAR, Chimeric Antigen Receptor; CMV, cytomegalovirus; GI, gastrointestinal; HCT, hematopoietic cell transplant; PCR, polymerase chain reaction.

[a]Quantitative PCR is not accepted as a diagnostic criterion for proven or probable CMV GI disease.

Olgu -1

- **Hasta:** 52 yaşında erkek
- **Öykü:** 4 ay önce canlı vericiden (D+/R+) böbrek nakli yapılmış
- **İmmünsüpresif tedavi:** Takrolimus, mikofenolat mofetil, prednizolon
- **Profilaksi:** İlk 3 ay valgansiklovir almış, sonrasında kesilmiş
- **Başvuru yakınmaları:** Son 10 gündür halsizlik, iştahsızlık, subfebril ateş (37.7°C), ishal ve 2 kg kilo kaybı

- **Fizik Muayene**
  - Ateş: 37.8°C
  - Nabız: 96/dk
  - Tansiyon: 120/75 mmHg
  - Hafif dehidratasyon bulguları, batında belirgin patoloji yok.

- **Laboratuvar**
  - **Lökosit**: 3.200 /mm³ (lenfopeni mevcut)
  - **CRP:** 42 mg/L
  - **Kreatinin:** 1.9 mg/dL (15 gün önceki: 1.4 mg/dL)
  - **CrCL:** % 65
  - **Dışkı Mikroskopisi:** Lökosit/ eritrosit/ parazit görülmedi
  - **Dışkı kültürü:** Patojen bakteri üremedi.

Ayırıcı tanı:

a) İlaç yan etkisi (ör. mikofenolat → diyare)

b) Graft rejeksiyonu (kreatinin yükselmesi)

c) Viral enteritler (adenovirüs, norovirüs, CMV)

Hangi tetkikleri isteyelim?

Laboratuvar

- **GİS PCR paneli** : Negatif
- **CMV serolojisi:**
- **CMV PCR (plazma)**:
- **Kolonoskopi**
- **Biyopsi**:

Laboratuvar

- **GİS PCR paneli** : Negatif
- **CMV serolojisi:** TANIYA YARDIMCI DEĞİL
- **CMV PCR (plazma)**: NEGATİF
- **Kolonoskopi** mukozal inflamasyon
- **Biyopsi**: Nonspesifik mukozal inflamasyon, CMV inklüzyonları NEGATİF

Laboratuvar

- **GİS PCR paneli** : Negatif
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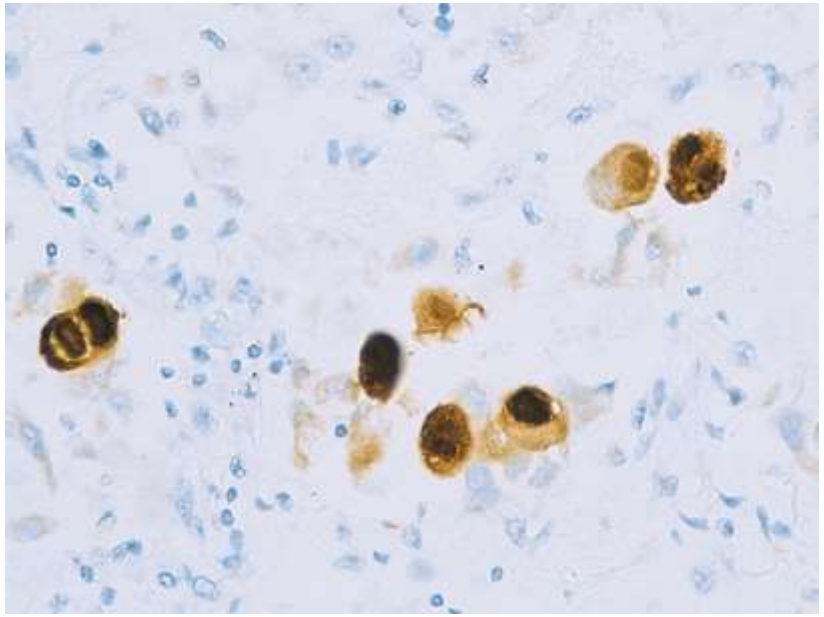

Süreç:

- Kolon biyopsisinde CMV immünohistokimyasal boyama istendi
- Sonuç: Pozitif

Kesin Tanı CMV koliti

Special Feature

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The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation

Camille N. Kotton, MD,[1] Deepali Kumar, MD,[2] Oriol Manuel, MD,[3] Sunwen Chou, MD,[4] Randall T. Hayden, MD,[5] Lara Danziger-Isakov, MD, MPH,[6] Anders Asberg, PhD,[7] Helio Tedesco-Silva, MD,[8] and Atul Humar, MD[2]; on behalf of The Transplantation Society International CMV Consensus Group*

Table 3. Definitions of Cytomegalovirus Gastrointestinal Disease

Patient Category	Proven CMV Disease	Probable CMV Disease	Possible CMV Disease
Allogeneic HCT patients	Upper and/or lower GI symptoms *plus* macroscopic mucosal lesions *plus* CMV documented in tissue[a]	Upper and/or lower GI symptoms and CMV documented in tissue[a] (not by PCR) but without the requirement for macroscopic mucosal lesions	Upper and/or lower GI symptoms and CMV documented in tissue by PCR but without the requirement for macroscopic mucosal lesions;
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Abbreviations: CAR, Chimeric Antigen Receptor; CMV, cytomegalovirus; GI, gastrointestinal; HCT, hematopoietic cell transplant; PCR, polymerase chain reaction.

*Quantitative PCR is not accepted as a diagnostic criterion for proven or probable CMV GI disease.

Tedavi seçenekleri;

a) Gansiklovir

b) Valgansiklovir

c) Valasiklovir

d) Letermovir

e) Maribavir

CMV Hastalığında Tedavi

Tedavinin iki komponenti:

1. Antiviral tedavi
2. Rejeksiyon riski yok ise immünsupresif tedavinin kontrollü olarak azaltılması

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Consensus Statements and Recommendations

- For initial and recurrent episodes of CMV disease, oral valganciclovir (900 mg every 12 h) or intravenous ganciclovir (5 mg/kg every 12 h) are recommended as first-line treatment in adults with normal kidney function (strong, moderate).
- Oral valganciclovir is recommended in patients with mild to moderate CMV disease who can tolerate and adhere to oral medication (strong, moderate).
- Intravenous ganciclovir is recommended in life- and severe diseases (strong, low).
- After clinical improvement, intravenous ganciclo transitioned to valganciclovir in patients who tolerate oral therapy (strong, moderate).
- Oral ganciclovir, acyclovir, or valacyclovir are mended for the treatment of CMV disease (strong

Başlangıç tedavisi;

- Oral valgansiklovir 2x900 mg (hafif/ orta ağırlıkta olgularda)
  veya
- IV gansiklovir 2x 5 mg/kg (ağır olgularda)
  Klinik iyileşmeyi takiben oral valgansiklovire geçilebilir

- Oral gansiklovir, asiklovir,valasiklovir **tedavide kullanılmaz**

(Böbrek fonsiyonuna göre doz ayarı)

İlk tercih antiviral tedaviler;

Böbrek fonksiyonu normal hastalarda

- **Ağır infeksiyonlarda:** Gansiklovir IV (2 x 5mg/kg)
- **Orta/ hafif infeksiyonlarda:** Valgansiklovir (2x900 mg)

- Gastrointestinal tutulum varlığında valgansiklovir biyoyararlanımı?

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TABLE 5.

Dosage recommendations for ganciclovir and valganciclovir and valacyclovir for adult patients with impaired kidney function (using the Cockcroft-Gault formula)

CrCL, mL/min	Treatment dose	Maintenance/prevention dose
Intravenous ganciclovir (adapted from[226])		
≥70	5.0 mg/kg q12h	5.0 mg/kg q24h
50–69	2.5 mg/kg q12h	2.5 mg/kg q24h
25–49	2.5 mg/kg q24h	1.25 mg/kg q24h
10–24	1.25 mg/kg q24h	0.625 mg/kg q24h
<10	1.25 mg/kg 3×/wk after hemodialysis	0.625 mg/kg 3×/wk after hemodialysis
Oral valganciclovir (adapted from[227,228])		
≥60	900 mg q12h	900 mg q24h
40–59	450 mg q12h	450 mg q24h
25–39	450 mg q24h	450 mg q48h
10–24	450 mg q48h	450 mg twice weekly
<10	200 mg 3×/wk after hemodialysis[a]	100 mg 3×/wk after hemodialysis[a]
Oral valacyclovir (high dose)[112]		
>75	—	2000 mg 4×/d
51–75	—	1500 mg 4×/d
26–50	—	1500 mg 3×/d
10–25	—	1500 mg 2×/d
<10 or dialysis	—	1500 mg 1×/d

[a]Oral solution must be used in this instance (as valganciclovir tablets cannot be split).
CrCL, creatinine clearance.

Optimal tedavi süresi

- En az iki hafta
- Haftalık viremi takibi yapılmalı
- Yüksek sensitivitedeki kit ile bir, düşük sensitivitedeki kitle iki ardışık negatif sonuç bulununca tedavi sonlandırılabilir
- Başlangıçta viral yük azalmayabilir hatta artabilir, bu durum tedavi değişikliği gerektirmez

- **Tedavi sırasında**
  - Mutlaka böbrek fonksiyonları takip edilmeli ;doz ayarlanmalı
  - Düzenli ararlıklarla kan sayımı yapılmalı; Lökopeni geliştiği durumlarda GCSF başlanır

Hastanın Tedavisi

- Valgansiklovir (GFR >%60) 2x 900 mg 2x1

GFR >%60	2x 900 mg
GFR %40-59	2x450 mg
GFR %25-39	1x450 mg
GFR %10-24	1x450 mg/48 saat
GFR < %10	Hemodiyalizden sonra haftada 3 kez 200 mg

Hastanın tedavi süresi?

- Haftalık viremi takibi yapılmalı
- Yüksek sensitivitedeki kit ile bir, düşük sensitivitedeki kitle iki ardışık negatif sonuç bulununca tedavi sonlandırılabilir
- En kısa tedavi süresi: iki hafta

- Bu hastada
  - Viremi takibi mümkün değil
  - En az iki hafta; semptomlara göre tedavi süresi belirlendi

- CMV hastalığı tanısı alan nakil hastasında ,
  - Birincil tedavi seçeneği;
    - Valgansiklovir
    - IV gansiklovir
  - Tedavi dozu:
    - GFR ye göre ayarlanır
  - Tedavi takibinde
    - haftalık PCR testi
    - böbrek fonsiyonları
    - Lökosit sayısı takip edilir
    - Tedavi süresi PCR negatifliğ görene kadar ; En az iki hafta

ÖZET

CMV hastalığı tanısı alan nakil hastasında ,

- **Birincil tedavi seçeneği?**
- **Tedavi dozu?**
- **Tedavi takibinde?**
- **Tedavi süresi ?**

ÖZET

CMV hastalığı tanısı alan nakil hastasında ,

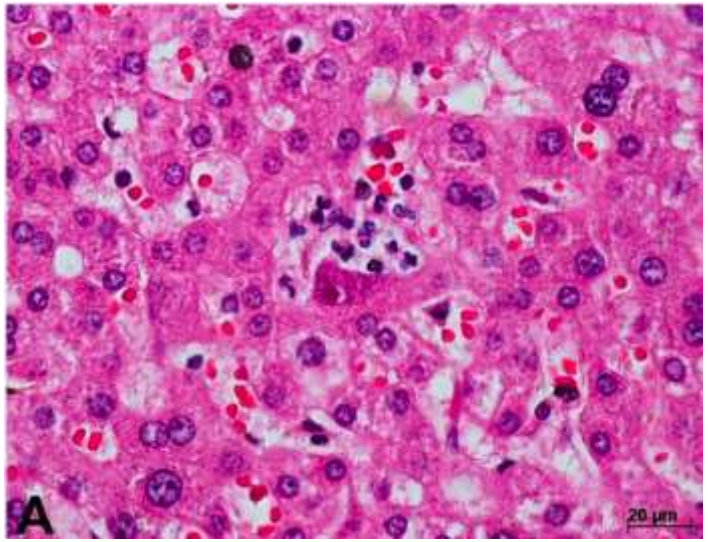
- **Birincil tedavi seçeneği;**
  - Valgansiklovir
  - IV gansiklovir
- **Tedavi dozu:**
  - GFR ye göre ayarlanır
- **Tedavi takibinde**
  - haftalık PCR testi
  - böbrek fonsiyonları takibi
  - Lökosit sayısı
- **Tedavi süresi**
  - PCR negatifliğ görene kadar ; En az iki hafta

2. Olgu

- **Hasta:** 58 yaşında erkek
- **Öykü:** 6 ay önce kadavradan (D+/R+) karaciğer nakli yapılmış
- **İmmünsüpresyon:** Takrolimus + mikofenolat mofetil + prednizolon
- **Profilaksi:** İlk 3 ay valgansiklovir
- **Başvuru:** 39°C ateş, halsizlik, karaciğer fonksiyon testlerinde bozulma

İlk Bulgular

- Lökosit: 2.000 /mm^3
- AST/ALT: 2 kat artmış
- CRP: 78 mg/L
- CMV PCR (plazma): $2.5x10^5$ kopya/mL



- Lökosit: 2.000 /mm³
- AST/ALT: 4 kat artmış
- CRP: 78 mg/L
- CMV PCR (plazma): 2.5x10⁵ kopya/mL
- **Karaciğer biyopsisi: CMV inklüzyon cisimcikleri ile uyumlu hepatit**

Table 1. Definitions of Cytomegalovirus Disease Not Changed From Previous Publication

Disease Entity	Proven	Probable
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Nephritis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a kidney allograft biopsy specimen obtained from a patient with renal dysfunction together with the identification of histologic features of CMV infection	Not defined
Cystitis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a bladder biopsy specimen obtained from a patient with cystitis together with the identification of conventional histologic features of CMV infection	Not defined
Myocarditis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a heart biopsy specimen obtained from a patient with myocarditis together with the identification of conventional histologic features of CMV infection	Not defined
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Hepatitis	Abnormal liver function tests *plus* CMV documented in tissue by histopathology, immunohistochemistry, virus isolation, rapid culture, or DNA hybridization techniques *plus* the absence of other documented cause of hepatitis	Not defined

- Tanı: Son organ tutulumlu CMV hastalığı
- CMV hepatiti

	biopsy specimen obtained from a patient with cystitis together with the identification of conventional histologic features of CMV infection	
Myocarditis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a heart biopsy specimen obtained from a patient with myocarditis together with the identification of conventional histologic features of CMV infection	Not defined
Pancreatitis	Detection of CMV by virus isolation, rapid culture, immunohistochemical analysis, or in situ hybridization in a pancreatic biopsy specimen obtained from a patient with pancreatitis together with the identification of conventional histologic features of CMV infection	Not defined
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Tedavi süreci:

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[a]Oral solution must be used in this instance (as valganciclovir tablets cannot be split).
CrCL, cre

Transplantation ■ July 2025 ■ Volume 109 ■ Number 7

Başlangıç : IV gansiklovir
GFR normal; 5mg/kg/gün

1. hafta:

CMV PCR $1.9x10^5$ kopya/mL

Lökosit sayısı 1000/mm3
GFR %70
(Gansiklovir ve türevlerinde en sık görülen yan etkiler)

Tedavi takibi

- Birinci haftanın sonunda
    - Yan etki; Lökopeni , renal toksisite
    - Tedavi yanıtı yok

Ne yapalım?


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- **Tedavi sırasında**
  - Başlangıçta viral yük azalmayabilir hatta artabilir, bu durum tedavi değişikliği gerektirmez
  - Mutlaka böbrek fonksiyonları takip edilmeli ;doz ayarlanmalı
  - Düzenli ararlıklarla kan sayımı yapılmalı; Lökopeni geliştiği durumlarda GCSF başlanır

Tedavi Süreci

- İmmünsupresif tedavi azaltıldı
- GFR’e göre doz ayarlanarak gansiklovirle devam edildi
- Toksisite nedeniyle hastaya granül stimüle edici faktör başlandı

Tedavi Süreci

- İkinci hafta
  - **Lökosit sayısı**: 3200 (GCSF desteği ile)
  - **CMV PCR:** $1x10^5$ kopya/mL

Ne yapalım?


Special Feature

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The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation

Camille N. Kotton, MD,[1] Deepali Kumar, MD,[2] Oriol Manuel, MD,[3] Sunwen Chou, MD,[4] Randall T. Hayden, MD,[5] Lara Danziger-Isakov, MD, MPH,[6] Anders Asberg, PhD,[7] Helio Tedesco-Silva, MD,[8] and Atul Humar, MD[2]; on behalf of The Transplantation Society International CMV Consensus Group*

Refrakter CMV hastalığı;

- İki haftalık uygun tedaviye rağmen CMV DNA yükünün değişmemesi ya da artması
- En önemli nedeni gansiklovir türevlerine gelişen **direnç**:

Gansiklovir direnci:

- Düzenli 2 haftalık tedavi sonrasında, semptomların düzelmediği veya CMV PCR düzeyinin 10 kat azalmadığı durumlar
- Proflaksi sırasında CMV-DNA emi yükselmesinin görüldüğü durumlar


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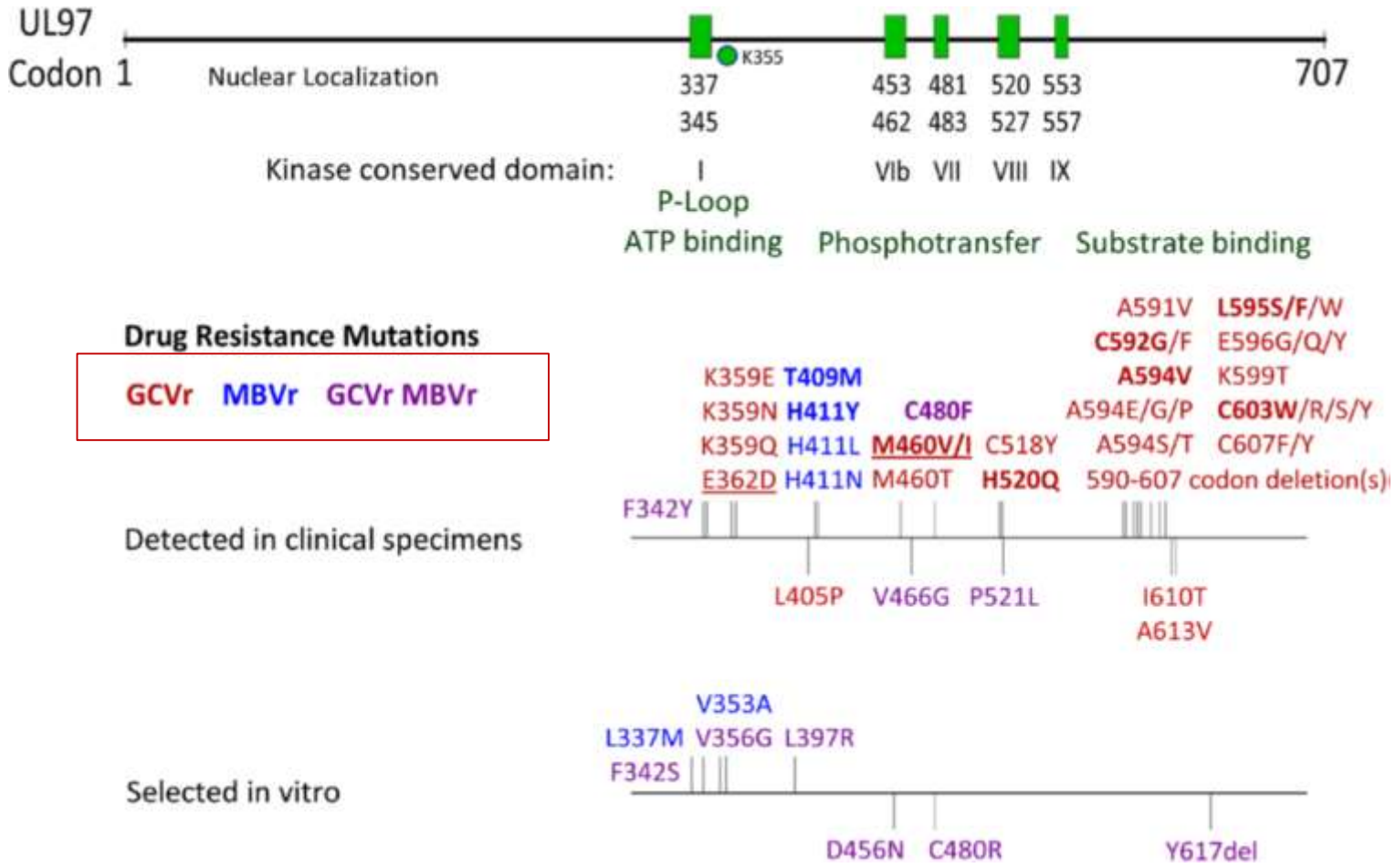
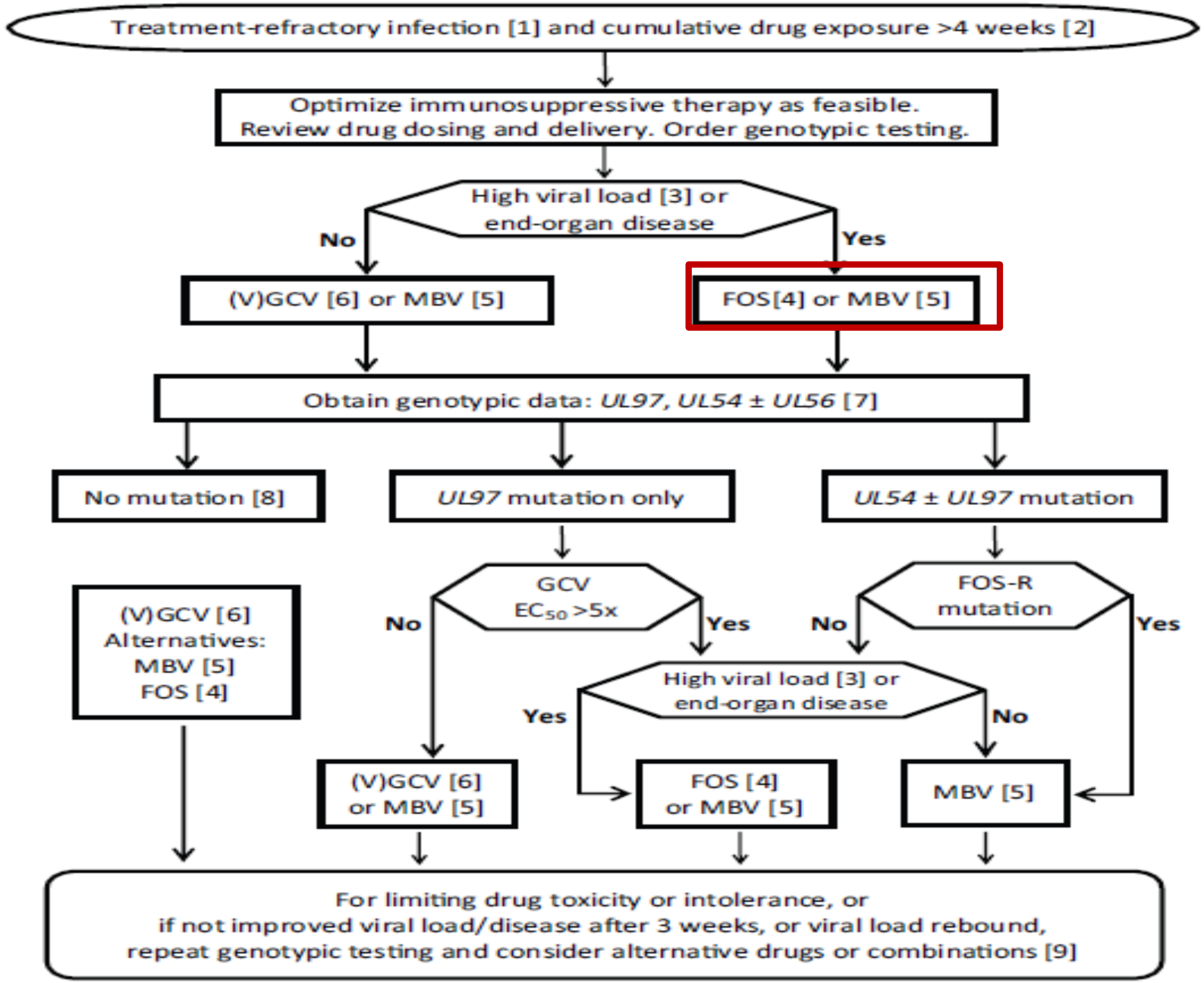
Refrakter CMV hastalığı;

- İki haftalık uygun tedaviye rağmen CMV DNA yükünün değişmemesi ya da artması
- **Öneri**: Alternatif tedavi ajanlarına geçilmesi
    - Uzun süreli gansiklovir tedavisi (8 hafta)
    - Foscarnet (En az 4 Hafta)
    - Sidofovir
    - Maribavir (4-8 Hafta)
    - Letermovir
    - Adaptif CMV spesifik T cell terapi: (KHN de kullanılmış, etkin)

Ek tetkik :

- **CMV direnç testi (UL97 gen mutasyonu) → Gansiklovir direnci saptandı.**




Treatment-refractory infection [1] and cumulative drug exposure >4 weeks [2]
Optimize immunosuppressive therapy as feasible.
Review drug dosing and delivery. Order genotypic testing.
High viral load [3] or end-organ disease
No
Yes
(V)GCV [6] or MBV [5]
FOS[4] or MBV [5]
Obtain genotypic data: UL97, UL54 ± UL56 [7]
No mutation [8]
UL97 mutation only
UL54 ± UL97 mutation
(V)GCV [6]
Alternatives:
MBV [5]
FOS [4]
GCV
EC50 >5x
No
Yes
FOS-R
mutation
No
Yes
High viral load [3] or end-organ disease
Yes
No
(V)GCV [6]
or MBV [5]
FOS [4]
or MBV [5]
MBV [5]
For limiting drug toxicity or intolerance, or
if not improved viral load/disease after 3 weeks, or viral load rebound,
repeat genotypic testing and consider alternative drugs or combinations [9]

Türkiye de ruhsatlı
Geri ödemesi var

Türkiye de ruhsatlı
Geri ödemesi yok

Onayı var ama henüz ülkeye girişi yok
Organ naklinde tedavide yeri?

Hastanın Tedavi süreci:

- **Foskarnet başlandı**
  - Nötropeni düzeldi
  - Renal toksisite GFR %50 (foskarnet tedavisi alan hastaların 1/ 3'ünde görülür)
  - Foskarnet 2. hafta CMV PCR 2.5x10^2kopya/mL

    4. hafta CMV PCR negatif

  - Tedavi kesildi

3.Olgu

- **Hasta:** 52 yaşında kadın MÜ
- **Başvuru tarihi 13.12 2023**
- **Başvurulan birim : Dermatoloji**

- **Öykü:** 10 yıl önce babadan böbrek nakli
- **İmmünsupresif:** Cellcept (Mikofenolat nofetil), Deltacortil, Prograf(tacrolimus)
- **Son 1 ay:** Humoral rejeksiyon için yüksek doz (>1000mg) steroid ve plazmaferez tedavisi almış.
- **Başvuru şikâyeti: bir haftadır devam eden a**ğız içinde gingiva ve mukozalarda yaygın ağrılı plaklar,

- **Enfeksiyon Hastalıkları Konsültasyonu***: Orofaringeal kandidiyazis* açısından danışılıyor
  - Kan değerleri normal
  - CMV PCR isteniyor
  - **CMV - PCR (DNA) - 1,7 X10^5 IU/mL (15/12/2023)**

- Hasta transplantasyon ünitesine yatırılıyor.
- Bu süreçte hastanın diyaresi başlıyor.
  - GİS PCR paneli Negatif
  - Genel durumu nedeniyle endoskopi/kolonoskopi planlanmıyor.

- **Tanısal Güçlükler**
  - **Belirti ve bulgular spesifik değil:**
    - Ateş, halsizlik, ishal; birçok viral/bakteriyel enfeksiyon veya ilaç yan etkisiyle karışabilir
    - CMV PCR yüksek değerde pozitif

Kesin tanı: Endoskopi ve biyopsi

Histopatoloji: CMV inklüzyonları her zaman saptanamayabilir; kesin tanı için immünohistokimyasal boyama gerekir

Ancak hastada genel durum bozukluğu nedeniyle GİS endoskopi yapılamıyor.

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Table 3. Definitions of Cytomegalovirus Gastrointestinal Disease

Patient Category	Proven CMV Disease	Probable CMV Disease	Possible CMV Disease
Allogeneic HCT patients	Upper and/or lower GI symptoms *plus* macroscopic mucosal lesions *plus* CMV documented in tissue[a]	Upper and/or lower GI symptoms and CMV documented in tissue[a] (not by PCR) but without the requirement for macroscopic mucosal lesions	Upper and/or lower GI symptoms and CMV documented in tissue by PCR but without the requirement for macroscopic mucosal lesions;
Solid organ transplant patients except small bowel transplant patients	Upper and/or lower GI symptoms *plus* macroscopic mucosal lesions *plus* CMV documented in tissue[a]	Upper and/or lower GI symptoms and CMV documented in tissue (not by PCR) but without the requirement for macroscopic mucosal lesions	diarrhea rated at least National Cancer Institute, Common Terminology Criteria for Adverse Events (version 4.0), grade 2 and CMV documented in blood and exclusion of other likely causes of diarrhea
Small bowel transplant patients	Upper and/or lower GI symptoms *plus* macroscopic mucosal lesions *plus* CMV documented in tissue[a]	Not applicable	
Autologous HCT and CAR T cell–treated patients	Upper and/or lower GI symptoms *plus* macroscopic mucosal lesions *plus* CMV documented in tissue[a]	Upper and/or lower GI symptoms and CMV documented in tissue (not by PCR) but without the requirement for macroscopic mucosal lesions	

Abbreviations: CAR, Chimeric Antigen Receptor; CMV, cytomegalovirus; GI, gastrointestinal; HCT, hematopoietic cell transplant; PCR, polymerase chain reaction.

[a]Quantitative PCR is not accepted as a diagnostic criterion for proven or probable CMV GI disease.

Muhtemel tanı:

- CMV PCR negatif → aktif CMV gastroenteritini dışlamaz
- CMV düşük kopya → aktif CMV gastroenteriti lehine

- **Tanı:**

  Olası CMV gastroenteriti

- Tedavi planı?

Tedavi seçenekleri;

a) Gansiklovir

b) Valgansiklovir

c) Valasiklovir

d) Letermovir

e) Maribavir

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2.5 mg/kg gün gansiklovir IV başlanıyor

TABLE 5.

Dosage recommendations for ganciclovir and valganciclovir and valacyclovir for adult patients with impaired kidney function (using the Cockcroft-Gault formula)

CrCL, mL/min	Treatment dose	Maintenance/prevention dose
Intravenous ganciclovir (adapted from[226])		
≥70	5.0 mg/kg q12h	5.0 mg/kg q24h
50–69	2.5 mg/kg q12h	2.5 mg/kg q24h
25–49	2.5 mg/kg q24h	1.25 mg/kg q24h
10–24	1.25 mg/kg q24h	0.625 mg/kg q24h
<10	1.25 mg/kg 3×/wk after hemodialysis	0.625 mg/kg 3×/wk after hemodialysis
Oral valganciclovir (adapted from[227,228])		
≥60	900 mg q12h	900 mg q24h
40–59	450 mg q12h	450 mg q24h
25–39	450 mg q24h	450 mg q48h
10–24	450 mg q48h	450 mg twice weekly
<10	200 mg 3×/wk after hemodialysis[a]	100 mg 3×/wk after hemodialysis[a]
Oral valacyclovir (high dose)[112]		
>75	—	2000 mg 4×/d
51–75	—	1500 mg 4×/d
26–50	—	1500 mg 3×/d
10–25	—	1500 mg 2×/d
<10 or dialysis	—	1500 mg 1×/d

[a]Oral solution must be used in this instance (as valganciclovir tablets cannot be split).
CrCL, creatinine clearance.

- **22. 12.2023** Genel durumu iyi, oral plaklar ve diyare geriledi
  - CMV - PCR (DNA) - 2,2 $X10^3$ IU/mL

- **23.12.2023** Valgansiklovir 1x450 mg po (GFR%34) başlanarak ve haftalık PCR takibi önerilerek taburcu ediliyor
- Tedavi süresi: PCR negatifliği gördükten sonra planlanacak

- **12.01.2024**
  - Hasta Göğüs Hastalıkları polikliniğine 2 haftadır olan öksürük ve dispne şikayetiyle başvuruyor

- **Fizik Muayene**

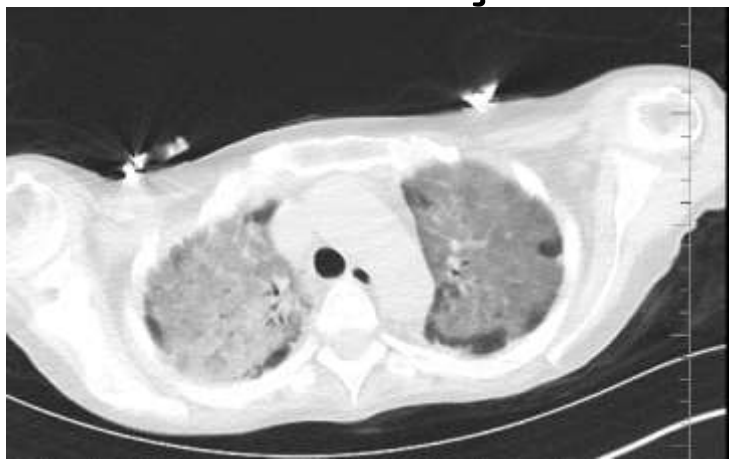
  - Genel durum orta
  - A: 38.9 °C
  - TA: 100/60 mmHg, Nabız: 110/dk
  - Solunum sayısı: 28/dk, O_2 sat: %85 (oda havasında)
  - Akciğer oskültasyonu: Bilateral yaygın ince raller
  - Hasta bu vital bulgularla YBÜ‘ne yatırılıyor

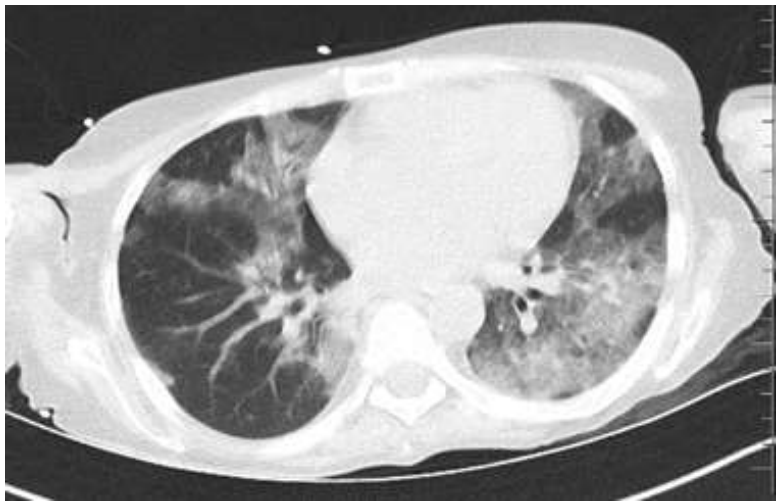
- **Ön tanılarınız ?**
- **Hangi tetkikleri isteyelim?**

- **Lökopeni:** 2.100/mm³
- **CRP**: 110 mg/L
- **LDH**: 420 U/L
- **Kreatinin**: 2.1 mg/dl
- **Solunum yolu paneli:** İnfluenza A

- **Kan galaktomannan:**
- **TBC Quantiferon:**
- **CMV PCR (plazma**):**3.2x10² IU/mL**

- **Görüntüleme**
  - **Toraks BT:**
  - Bilateral Üst loblarda konsolidasyon alanları ve ön planda viral pnömoni lehine değerlendirilen yaygın buzlu cam infiltrasyon alanları izlendi ve ayırıcı tanıda ARDS düşünülmelidir





- **Tedavi önerileriniz?**

- **Tedavi:**
  - Oseltamivir
  - Piperasilin Tazobactam
  - Ciprofloksasin
  - Gansiklovir

Yatışın 2. günü:

- Bronkoskopi:
- **BAL**
  - Solunum paneli: İnfluenza A
  - Kültür:
    - Bakteri: Gram negatif bakteri
    - Mantar kültürü devam ediyor.
  - Galaktomannan 6.8 (ODI)
  - CMV PCR:2.4x10^4 IU/ml
  - PCP PCR Halk sağlığı kurumuna gönderiliyor.

- Hasta Bronkoskopi sonrası entübe oluyor.

- Tedaviyi nasıl düzenleyelim?

Tedavi:

- Oseltamivir
- Piperasilin Tazobactam ⟶ Meropenem+Kolistin
- Ciprofloksasin
- Gansiklovir

- Amfoterisin B
- TMP-SMZ (PCP dozu)

- BAL
  - Solunum paneli: İnfluenza A
  - Kültür:
    - Bakteri: Gram negatif bakteri ÇID E.coli
    - Mantar: Aspergillus niger
    - Galaktomannan 6.8 (ODI)

  - CMV PCR:2.4x10³IU/ml
  - PCP PCR Pozitif

- Bu hastalarda kesin tanılarınız hangileridir?

Tanılar:

- Bakteriyel pnömoni?
- Aspergillozis
- İnfluenza Pnömonitisi?
- PCP ?
- Olası CMV Pnömonitisi?

Nakli –Enfeksiyon Zaman Çizelgesi

İLK BİR AY	1-12 AY	>12 AY
• **Donör kaynaklı** Bilinen DKE Bilinmeyen DKE (dirençli bakteri enf) • **Hastane kökenli** ÜSE Kan dolaşım enf. Pnömoni (bakteriyel, viral) GİS enf. • **Teknik kaynaklı** Anastomoz kaçakları Darlıklar Stentler	• **Latent enfeksiyonların aktivasyonu** **Viral:** CMV, EBV, BKV, HBV, HCV, VZV • **Fırsatçı enfeksiyonlar** **Fungal:** Aspergillus, Kandida, Kriptokok, Mukor, P.jirovecii **Bakteriyel:** Listeria, Nocardia, M.tuberculosis vb. **Paraziter:** Toksoplazma, Strongyloides... • **Rekürrensler, relapslar** HBV,HCV,TBC vb.	• **Toplum kökenli** • **Organ disfonksiyonu veya Rejeksiyon gelişenlerde** Fırsatçı enfeksiyonlar Latent enf. aktivasyonu

- Hasta tedavinin 9. gününde ex oluyor.

İmmünoterapi

- Polikonal antikor tedavileri:Anti-HCMV hiperimmunglobulin (Cytotec, Cytogam)

  Bugün için torasik ve çoklu organ naklinde gansiklovir tedavisiyle birlikte uygulanmasının başarılı sonuçlarını bildiren çalışmalar var

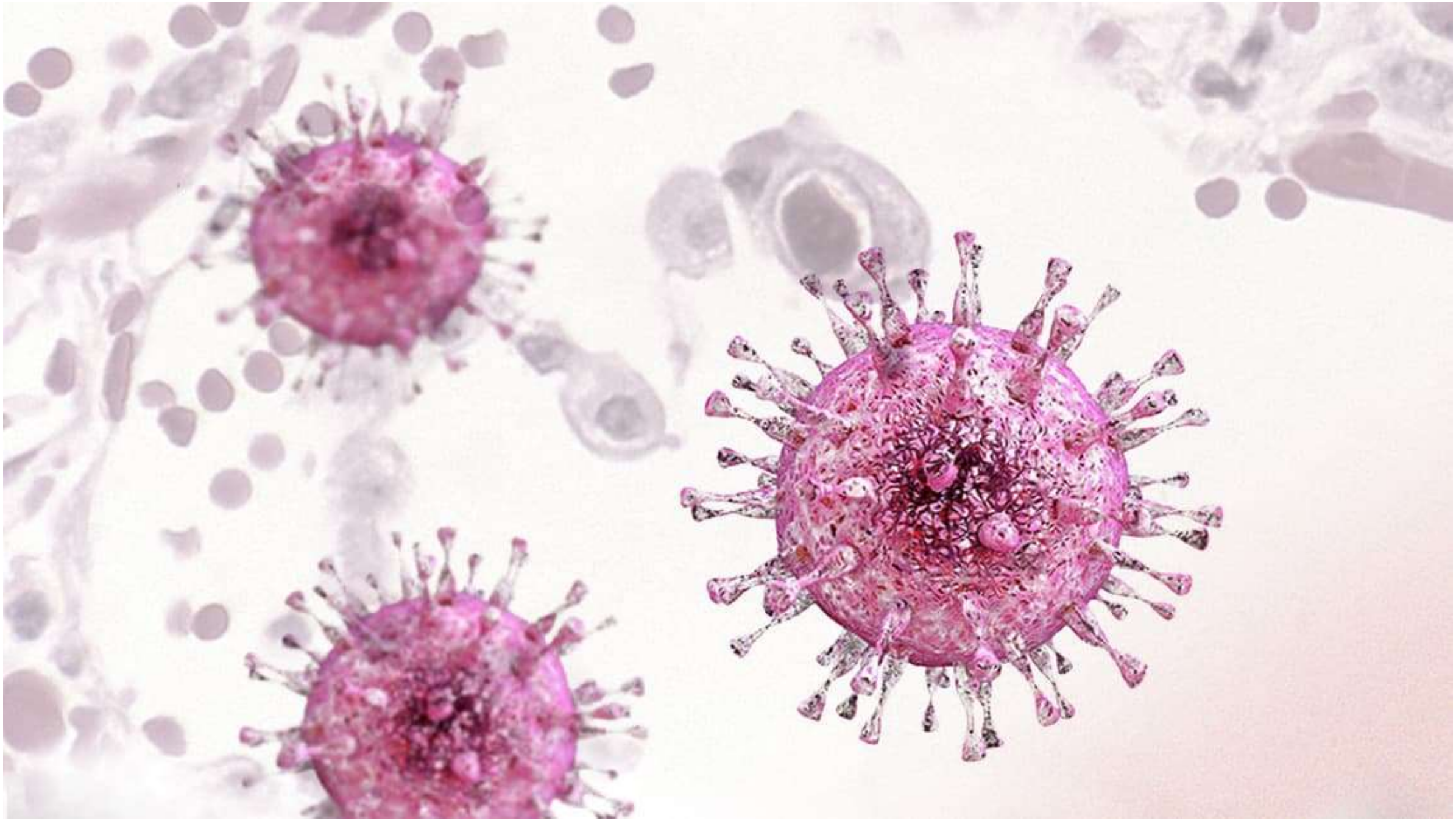
- Monoklonal antikor tedavileri:

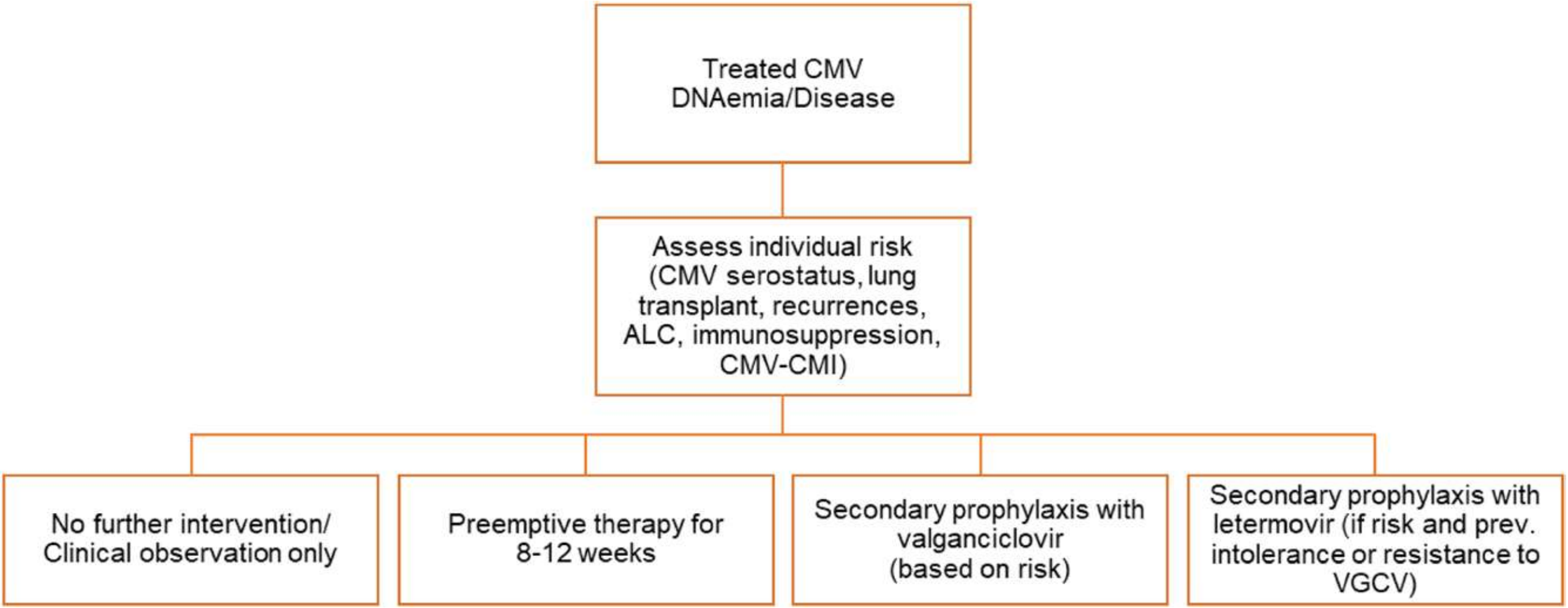
  Primer enfeksiyonu önlemek üzere

  Çalışmalar devam ediyor

Aşılar

- Sonuçlar karmaşık
  - Viral protein subunit aşısı
  - Plazmid DNA aşısı:
  - Bivalan rekombinant RNA viral vektör subunit aşısı
  - Vaccinia Ankara peptid aşısı




Treated CMV DNAemia/Disease
Assess individual risk (CMV serostatus, lung transplant, recurrences, ALC, immunosuppression, CMV-CMI)
No further intervention/ Clinical observation only
Preemptive therapy for 8-12 weeks
Secondary prophylaxis with valganciclovir (based on risk)
Secondary prophylaxis with letermovir (if risk and prev. intolerance or resistance to VGCV)

- **Tanısal Güçlükler**

  - **Belirti ve bulgular spesifik değil:** Ateş, halsizlik, ishal; birçok viral/bakteriyel enfeksiyon veya ilaç yan etkisiyle karışabilir

  - **Laboratuvar:** CMV PCR negatif → aktif CMV gastroenteritini dışlamaz

    CMV düşük kopya → aktif CMV gastroenteriti lehine

  - **Histopatoloji:** CMV inklüzyonları her zaman saptanamayabilir; kesin tanı için immünohistokimyasal boyama gerekir