Karaciğer nakli sonrası CMV pnömonisi tanısal yolculuk

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- 55, E
- Otoimmun hepatit, 30 p/yıl, KOAH
- 5 mg/gün prednisolon, takrolimus (7 ng/mL), mycophenolate mofetil

- **CMV serostatus: D+/R+** *(intermediate-risk group)*.
- **Postop profilaksi**: 3 ay valgansiklovir

Şikayet:

- Efor sırasında nefes darlığı
- Kuru öksürük
- Halsizlik

FM

- Hipoksi: SpO_2 89% on RA, 2L O_2
- Ateş: 37.8°C
- Pulse: 105
- Ral+ ronküs +
- İnsizyon yeri temiz.
- Batın rahat.

Görüntüleme

- *CXR*: Bilateral interstitial opacities.
- *CT Chest*: **Bilateral infiltrates**

Laboratuvar (Başvuru):

- WBC: 3,200/µL (Low - leukopenia) Neutrophils: 1,500/µL (Borderline low)
- Lymphopenia (ABS lymph count 220 /µL), ↑LDH (455 U/L).
- Platelets: 79,000/µL (Low -thrombocytopenia)
- ALT (SGPT): 110 U/L , AST (SGOT): 95 U/L (Slightly elevated)
- ALP and GGT: Mildly elevated.
- CRP:12 PCT: 0.8
- Blood, urine, sputum culture
- Respıratory Tract Vıruses Mıcroarray PCR for Influenza, RSV…
- Blood EBV, HSV, CMV PCR: Pending (sent on admission).
- Tacrolimus level: Within target range (7.27ng/mL).

Tanı İkilemi

3.gün:

- **EBV, HSV, CMV PCR: Negative** (kan) yanıltıcı! *(misleading!)*
- Blood, urine, sputum culture: Negative
- ANA, ANCA, ds-DNA: Negative
- Vorikonazol +

Görüntüleme

4.Gün :CT Chest: **Diffuse ground-glass opacities** + scattered nodules.

Her iki akciğerde sol daha belirgin olmak üzere intersitisyel septalarda kalınlaşmasının eşlik ettiği yamasal tarzda buzlu cam görünümünde infiltratif değişiklikler izlenmektedir (Enfeksiyoz proçes?). **19.11. 2015 tarihli toraks BT filmi ile karşılaştırıldığında; Bulgularda artış izlenmektedir.**

Ayırıcı Tanı
Dönüm Noktası: Bronkoskopi

- 5.gün:
- **HFNC 50L/min**. Entübasyon. Bronkoskopi
- **BAL studies**:
  - *Cell count*: Lymphocytic predominance (65%)
  - *Fungal/AFB stain*: Negative.
  - Galactomannan: 0.25
  - *PJP PCR*: Negative.
  - HSV 1/2: Negative.
  - EBV PCR: Negative.
  - ***CMV PCR: POSITIVE (50,455 copy/mL)***

Ayırıcı Tanı
Dönüm Noktası: Bronkoskopi

- **BAL studies**

CMV PCR: POSITIVE (50,455 copy/mL)

***Kültür:** Pseudomonas aeroginosa-carbapenem sustainable

Diagnosis: Proven? Probable? Possible? **CMV pneumonitis** .

IV ganciclovir (5 mg/kg q12h) + mycophenolate mofetil stoplandı, IV metilprednisolone

Yönetim ve Zorluklar / Takip

- ***Tedavinin 2.günü:***

CMV viremia now detectable in blood (220 copy/mL).

- ***Tedavinin 7.günü:***

Extübasyon. 10 L

CMV PCR undetectable

- ***Tedavinin 28.gün*:**

- **Valgansiklovir** (900 mg) sekonder profilaksi ile taburcu

Nakil sonrası CMV önleme strateji

R⁺ Recommendations

- We recommend either prophylaxis (strong, high) or preemptive therapy (strong, moderate) for seropositive recipients (R⁺) after kidney transplant. Where CMV-CMI testing is available, this can be used to determine and tailor the strategy in kidney transplant (see CMV-CMI recommendations).
- We recommend either prophylaxis (strong, moderate) or preemptive therapy (strong, high) for seropositive recipients (R⁺) after liver transplant.
- We suggest prophylaxis may be preferred in R⁺ liver and kidney transplant patients at greater risk of CMV, such as those receiving higher immunosuppression exposure with lymphocyte-depleting antibodies, second signal inhibitors, desensitization protocols, treatment of T cell–mediated rejection, steroid-resistant acute rejection, treatment of antibody-mediated rejection, and those with HIV (weak, moderate).

•Karaciğer nakli sonrası seropozitif alıcılara (R^+) profilaksi (güçlü, orta) veya önleyici tedavi (güçlü, yüksek) öneriyoruz .

•Lenfosit azaltıcı antikorlar, ikinci sinyal inhibitörleri, desensitizasyon protokolleri, T hücre aracılı rejeksiyon tedavisi, steroid dirençli akut rejeksiyon, antikor aracılı rejeksiyon tedavisi ve HIV'li (zayıf, orta) hastalar gibi CMV riski daha yüksek olan R^+ karaciğer ve böbrek nakli hastalarında profilaksinin tercih edilebileceğini öneriyoruz.

R^+ Süre:

•R^+ hastalarda (D^+ veya D^-) profilaksi stratejisi kullanıldığında , rutin böbrek (güçlü, yüksek), pankreas, karaciğer ve kalp (güçlü, orta) ve adacık (zayıf, düşük) nakli alıcıları için 3 ay antiviral ilaç önerilir.

Kotton, C. N., Kumar, D., Manuel, O., Chou, S., Hayden, R. T., Danziger-Isakov, L., ... & Transplantation Society International CMV Consensus Group. (2025). The Fourth International Consensus Guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation*, *109*(7), 1066-1110.

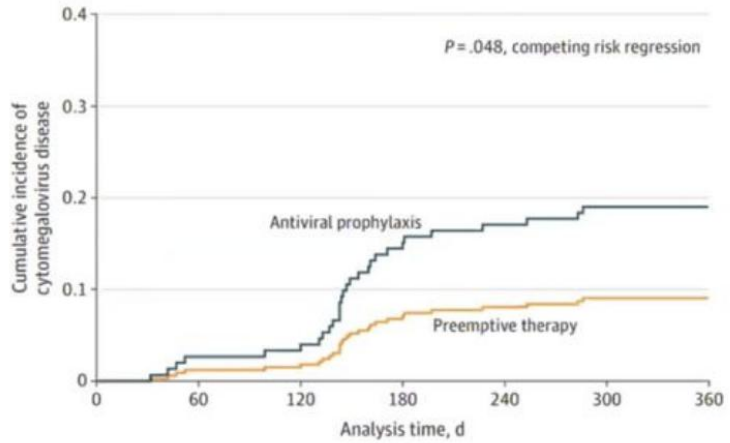
D+R-

JAMA | Original Investigation

Effect of Preemptive Therapy vs Antiviral Prophylaxis on Cytomegalovirus Disease in Seronegative Liver Transplant Recipients With Seropositive Donors
A Randomized Clinical Trial

- D+/R- liver
- 100 PET; 105 Prophylaxis
- CMV disease 9% vs 19% (=0.039)

Figure 2. Cumulative Incidence of Cytomegalovirus (CMV) Disease With Death as a Competing Risk



No. at risk

Preemptive therapy	100	94	89	85	82	81	80
Antiviral prophylaxis	105	101	101	84	82	79	79

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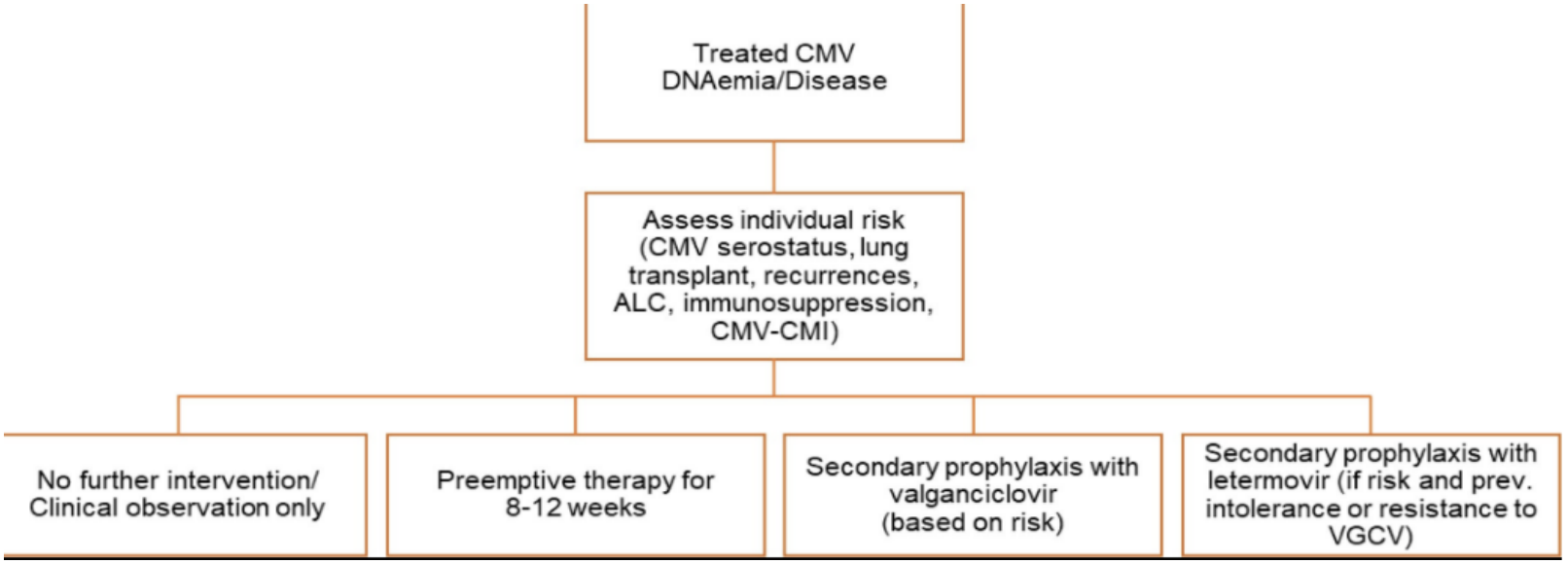
Uzun Vadeli Önlemler

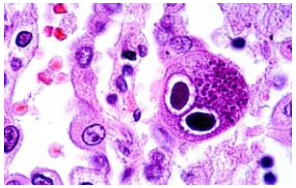


Konsensüs uzmanları, CMV D^{+}/R^{-} serostatusu olan, akciğer nakli yapılan, başlangıçta yüksek CMV viral yükü olan, yakın zamanda antilenfosit ajanların kullanımı veya immünosupresyonun artırılması olan, düşük mutlak lenfosit sayımı (ALC), negatif CMI testleri olan ve tekrarlayan CMV ile mücadele eden hastalarda sekonder profilaksiyi değerlendirmiştir

Kotton, C. N., Kumar, D., Manuel, O., Chou, S., Hayden, R. T., Danziger-Isakov, L., ... & Transplantation Society International CMV Consensus Group. (2025). The Fourth International Consensus Guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation*, *109*(7), 1066-1110.

Organa Dayalı CMV Hastalık Tanımları

Proven?



Probable?

Possible?

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	Not defined

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Ljungman P, Chemaly RF, Khawaya F, et al. 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. *Clin Infect Dis*. 2024;79(3):787-794. doi:10.1093/cid/ciae321

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.

BAL'da CMV DNA'sının yokluğu, CMV pnömonisine karşı çok yüksek bir negatif öngörü değerine sahiptir.

"doğru" klinik sendromlu BAL'da çok yüksek bir viral yükün, klinik çalışmalarda olası bir CMV pnömonisi olayı olarak tanımlanması gerektiği konusunda fikir birliği vardır.

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- CMV pnömonisi viremiden önce ortaya çıkabilir.
- Orta risk grubundaki hastaların profilaksi sonrası gözetime ihtiyacı vardır.

THE FOURTH INTERNATIONAL CONSENSUS GUIDELINES IN THE MANAGEMENT OF CYTOMEGALOVIRUS IN SOLID ORGAN TRANSPLANTATION

Background

Many exciting advances in CMV management have recently occurred, necessitating an update to guidelines.

Methods

In 2024, with support from The Transplantation Society, CMV experts from across the world reviewed current evidence in 6 working groups and updated CMV recommendations using GRADE.

Diagnostics: A greater emphasis on CMV-QNAT testing calibrated to the WHO standard.

Prevention: New data support the option of letermovir prophylaxis in D+/R- kidney and the use of PET in D+/R- liver transplant. Surveillance after prophylaxis increasing.

Immunology: New CMV-CMI testing recommendations in R+ kidney transplant to help personalize prophylaxis.

Treatment: Valganciclovir and ganciclovir remain mainstays of treatment; thresholds for discontinuation remain challenging in the era of highly sensitive testing.

Resistance: Maribavir is now recommended as a principal alternative in cases of resistance, unless clinically unwell with high viral loads when foscarnet is preferred.

Pediatrics: Prevention strategies include prophylaxis, PET, or surveillance after short-term prophylaxis. More data on new drugs needed.

Conclusion

This new edition of the guidelines provides a comprehensive look at best-practices related to CMV management after organ transplantation.

Future Directions

The future of CMV management looks very promising and we are well on our way to defeating the "Troll of Transplantation".

Camille N. Kotton and Atul Humar on behalf of the TTS International CMV Consensus Group. *Transplantation*. January 2025

@TransplantJrnl @KottonNelson

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Referances

- Ljungman P, Chemaly RF, Khawaya F, et al. 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. *Clin Infect Dis*. 2024;79(3):787-794. doi:10.1093/cid/ciae321

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Teşekkürler