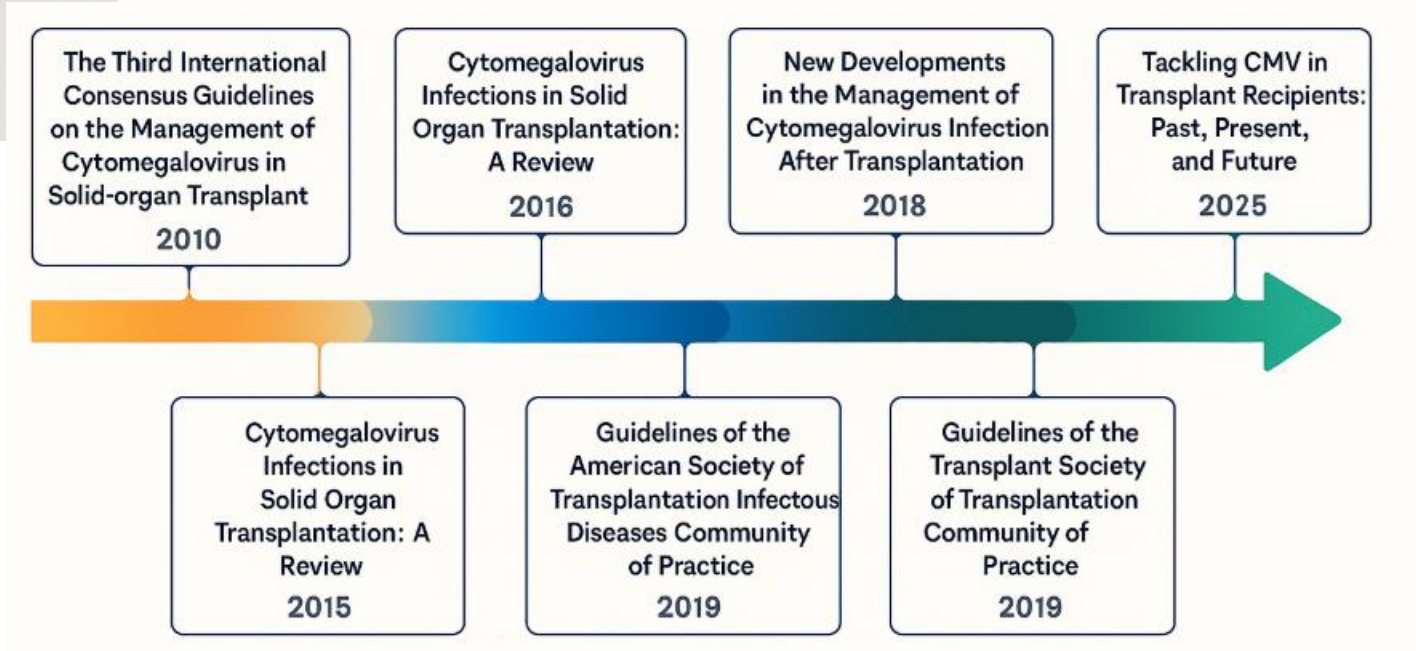
Solid Organ Transplantasyonları ve CMV: Gelişmeler

Doç. Dr. Sibel Altunışık Toplu

İnönü Üniversitesi Tıp Fakültesi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Anabilim Dalı, Malatya

CMV


The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplant
2010
Cytomegalovirus Infections in Solid Organ Transplantation: A Review
2016
New Developments in the Management of Cytomegalovirus Infection After Transplantation
2018
Tackling CMV in Transplant Recipients: Past, Present, and Future
2025
Cytomegalovirus Infections in Solid Organ Transplantation: A Review
2015
Guidelines of the American Society of Transplantation Infectous Diseases Community of Practice
2019
Guidelines of the Transplant Society of Transplantation Community of Practice
2019

Curr Infect Dis Rep (2012) 14:633–641
DOI 10.1007/s11908-012-0292-2

TRANSPLANT AND ONCOLOGY (MG ISON, SECTION EDITOR)

Cytomegalovirus in Solid Organ Transplantation: Epidemiology, Prevention, and Treatment

Elena Beam · Raymund R. Razonable

- **2012 yılında CMV = SOT için en önemli enfeksiyon komplikasyonu olarak tanımlandı**
- CMV'nin hem **direkt** (viremi, hastalık) hem **indirekt etkileri** (rejeksiyon, graft disfonksiyonu, fırsatçı enfeksiyonlar) vurgusu!

CMV yönetiminin temel klinik çerçevesi çizildi

2013 yılında yayımlanan ve Raymund Razonable'ın CMV alanındaki en çok alıntı alan klasik derlemelerinden biri

CMV'nin SOT'taki yükü ilk kez geniş kapsamlı bir şekilde tanımlandı

Morbidite ve mortalitenin en önemli nedeni

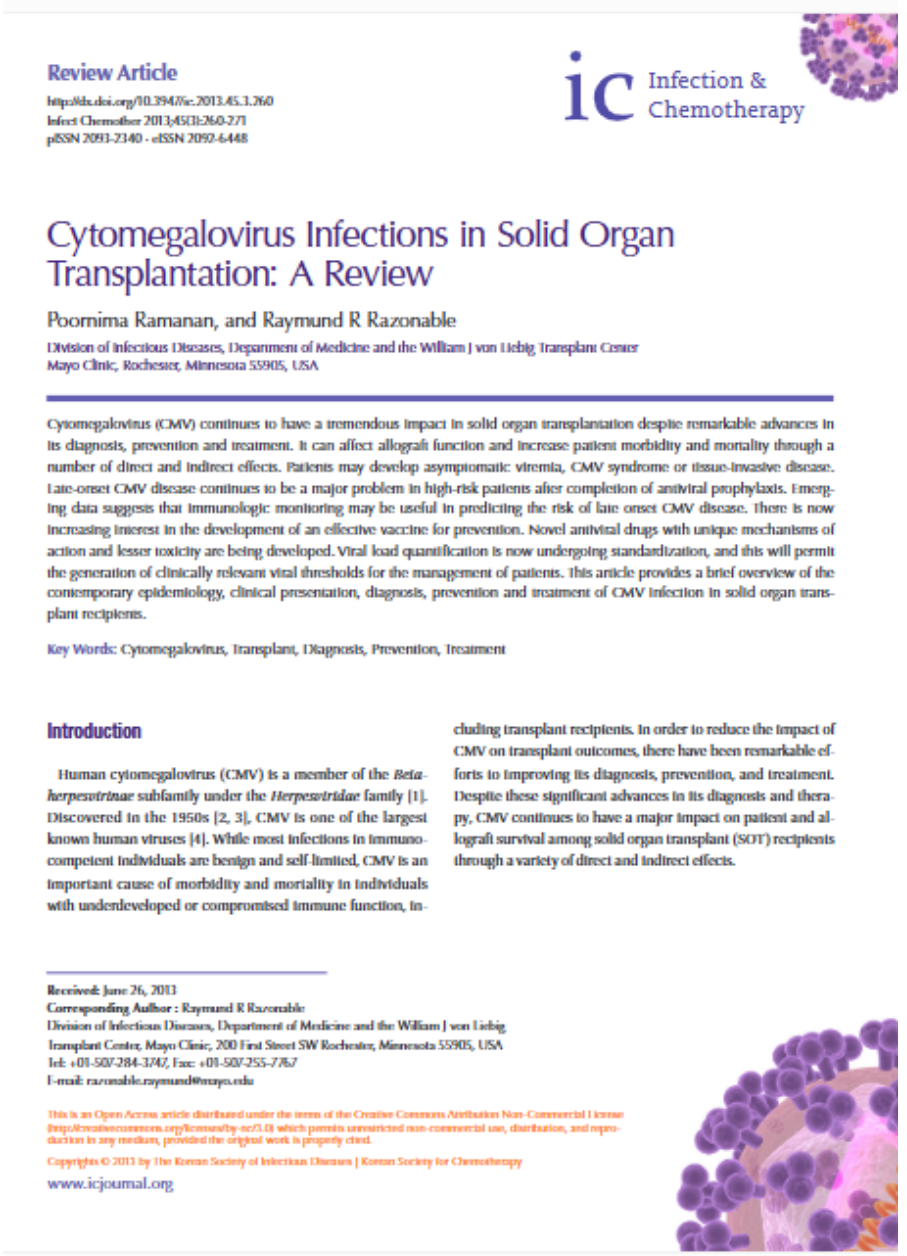
VGCV/gansiklovir → tüm profilaksi ve tedavi yaklaşımının temeli

Foscarnet / Cidofovir → dirençli CMV için "kurtarma" tedavisi

PCR temelli viremia takibi → standart olma yolunda

Preemptif tedavi → VGCV toksisitesi nedeniyle yaygınlaşmakta

Bu yayın, 2013 Uluslararası Kılavuzu'na (Kotton et al.) giden bilimsel yolu hazırladı.



Review Article
http://dx.doi.org/10.3947/ic.2013.45.3.260
Infect Chemother 2013;45(3):260-271
pISSN 2093-2340 · eISSN 2092-6448

ic Infection & Chemotherapy

Cytomegalovirus Infections in Solid Organ Transplantation: A Review

Poornima Ramanan, and Raymund R Razonable

Division of Infectious Diseases, Department of Medicine and the William J von Liebig Transplant Center
Mayo Clinic, Rochester, Minnesota 55905, USA

Cytomegalovirus (CMV) continues to have a tremendous impact in solid organ transplantation despite remarkable advances in its diagnosis, prevention and treatment. It can affect allograft function and increase patient morbidity and mortality through a number of direct and indirect effects. Patients may develop asymptomatic viremia, CMV syndrome or tissue-invasive disease. Late-onset CMV disease continues to be a major problem in high-risk patients after completion of antiviral prophylaxis. Emerging data suggests that immunologic monitoring may be useful in predicting the risk of late onset CMV disease. There is now increasing interest in the development of an effective vaccine for prevention. Novel antiviral drugs with unique mechanisms of action and lesser toxicity are being developed. Viral load quantification is now undergoing standardization, and this will permit the generation of clinically relevant viral thresholds for the management of patients. This article provides a brief overview of the contemporary epidemiology, clinical presentation, diagnosis, prevention and treatment of CMV infection in solid organ transplant recipients.

Key Words: Cytomegalovirus, Transplant, Diagnosis, Prevention, Treatment

Introduction

Human cytomegalovirus (CMV) is a member of the *Betaherpesvirinae* subfamily under the *Herpesviridae* family [1]. Discovered in the 1950s [2, 3], CMV is one of the largest known human viruses [4]. While most infections in immunocompetent individuals are benign and self-limited, CMV is an important cause of morbidity and mortality in individuals with underdeveloped or compromised immune function, including transplant recipients. In order to reduce the impact of CMV on transplant outcomes, there have been remarkable efforts to improving its diagnosis, prevention, and treatment. Despite these significant advances in its diagnosis and therapy, CMV continues to have a major impact on patient and allograft survival among solid organ transplant (SOT) recipients through a variety of direct and indirect effects.

Received: June 26, 2013
Corresponding Author : Raymund R Razonable
Division of Infectious Diseases, Department of Medicine and the William J von Liebig Transplant Center, Mayo Clinic, 200 First Street SW Rochester, Minnesota 55905, USA
Tel: +01-507-284-3747, Fax: +01-507-255-7767
E-mail: razonable.raymund@mayo.edu

www.icjournal.org

ELSEVIER

Transplantation Reviews
Volume 30, Issue 3, July 2016, Pages 119-143

Management of cytomegalovirus infection in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations

J. Torre-Cisneros [a b], J.M. Aguado [b c], J.J. Caston [b d], L. Almenar [e], A. Alonso [f], S. Cantisán [a], J. Carratalá [b g], C. Cervera [h], E. Cordero [b i], M.C. Fariñas [b j], M. Fernández-Ruiz [c], J. Fortún [b k], E. Frauca [l], J. Gavaldá [b m], D. Hernández [n], I. Herrero [o], O. Len [b m], F. Lopez-Medrano [c], N. Manito [p], M.A. Marcos [q]...E. Vidal [a b]

- 2016 — Avrupa CMV kılavuzu: profilaksi ve preemptif tedavi algoritmaları standardize edildi.
- CMV yönetimi Avrupa’da ilk kez tamamen yapılandırıldı.

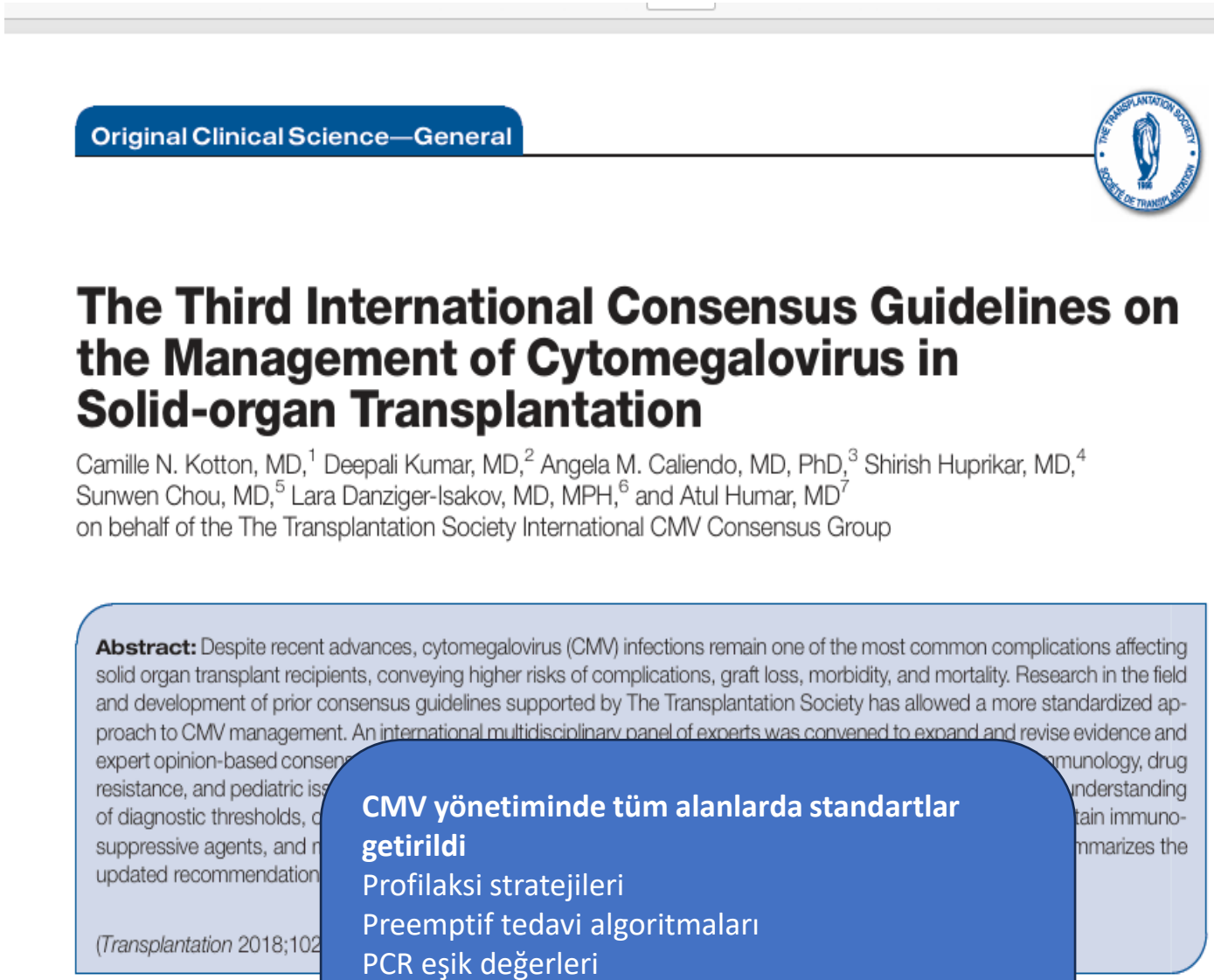
Modern CMV yönetiminin resmi başlangıcı

Moleküler ve immün tanıda yenilikler ilk kez yoğun olarak vurgulandı

Duyarlılığı yüksek PCR sistemleri

Viral yük kinetiği

CMV-spesifik immün yanıt testleri (T hücre ölçümü) ilk kez güçlü bir şekilde yer aldı
Bu, 2018 sonrası dönemin temelini oluşturdu.



Original Clinical Science—General

The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation

Camille N. Kotton, MD,[1] Deepali Kumar, MD,[2] Angela M. Caliendo, MD, PhD,[3] Shirish Huprikar, MD,[4] Sunwen Chou, MD,[5] Lara Danziger-Isakov, MD, MPH,[6] and Atul Humar, MD[7]
on behalf of the The Transplantation Society International CMV Consensus Group

Abstract: Despite recent advances, cytomegalovirus (CMV) infections remain one of the most common complications affecting solid organ transplant recipients, conveying higher risks of complications, graft loss, morbidity, and mortality. Research in the field and development of prior consensus guidelines supported by The Transplantation Society has allowed a more standardized approach to CMV management. An international multidisciplinary panel of experts was convened to expand and revise evidence and expert opinion-based consen... mmunology, drug resistance, and pediatric iss... understanding of diagnostic thresholds, c... tain immuno-suppressive agents, and r... mmarizes the updated recommendation...

(*Transplantation* 2018;102...

CMV yönetiminde tüm alanlarda standartlar getirildi
Profilaksi stratejileri
Preemptif tedavi algoritmaları
PCR eşik değerleri
Direnç yönetimi (UL97 / UL54 mutasyonları)
İmmünolojik değerlendirme
Pediatrik transplant
Yeni antiviraller ve immünosupresyon etkileri

CMV yönetiminin altın standardı

Received: 2 February 2019 | Accepted: 11 February 2019

DOI: 10.1111/ctr.13512

SPECIAL ISSUE-TRANSPLANT INFECTIOUS DISEASES

WILEY Clinical TRANSPLANTATION
The Journal of Clinical and Translational Research

Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice

Raymund R. Razonable[1] | Atul Hum

[1]Mayo Clinic, Rochester, Minnesota

[2]University Health Network, Toronto, Ontario, Canada

[3]Transplant Institute, University of Toronto, Toronto, Ontario, Canada

Correspondence
Raymund R. Razonable, MD, Division of Infectious Diseases, William J von Liebig Center for Transplantation and Clinical Regeneration, Mayo Clinic, Rochester, MN.
Email: Razonable.raymund@mayo.edu

Abstr
Cyton
fect t
Ameri
vides
tion, a
detec
ing of
apy ar
threshold
of CMV nucleic acid testing, even in the contemporary era when calibrators are

- **CMV serolojisi (IgG)** → pretransplant taramada standart
- PCR temelli CMV DNA ölçümü → viremi & preemptif tedavinin temel aracı
- Viral yük eşiklerinin laboratuvarlar arasında heterojenliği vurgulandı

Bu nokta, 2020 sonrası **dPCR** tartışmalarının zemini oldu.

Transplantation Reviews 38 (2024) 100875

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Review article

Management of cytomegalovirus in adult solid organ transplant patients: GESITRA-IC-SEIMC, CIBERINFEC, and SET recommendations update

Elisa Ruiz-Arabi [a], Julian Torre-Cisneros [b,c,*], Victoria Aguilera [d], Rodrigo Alonso [e], Marina Berenguer [d], Oriol Bestard [f], Marta Bodro [g,c], Sara Cantisán [b,c], Jordi Carratalà [h,c], Juan José Castón [b,c], Elisa Cordero [i,j,c], Carme Facundo [k], María Carmen Fariñas [l,c], Mirian Fernández-Alonso [m], Mario Fernández-Ruiz [n,c], Jesús Fortún [o,c], Maria Dolores García-Cosío [p], Sabina Herrera [g], David Iturbe-Fernández [q], Oscar Len [r,c], Francisco López-Medrano [n,c], María Ovidia López-Oliva [s], Ibai Los-Arcos [r], María Ángeles Marcos [t,c], Pilar Martín-Dávila [o,c], Víctor Monforte [u,v], Patricia Muñoz [w,v], David Navarro [x,c], Aurora Páez-Vega [y], Ana Belén Pérez [z,c], Natalia Redondo [n,c], Rodríguez Álvarez R. [aa], Alberto Rodríguez-Benot [ab], Isabel Rodríguez-Goncer [n,c], Rafael San-Juan [n,c], Javier Sánchez-Céspedes [i,c], Maricela Valerio [w,v], José Manuel Vaquero [ac], Diego Viasus [ad], Elisa Vidal [b,c], José María Aguado [c,n,**]

- Letermovir profilaksisi ilk kez SOT için resmi olarak kılavuza entegre edildi
  - **2024 güncellemesinin en kritik noktalarından biri**
- CMV-spesifik immünite testleri (T hücre değerlendirmesi) kılavuzda açıkça önerildi
- Kişiselleştirilmiş CMV yönetimi Avrupa kılavuzlarında resmileşti.

Your search for *Cytomegalovirus Treatment* ... retrieved no results.

Save | Email

Review > Ann Pharmacother. 2024 Nov;58(11):1122-1133. doi: 10.1177/10600280241237534. Epub 2024 Mar 19.

Cytomegalovirus Treatment in Solid Organ Transplantation: An Update on Current Approaches

Karen L Hardinger [1], Daniel C Brennan [2]

Affiliations + expand

PMID: 38501850 DOI: 10.1177/10600280241237534

Abstract

Objective: The article reviews the safety and efficacy of treatments for cytomegalovirus (CMV) in solid organ transplantation.

Data sources: A literature review was conducted in PubMed, MEDLINE, and Clinicaltrials.gov from database inception through January 2024, using terms CMV, therapy, and solid organ transplantation.

Study selection and data extraction: Clinical trials, meta-analyses, cohort studies, case reports, and guidelines were included. Letters to the editor, reviews, and commentaries were excluded.

Data synthesis: After abstract screening and full-text review of 728 citations for eligibility, 53 were included. Valganciclovir and intravenous ganciclovir are drugs of choice for CMV management and, until recently, the availability of alternative options has been restricted due to toxicity. For instance,

728 makale tarama → 53 dahil

- Kohortlar
- Kılavuzlar
- Direnç yönetimi verileri
- Klinik çalışmalar
- Meta-analizler

- Klasik antivirallerin sınırları → modern tedavilerin yükselişi
- Letermovir → profilaksi

Maribavir → tedavi

Infect Dis Ther (2025) 14:1183–1200
https://doi.org/10.1007/s40121-025-01159-6

REVIEW

Tackling CMV in Transplant Recipients: Past, Present, and Future

Tal Schlaeffer-Yosef · Lior Nesher

Received: March 7, 2025 / Accepted: April 9, 2025 / Pub

ABSTRACT

Cytomegalovirus (CMV), a beta-herpesviru
capable of maintaining lifelong latency
presents a substantial risk to transplan
recipients, resulting in significant morbidity
and mortality among both hematopoietic stem
cell and solid organ transplantation recipients.
Recent advances have shifted management
from reactive approaches, such as preemptive
therapy, to preventive strategies to reduce active
infections and disease burden. Letermovir, a
selective CMV terminase inhibitor, has emerged
as a critical prophylactic agent in high-risk
transplant populations, significantly lowering
infection rates and improving survival with
follow-up. Looking into the future, ongoing
innovations in immune monitoring and
antiviral development will likely lead to a more
personalized approach to CMV prevention and
treatment, optimizing care based on patient-
specific risk profiles and immune competence.

- Geçmiş: reaktif → preemptif dönem
- Şimdi: profilaksi temelli yaklaşım (özellikle Letermovir)
- Gelecek: immün-rehberli kişiselleştirilmiş CMV yönetimi

CMV 2025 Uluslararası Konsensus Kılavuzu

Profilakside yeni dönem: LETERMOVIR

D+/R– böbrek naklinde **valgansiklovire eşdeğer etkinlik**

Miyelosupresyon yok

Yüksek risk gruplarında birinci basamak profilaksi seçeneği

QNAT (CMV DNA) için yeni standartlar

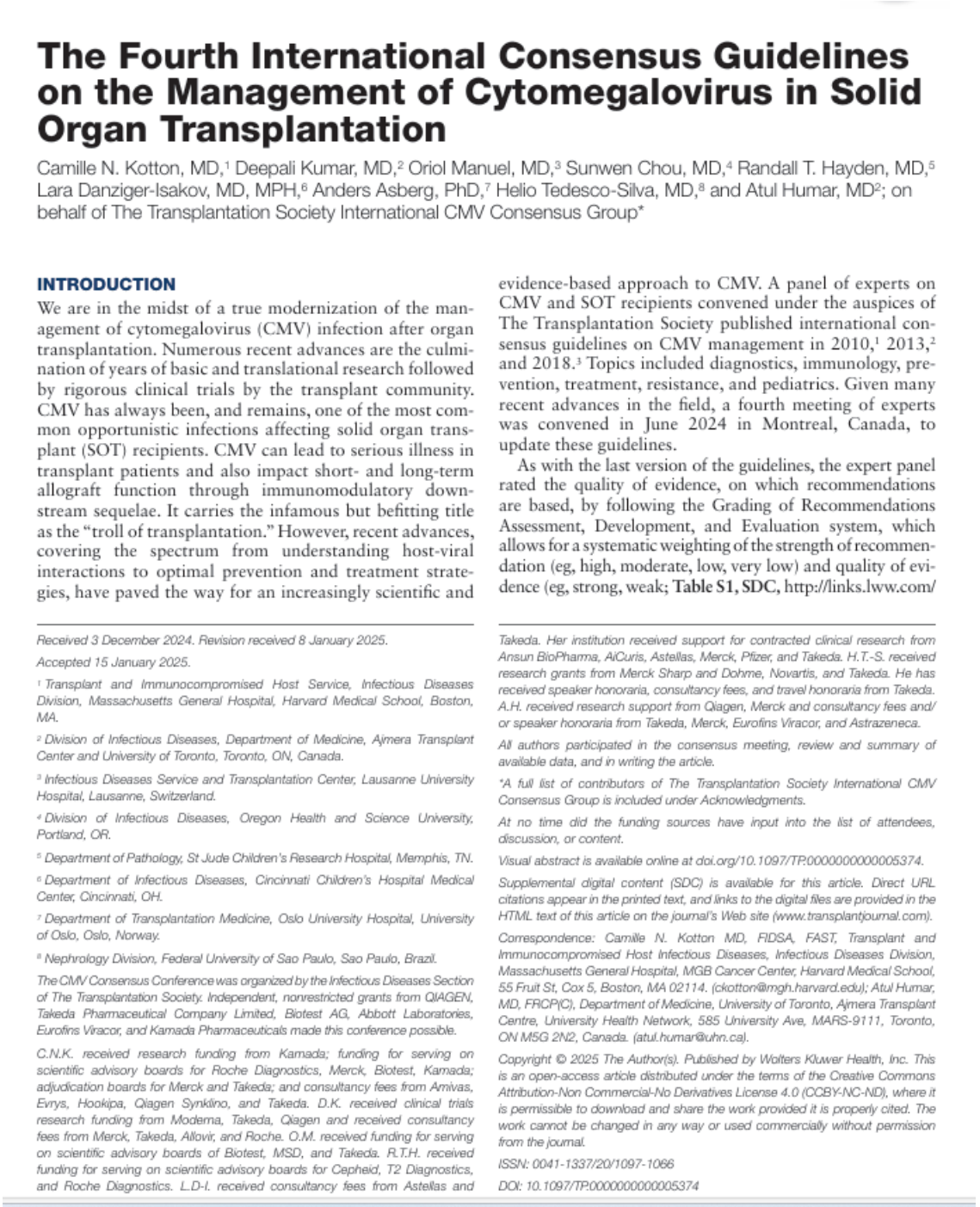
<0.5 log10 IU/mL değişiklik klinik olarak anlamlı değil

Çok düşük pozitiflik → **blip** olarak değerlendirilebilir

Sekonder profilaksi için net algoritma

Refrakter/dirençli CMV sonrası zorunlu

İmmün yanıt-temelli yönetim



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*

INTRODUCTION

We are in the midst of a true modernization of the management of cytomegalovirus (CMV) infection after organ transplantation. Numerous recent advances are the culmination of years of basic and translational research followed by rigorous clinical trials by the transplant community. CMV has always been, and remains, one of the most common opportunistic infections affecting solid organ transplant (SOT) recipients. CMV can lead to serious illness in transplant patients and also impact short- and long-term allograft function through immunomodulatory downstream sequelae. It carries the infamous but befitting title as the "troll of transplantation." However, recent advances, covering the spectrum from understanding host-viral interactions to optimal prevention and treatment strategies, have paved the way for an increasingly scientific and evidence-based approach to CMV. A panel of experts on CMV and SOT recipients convened under the auspices of The Transplantation Society published international consensus guidelines on CMV management in 2010,[1] 2013,[2] and 2018.[3] Topics included diagnostics, immunology, prevention, treatment, resistance, and pediatrics. Given many recent advances in the field, a fourth meeting of experts was convened in June 2024 in Montreal, Canada, to update these guidelines.

As with the last version of the guidelines, the expert panel rated the quality of evidence, on which recommendations are based, by following the Grading of Recommendations Assessment, Development, and Evaluation system, which allows for a systematic weighting of the strength of recommendation (eg, high, moderate, low, very low) and quality of evidence (eg, strong, weak; **Table S1, SDC,** http://links.lww.com/

Received 3 December 2024. Revision received 8 January 2025.

Accepted 15 January 2025.

[1] *Transplant and Immunocompromised Host Service, Infectious Diseases Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA.*

[2] *Division of Infectious Diseases, Department of Medicine, Ajmera Transplant Center and University of Toronto, Toronto, ON, Canada.*

[3] *Infectious Diseases Service and Transplantation Center, Lausanne University Hospital, Lausanne, Switzerland.*

[4] *Division of Infectious Diseases, Oregon Health and Science University, Portland, OR.*

[5] *Department of Pathology, St Jude Children's Research Hospital, Memphis, TN.*

[6] *Department of Infectious Diseases, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

[7] *Department of Transplantation Medicine, Oslo University Hospital, University of Oslo, Oslo, Norway.*

[8] *Nephrology Division, Federal University of Sao Paulo, Sao Paulo, Brazil.*

The CMV Consensus Conference was organized by the Infectious Diseases Section of The Transplantation Society. Independent, nonrestricted grants from QIAGEN, Takeda Pharmaceutical Company Limited, Biotest AG, Abbott Laboratories, Eurofins Viracor, and Kamada Pharmaceuticals made this conference possible.

C.N.K. received research funding from Kamada; funding for serving on scientific advisory boards for Roche Diagnostics, Merck, Biotest, Kamada; adjudication boards for Merck and Takeda; and consultancy fees from Amivas, Evrys, Hookipa, Qiagen Synklino, and Takeda. D.K. received clinical trials research funding from Modema, Takeda, Qiagen and received consultancy fees from Merck, Takeda, Allovir, and Roche. O.M. received funding for serving on scientific advisory boards of Biotest, MSD, and Takeda. R.T.H. received funding for serving on scientific advisory boards for Cepheid, T2 Diagnostics, and Roche Diagnostics. L.D-I. received consultancy fees from Astellas and Takeda. Her institution received support for contracted clinical research from Ansun BioPharma, AiCuris, Astellas, Merck, Pfizer, and Takeda. H.T.-S. received research grants from Merck Sharp and Dohme, Novartis, and Takeda. He has received speaker honoraria, consultancy fees, and travel honoraria from Takeda. A.H. received research support from Qiagen, Merck and consultancy fees and/or speaker honoraria from Takeda, Merck, Eurofins Viracor, and Astrazeneca.

All authors participated in the consensus meeting, review and summary of available data, and in writing the article.

**A full list of contributors of The Transplantation Society International CMV Consensus Group is included under Acknowledgments.*

At no time did the funding sources have input into the list of attendees, discussion, or content.

Visual abstract is available online at doi.org/10.1097/TP.0000000000005374.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

Correspondence: Camille N. Kotton MD, FIDSA, FAST, Transplant and Immunocompromised Host Infectious Diseases, Infectious Diseases Division, Massachusetts General Hospital, MGB Cancer Center, Harvard Medical School, 55 Fruit St, Cox 5, Boston, MA 02114. (ckotton@mgh.harvard.edu); Atul Humar, MD, FRCP(C), Department of Medicine, University of Toronto, Ajmera Transplant Centre, University Health Network, 585 University Ave, MARS-9111, Toronto, ON M5G 2N2, Canada. (atul.humar@uhn.ca).

ISSN: 0041-1337/20/1097-1066

DOI: 10.1097/TP.0000000000005374

İmmün yanıt ölçümünün (QuantiFERON-CMV) klinik önemini *gerçek verilerle* gösteren merkezimizden bir çalışma

- *334 karaciğer nakli hastasında*
- *CMV-QF negatif olanlarda CMV enfeksiyonu riskinin 26 kat arttığını* gösterildi

ELSEVIER

Predictive Value of Pretransplant Cytomegalovirus-Specific Cellular Immunity for Posttransplant CMV Infection in Liver Transplant Recipients Under Antiviral Prophylaxis

Elif Seren Tanriverdi[a*], Yusuf Yakupogullari[a], Yasar Bayindir[b], Sami Akbulut[c], Sibel Altunisik Toplu[d], Harika Gozde Gozukara Bag[e], Burak Isik[c], Baris Otlu[a], and Sezai Yilmaz[c]

[a]Department of Medical Microbiology, Inonu University Faculty of Medicine, Malatya, Türkiye; [b]Department of Infectious Diseases and Clinical Microbiology, Guven Health Group Guven Private Hospital Ayranc, Ankara, Türkiye; [c]Department of Surgery and Liver Transplant Institute, Inonu University Faculty of Medicine, Malatya, Türkiye; [d]Department of Infectious Diseases and Clinical Microbiology, Inonu University Faculty of Medicine, Malatya, Türkiye; and [e]Department of Biostatistics and Medical Informatics, Inonu University Faculty of Medicine, Malatya, Türkiye

ABSTRACT

Background. Existing data suggest that cytomegalovirus (CMV)-specific cell-mediated immunity (CMV-CMI) in solid organ recipients may predict post-transplant CMV infection, but the available information is still limited, and needs to be validated for larger patient populations under certain circumstances. This study aimed to determine whether CMV-CMI could predict post-transplant CMV infection in liver transplant recipients (LTRs) receiving antiviral prophylaxis (AVP).

Methods. A total of 1769 LTRs at the Inonu University Liver Transplantation Institute were retrospectively analyzed. CMV-CMI in a total of 334 patients (> 91% were CMV donor [D] positive/recipient [R] positive) who received AVP were analyzed using the CMV-Interferon (CMV-QF; QuantiFERON-CMV, Qiagen, Germany) assay within the week before transplantation. Patients were divided into two groups: group 1 (positive; n = 171, 51.2%) and group 2 (negative; n = 163, 48.8%). Patient variables were analyzed statistically.

Results. A total of 124 LTRs developed CMV infection. Patients' pre-transplant characteris-

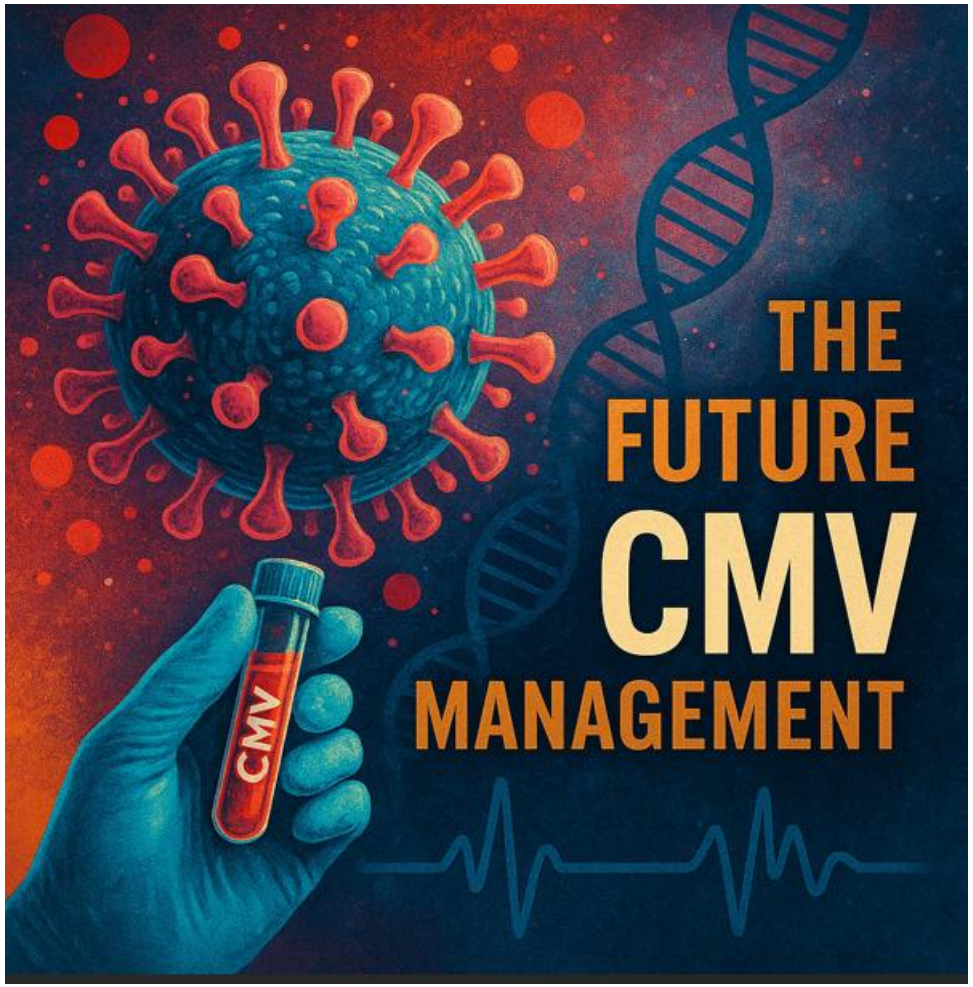
plant CMV infection for LTRs receiving AVP. Therefore, further consideration should be made for the LTRs with negative CMV-CMI.

- **CMV-QF pozitif = Hücresel immünitesi var (n=171)**
- **CMV-QF negatif = Hücresel immünitesi zayıf/yok (n=163)**

Geleceği şekillendirecek: İmmün monitorizasyon

- ***IFN-γ release assays (IGRAs) for CMV***
- CMV-spesifik T hücre yanıtının ölçülmesi
  → profilaksi süresini bireyselleştirmeyi mümkün kılar.
- ***Immune reconstitution profiling***
- Güçlü T hücre yanıtı olan hastalarda erken profilaksi sonlandırma
  Zayıf yanıtı olanlarda uzatma
- ***Kişiye özel CMV önleme ve tedavi***
- CMV yönetimi artık bir “tek boyutlu protokol” değil,
  → **bireyselleştirilmiş algoritmalara** doğru gidiyor.

“Gelecek dekad: antiviral gelişmeleri+ immün aracılı tedaviler = kişiselleştirilmiş CMV çağı”



Teşekkür ederim