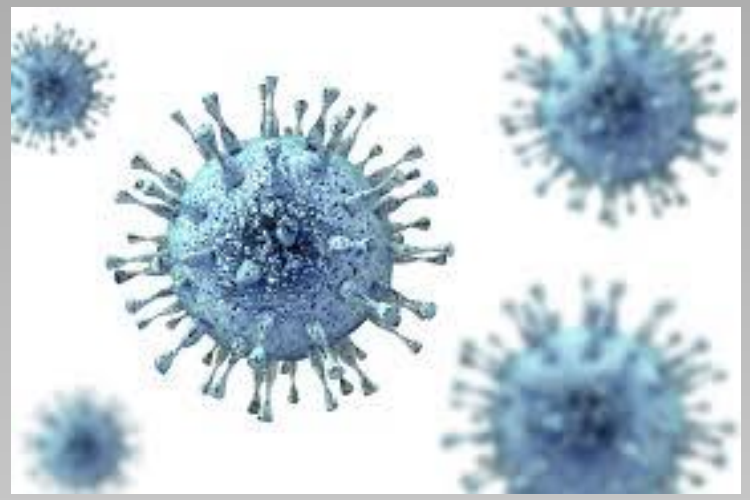
Solid Organ Transplantasyonunda CMV: Riskler ve Önleme

Dr Ayşe Özlem Mete
Gaziantep Üniversitesi Tıp Fakültesi
Enfeksiyon Hast. ve Klin. Mik. AD

CMV



- Herpesviridea (HHV5)

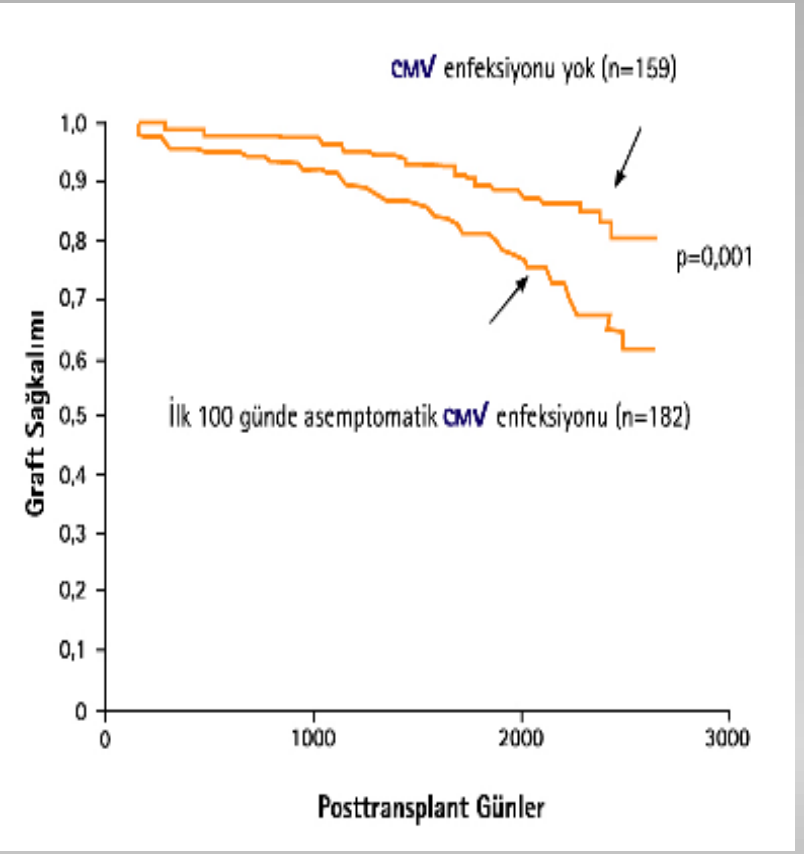
- Seroprevalans:
  - USA---%50
  - Avrupa 56.7%
  - Türkiye
    - 1-6, 7-14 ve 15-49 yaş gruplarında sırasıyla %82.1, %92 ve **%97.8 olarak** bulunmuştur.

Mikrobiyol Bül 2007; 41: 545-555 Mikrobiyoloji Bülteni
Lachmann R, Et Al. (2018) Cyt Plos ONE 13(7

Greftte CMV Viral Replikasyonu

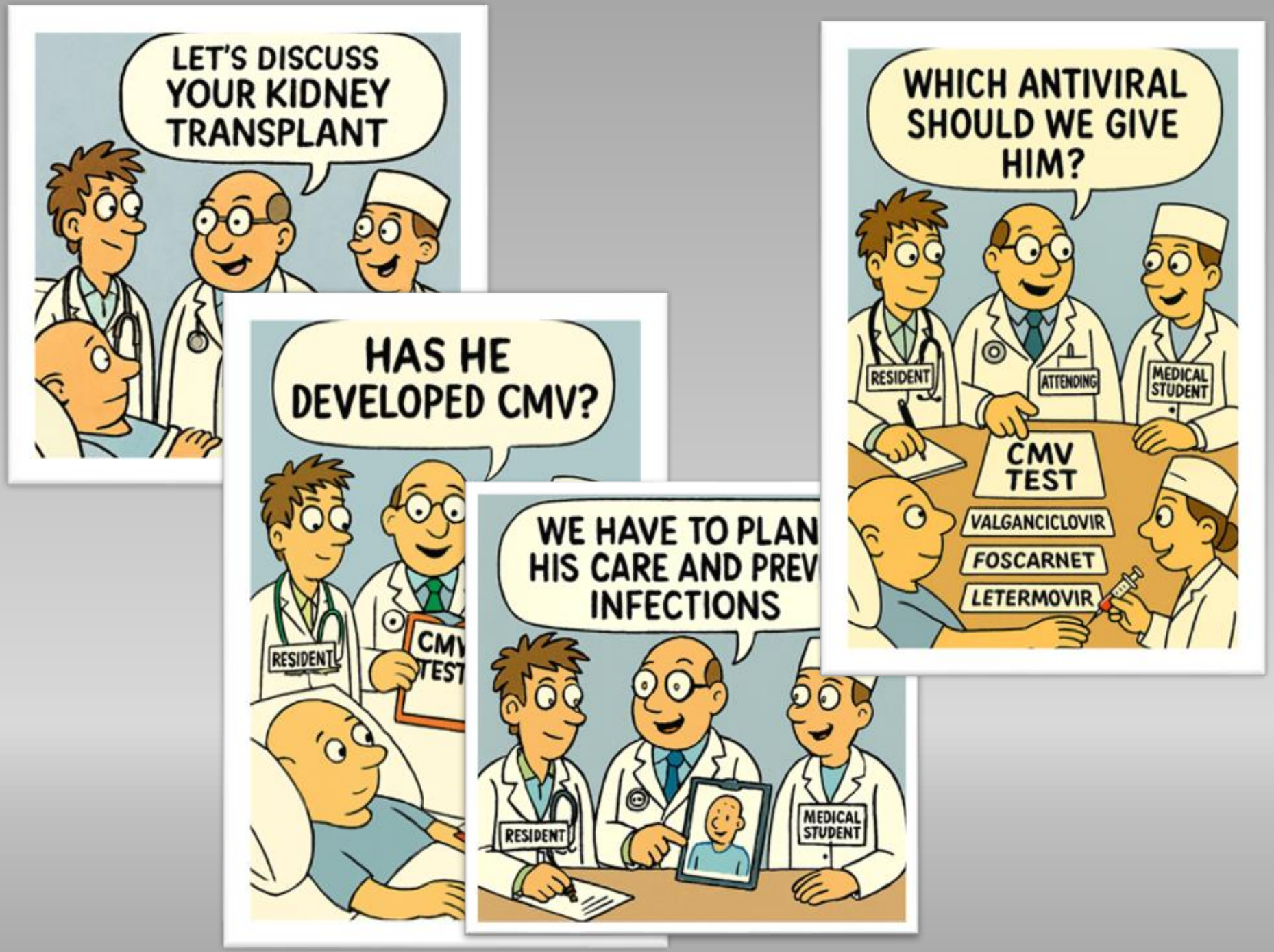
- Kanda **tespit edilemeyen düşük düzeydeki replikasyonun dokularda devam ettiğini göstermektedir.**

- Posttransplant ilk 100 gündeki asemptomatik CMV enfeksiyonu, graft sağkalımını anlamlı derecede azaltır.



Legendre C et al., Clin Infect Dis 2008; 46:732-40;
Sagedal S et al. Kidney International, Vol. 66 (2004), pp. 329 337;
Razonable et al. J Infect Dis 2003; 187:1801-8

- Tarama
- Tanı
- Profilaksi
- Tedavi



Terminoloji…

CMV infeksiyonu:

- CMV Hastalığı
  - CMV Sendromu
  - Uç-organ hastalığı

- Asemptomatik CMV İnfeksiyonu

İndirekt etki…?

- İmmün sistem modulasyonu
- Artmış infeksiyon riski
- Akut rejeksiyon ile ilişkili
- Kronik allograft hasarı:
  - Kronik allograft nefropatisi
  - Bronşiolitis obliterans
  - Koroner vaskülopati

Risk faktörleri:

- Kalitatif ve kantitatif immünyetmezlik
  - Nonspesifik
  - CMV spesifik

- CMV spesifik T-hücreler

- Transplantasyon öncesi CMV serolojisi
  - D+ / R-
  - D+/ R+ > D-/R+
  - D-/R-

Risk faktörleri:

- Transplante edilen organ
  - Akciğer
  - İnce bağırsak
  - Kompozit doku

- Lenfosit deplase edici tedavi
  - ATG
  - Alemtuzumab

Nakil Öncesi:

- Transplantasyon öncesi D ve R' den CMV IgG mutlaka çalışılmalı.

- CMV IgM ise yalancı pozitifliği sık olduğu için yanlış risk hesaplamasına neden olacağından rutin çalışılmamalı

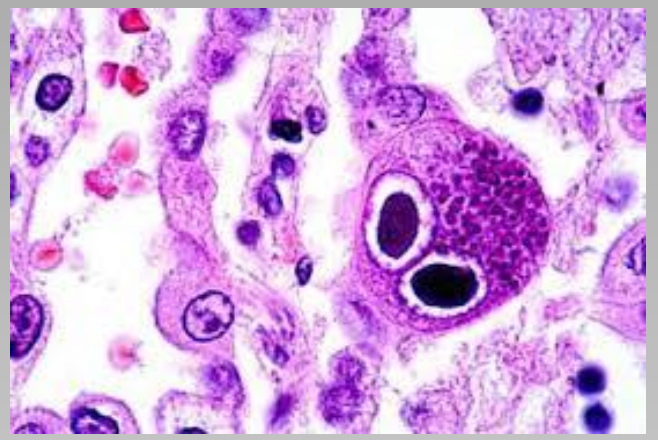
- Kan transfüzyonu test sonucunu bozacaktır

- Borderline sonuç…… kötü ihtimale göre değerlendir
  - Donör için +
  - Donör + ise alıcı için - negatif
  - Donör - ise alıcı için + kabul et

SOT sonrası takip

- Moleküler tetkikler → QNAT ---- CMV DNA / CMV RNA
- Antijenemi → pp65
- Histopatoloji → Organ tutulumunda **altın standart**….
- Viral kültür → Yavaş sonuç, Düşük duyarlılık
- mRNA (pp67) → Aktif hastalığı ayırt etmede spesifik, Aktif viral transkripsiyon
- Hücresel immünite…

- Hücresel immünite…
  - non spesifik:
    - lenfosit sayımı
    - CD4 sayımı
  - spesifik:
    - IGRA
    - ELISPOT
    - ICS for IFNγ
    - MHC multimer based assay



Tedaviyi kesme zamanı veya risk analizi için kullanılır.

Fernández-Ruiz M et al. Clin Microbiol Infect. 2019 Mar;25(3)
Lee H. et al. PLoS One. 2017 Dec 12;12(12)

- SOT sonrası takip QNAT ile yapılmalıdır

- Alterantif yöntem ise pp65 antijenemi takibi olabilir

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Cytomegalovirus (CMV) Monitoring After Liver Transplantation: Comparison of CMV Pp65 Antigenemia Assay with Real-Time PCR Calibrated to WHO International Standard

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDEF 1 Hideya Kamei
ADE 2 Yoshinori Ito
BC 1 Yasuharu Onishi
CDE 2 Michio Suzuki
B 1 Hisashi Imai
B 1 Nobuhiko Kurata
B 1 Tomohide Hori
BF 3 Takahisa Tainaka
CD 3 Hiroo Uchida
ADE 1 Yasuhiro Ogura

1 Department of Transplantation Surgery, Nagoya University Hospital, Nagoya, Japan
2 Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan
3 Department of Pediatric Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

Significant correlation was found between results of the 2 assay methods ($p<0.001$, $r=0.715$); a PCR result of ≥288 IU/mL predicted a positive result by the CMV AG assay (1 positive cells/150 000 leukocytes) with a sensitivity of 67.4% and specificity of 94.8%.

- SOT sonrası takip QNAT ile yapılmalıdır
- Alterantif yöntem ise pp65 antijenemi takibi olabilir
- **CMV-CMI Ölçümü????**

Review

What's New: Updates on Cytomegalovirus in Solid Organ Transplantation

Adam G. Stewart, MBBS[1] and Camille N. Kotton, MD[2]

(*Transplantation* 2024;108: 884–897).

TABLE 1.
Clinical studies evaluating immune assays used to prevent CMV infection from 2018 onwards

Platform	Reference	Year	Type of study	No. patients	Transplant type	% D+/R–	Groups	Timing of assay	Outcome
QuantiFERON-CMV	52	2019	Randomized controlled trial	118	Lung	25.4	Fixed duration (5 mo) vs QFN-CMV directed prophylaxis	5-mo posttransplant	Reduced incidence of CMV infection in QFN-CMV-directed group at 18-mo posttransplant, $P=0.03$
	53	2022	Cohort	263	Lung	22.4	Fixed duration (5 mo) vs QFN-CMV-directed prophylaxis	5-mo posttransplant	Reduced incidence of CMV infection in QFN-CMV-directed group at 24-mo posttransplant, $P<0.001$
	54	2022	Cohort	92	Lung	–	6-mo fixed prophylaxis (86%), 3- to 6-mo prophylaxis (14%)	3-, 6-, and 12-mo posttransplant	Incidence of CMV infection and disease was similar at the end of prophylaxis in the positive QFN-CMV group (78.6) vs the negative QFN-CMV group (81.3%), $P=0.87$
	55	2021	Cohort	60	Lung	18.3	6-mo fixed prophylaxis	6-mo posttransplant	Lower QFN-CMV values associated with late-onset CMV infection and high viral load
	56	2020	Cohort	154	Heart	14.5	Fixed duration (100 d) vs QFN-CMV-directed prophylaxis	100 d	Lower rates of CMV infection with QFN-CMV-directed prophylaxis (mean duration 155 d), 5% vs 19%, $P=0.03$
	57	2018	Cohort	44	Heart	0	3-mo fixed prophylaxis vs preemptive therapy	1-, 3-, 6- and 12-mo posttransplant	In those in the fixed prophylaxis strategy group, a higher proportion with indeterminant QFN-CMV results developed CMV infection, $P=0.036$
	58	2022	Randomized controlled trial	150	Kidney	0	3-mo fixed prophylaxis vs QFN-CMV-directed prophylaxis	30-, 45-, 60-, and 90-d posttransplant	No difference in incidence of CMV disease and replication between both arms
	59	2022	Cohort	55	Kidney	0	CMV R+, surveillance, no prophylaxis	1-mo posttransplant	CMV viremia incidence in patients with positive and negative QFN-CMV results did not differ significantly at 6 mo, $P=0.57$
	60	2018	Cohort	86	Kidney	20.9	3-mo fixed prophylaxis	1- and 3-mo posttransplant	CMV infection occurred in ~40% in CMV-QFN negative and 16% in CMV-QFN positive
	61	2018	Cohort	54	Kidney Heart Lung Liver	22	3- to 12-mo fixed prophylaxis (clinician-dependent)	End-of-prophylaxis and 2-mo posttransplantation	Negative QFN-CMV results at end-of-prophylaxis was associated with earlier onset, high-level CMV viremia
CMV ELISpot	62	2020	Cohort	133	Kidney	0	CMV R+, surveillance, no prophylaxis	Before induction immunosuppression	CMV infection developed in 47% of those with negative ELISPOT vs 39% in those with positive ELISPOT, $P=0.02$
	63	2019	Cohort	583	Kidney	48	3- to 6-mo fixed prophylaxis	End-of-prophylaxis and 1-, 2-, 3-, 4-, and 6-mo postprophylaxis	CMV events were lower in those with positive ELISPOT vs negative ELISPOT, 3% vs 19.5%, $P<0.001$

TABLE 1. (Continued)

Platform	Reference	Year	Type of study	No. patients	Transplant type	% D+/R–	Groups	Timing of assay	Outcome
	64	2018	Cohort	86	Kidney	0	CMV R+, surveillance, no prophylaxis	Pretransplant and 1–6-mo posttransplant	Median prespecific response 9-fold higher in patients with self-clearing viral load, $P<0.001$ Poor IFN-gamma response indicated general susceptibility to infection
	65	2021	Cohort	56	Liver	25	100 (low risk) vs 200 (high-risk) d fixed prophylaxis	1–6-mo post-prophylaxis	Predictive of protection from CMV DNAemia (>500 copies/mL) T-Track-CMV with IE-1 stimulation, sensitivity (67%) and specificity (87%)
	66	2018	Cohort	32	Liver	0	Preemptive strategy for prophylaxis	Pretransplant	No correlation with CMV DNAemia (sensitivity of 12% for predicting CMV DNAemia) Those positive for IE-1 had no CMV DNAemia at 2-mo posttransplant
	67	2020	Cohort	43	Lung	21	12-mo fixed prophylaxis	1-mo posttransplant	Among CMV ELISpot responders (ie, ≥20 SFU), significant CMV DNAemia occurred less frequently (11.8% vs 30.4%), $P=0.027$
Pathogen-agnostic assays									
QuantiFERON Monitor	68	2021	Cohort	80	Lung	25	Fixed duration	Pretransplant	Beyond 3 mo, patients with
ImmunoKnow	69	2023	Cohort						
	54	2022	Cohort						
TTV	70	2018	Cohort						
	71	2021	Cohort				prophylaxis	and 1-, 3-, 6-, 9-, and 12-mo posttransplant	predict CMV infection
	72	2021	Cohort	297	Lung	0	3-mo fixed prophylaxis	3-, 4-, and 5-mo posttransplant	TTV load at end-of-prophylaxis in CMV D+/R+ was not associated with subsequent

TABLE 1. (Continued)

Platform	Reference	Year	Type of study	No. patients	Transplant type	% D+/R–	Groups	Timing of assay	Outcome
	73	2019	Cohort	63	Liver	–	3-mo fixed prophylaxis for D+/R–	Pretransplant and 1-, 3-, 9-, and 12-mo posttransplant	TTV load was significantly higher during CMV infections, $P=0.009$
	74	2018	Cohort	169	Kidney	–	3-mo fixed prophylaxis for D+/R–	Pretransplant every 3-mo posttransplant	Patients without CMV IgG before transplantation and positive CMV viremia after transplant had TTV load
NK and $CD8^+$ T-cell function	75	2021	Cohort	31	Kidney	–	3- to 6-mo fixed prophylaxis	3- and 12-mo after transplant	Memory c cells and NK-like CD28– CD8+ T cells were associated with control of viremia

CMV-CMI Ölçü

- CMV antijeni olan fosfoprote
  efektör immün yanıtlarını ölç

Kullanılan Yöntemler:

- Akış sitometrisi ile hücre içi
- Interferon (IFN)-γ salınım t

Ticari Olarak Mevcut Testler

- QuantiFERON®-CMV: (QTF-CM
- T-SPOT®: CMVOxford Immuno
- T-Track®: CMVMikrogen, Neuri

Özellik	QuantiFERON-CMV	T-SPOT.CMV (ELISPOT Tabanlı)	ELISPOT (Genel/In-house)
Yöntem	ELISA (Sıvı fazda IFN-γ ölçümü)	ELISPOT (Hücre bazında IFN-γ sayımı)	ELISPOT
Örnek Tipi	Tam Kan (Özel tüplere alınır)	İzole PBMC (Lökositler ayrıştırılır)	İzole PBMC
Hedef Hücreler	**Sadece CD8+** T hücreleri	**Hem CD4+ hem CD8+** T hücreleri	Genelde hem CD4 hem CD8
Hassasiyet	Orta (HLA kısıtlılığı olabilir)	**Yüksek** (Tek bir hücreyi bile sayabilir)	Yüksek
Uygulama	Kolay, otomatize edilebilir.	Daha zahmetli, manuel emek ister.	Araştırma odaklı, standart dışı.

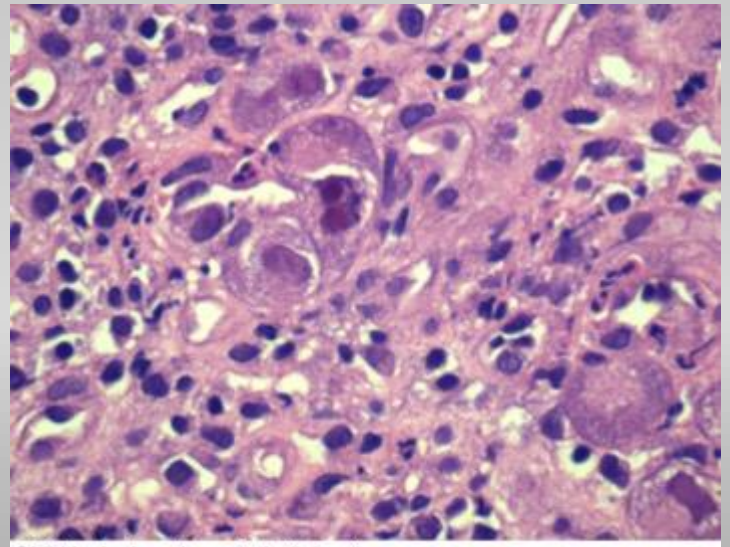
Table 4. Prospective Observational Studies With Over 100 Participants Investigating the Predictive Value of Commercial Cytomegalovirus Cell-mediated Immunity (CMV-CMI) Assays in Solid Organ and Allogeneic Hematopoietic Cell Transplant Recipients

Assessment Timepoint	Assay	Antigen Stimulation and Threshold For CMV-CMI[a,b]	Primary CMV Endpoint	Population	PPV[c]	NPV[d]	Reference
Pre-transplant	T.SPOT.CMV	IE-1, > 20 spots	CMV infection by 12 months post-transplant	D + R + kidney recipients who received prophylaxis	33.3%	95.9%	Jarque et al[31]
	…	…	…	D + R + kidney recipients who underwent PET	73.3%	55.6%	Jarque et al[31]
End of prophylaxis	T.SPOT.CMV	IE-1 and pp65 > 20 spots[e]	csCMVi by 12 months post-transplant	R + kidney recipients	10%	98.7%	Kumar et al[32]
	T.SPOT.CMV	IE-1 and pp65 > 20 spots[e]	csCMVi by 12 months post-transplant	D + R– kidney recipients	23.6%	87%	Kumar et al[32]
	QuantiFERON-CMV	IFN-γ ≥ 0.2 IU/mL	CMV infection by 12 months post-transplant	R + kidney recipients, received ATG	45.8%	63.9%	Fernandez Ruiz et al[33]
	QuantiFERON-CMV	IFN-γ ≥ 0.1 IU/mL	CMV disease by 12 months post-transplant	D + R– SOT recipients	23.8%	93.3%	Manuel et al[34]
	QuantiFERON-CMV	IFN-γ ≥ 0.2 IU/mL	CMV disease by 12 months post-transplant	D + R– kidney recipients	17.5%	87.5%	Limaye et al[35]
During PET (every 2 weeks)	T.SPOT.CMV	…	csCMVi by 6 months post-transplant	R + allogeneic HCT	…	…	Chemaly et al[36]
		Cutoff 1: IE-1 > 100 spots			Cutoff 1: 36.2%	Cutoff 1: 94%	
		…			…		
		Cutoff 2: 1E-1 or pp65 > 100 spots			Cutoff 2: 36.6%	Cutoff 2: 96%	
		…			…	…	
Pre-transplant, week 2, and week 4 (change in response)	T. SPOT.CMV	Positive or no change in pp65 or IE-1 spots between time points:	csCMVi by 6 months post-transplant	R + allogeneic HCT	Pre-Tx to Wk 2	Pre-Tx to Wk 2	Ariza-Heredia[37]
		A. Pre-Tx and Wk 2			IE-1: 42%	IE-1: 84%	
		B. Pre-Tx and Wk 4			pp65: 41%	pp65: 87%	
		…			…	…	
		…			Pre-Tx to Wk 4	Pre-Tx to Wk 4	
		…			IE-1: 40%	IE-1: 84%	
		…			pp65: 37%	pp65: 83%	
Onset of DNAemia[f]	QuantiFERON-CMV	IFN-γ ≥ 0.2 IU/mL	Failure to spontaneously clear DNAemia	All SOT (95% R+)	55.5%	92.3%	Lisboa et al[38]
	T.SPOT.CMV	pp65 > 100 spots and/or IE-1 > 50 spots/	Progression to csCMVi within 60 days	R + allogeneic HCT	83%	90%	El Haddad et al[39]
End of treatment	T-Track® CMV	See comment[f]	Recurrent CMV infection	D-R + allogeneic HCT	74.3%	75.0%	Wagner-Drouet[40]

Farklı PCR yöntemlerinin sonuçları farklı olabilir…

- Başlangıç volümü farklı
- Ekstraksiyon yöntemi farklı
- Primer prob farklı
- PCR koşulları farklı
- Tam kan/plazma: Seçilen örnek farklı

- CMV viral yükü tam kan > plazma
- Tek tip örnek ile çalışılmalı ve takip edilmeli



CMV inclusions in endothelial cells

CMV hastalığından korunma

Kan ve Kan Ürünleri Hazırlığı:

- Eğer alıcı CMV-negatif (**R-**) kan transfüzyonu gerekiyorsa:

- **CMV-seronegatif** kan ürünleri veya,

Lökoreduksiyon (lökositleri filtre edilmiş) uygulanmış kan ürünleri kullanılmalıdır. Bu, primer infeksiyonu engeller.

(3, 4. nesil filtrelerle 1000'de 1'e düşürülür)

1. The Fourth International Consensus Guidelines (2025/2026 Güncellemesi)
2. American Society of Transplantation (AST) Kılavuzu
3. AABB (Association for te Advancement of Blood & Biotherapies) Standartları
4. KDIGO 2026 güncellemesi

CMV hastalığından korunma

- Preemptif???
- Profilaksi???

«Post –profilaksi Geç Başlangıçlı CMV Hastalığı»

Profilaksi bitişini takiben 3-6. aylarda gelişir

D+/R-

Hibrit Yaklaşım

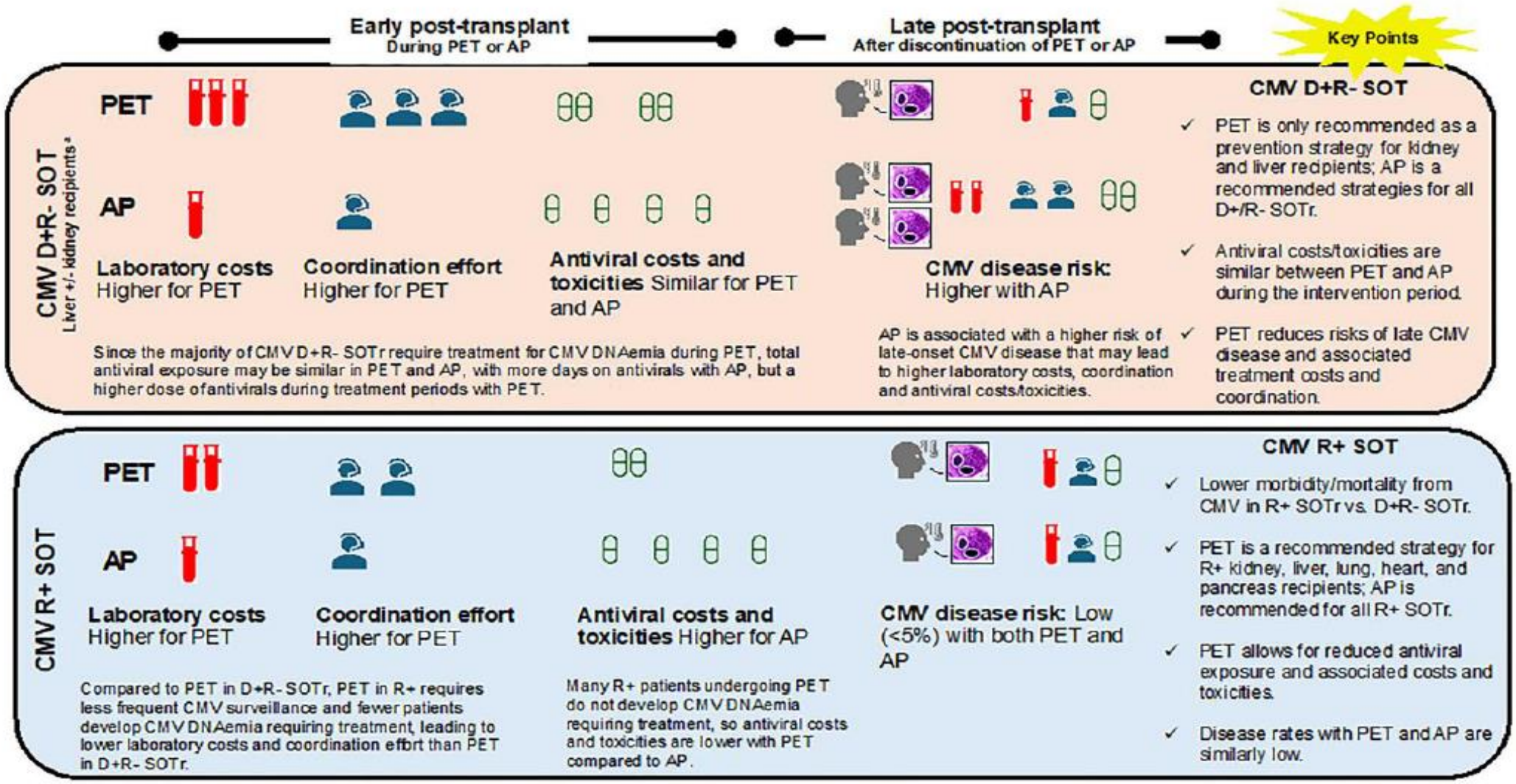


Figure 2. Advantages and disadvantages of antiviral prophylaxis and preemptive therapy in CMV D + R− and CMV R + solid organ transplant recipients. Abbreviations: AP, antiviral prophylaxis; CMV, cytomegalovirus; PET, preemptive therapy; SOT, solid organ transplant; SOTr, solid organ transplant recipients. [a]Represents the concept of PET in D + R− SOTr, although robust head-to-head clinical trial evidence comparing PET and AP exists only for D + R− liver transplant recipients. Liver and kidney transplant recipients are the only groups of SOTr for whom PET is a guideline recommended strategy.

	Antiviral prophylaxis	Preemptive therapy
Clinical efficacy	Yes (based on large randomized controlled clinical trials)	Yes (based on fewer and smaller trials), including D+/R− kidney and liver recipients
Ease of application	Easier to coordinate	More difficult to coordinate Viral load thresholds not defined; each program should develop viral load thresholds for various clinical indications
Delayed-onset CMV disease	Common in CMV D+/R− transplant recipients (post-prophylaxis delayed-onset CMV disease)	Less common
Cost	Higher drug costs	Higher laboratory costs
Toxicity	Greater drug toxicity (myelosuppression)	Lesser drug toxicity with shorter courses of antiviral therapy
Indirect effects (graft loss, mortality, and opportunistic infections)	Positive impact (meta-analyses and limited comparative trials)	Very limited data
Drug resistance	Yes	Yes

Risks and benefits may help guide the choice for CMV prevention after solid organ transplantation.

Profilaksi:

Organ	Risk category	Recommendation/Options (see Table 3 for dose and text for special pediatric issues)	Level of evidence
Kidney	D+/R−	Antiviral prophylaxis Drugs: valganciclovir (preferred), intravenous ganciclovir, or valacyclovir Duration: 6 mo	Strong, high
		Preemptive therapy (if logistic support is available) Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after kidney transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] p.o. BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, high
	R+	Antiviral prophylaxis Drugs: valganciclovir (preferred), intravenous ganciclovir, or valacyclovir Duration: 3 mo	Strong, high
		Preemptive therapy (if logistic support is available) Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after kidney transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, high

Pancreas and kidney/ pancreas	D+/R−	Antiviral prophylaxis is preferred	Strong, high (3-month prophylaxis)
		Drugs: valganciclovir (preferred) or intravenous ganciclovir	Strong, moderate (6-month prophylaxis)
		Duration: 3-6 mo	
		Preemptive therapy is an option (if logistic support is available) Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after pancreas alone or kidney-pancreas transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, moderate
	R+	Antiviral prophylaxis Drugs: valganciclovir (preferred) or intravenous ganciclovir	Strong, moderate
		Duration: 3 mo	
		Preemptive therapy (if logistic support is available). Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after pancreas alone or kidney-pancreas transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	Strong, moderate

Liver	D+/R−	Antiviral prophylaxis	Strong, high (3-month prophylaxis)
		Drugs: valganciclovir (note FDA caution[a]) or intravenous ganciclovir	Strong, moderate (6-month prophylaxis)
		Duration: 3-6 mo	
		Preemptive therapy (if logistic support is available)	Strong, high
		Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after liver transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	
	R+	Antiviral prophylaxis	Strong, high
		Drugs: valganciclovir (note FDA caution[a]) or intravenous ganciclovir	
		Duration: 3 mo	
		Preemptive therapy (if logistic support is available)	Strong, high
		Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after liver transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	

Heart	D+/R−	Antiviral prophylaxis is preferred.	Strong, high (3-month prophylaxis)
		Drugs: valganciclovir (preferred), or intravenous ganciclovir. Some centers add adjunctive CMV immune globulin.	Strong, moderate (6-month prophylaxis)
		Duration: 3-6 mo	Weak, low (immune globulin)
		Preemptive therapy is an option (if logistic support is available), but not preferred.	Weak, low
		Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after heart transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	
	R+	Antiviral prophylaxis	Strong, moderate
		Drugs: valganciclovir (preferred) or intravenous ganciclovir. Some centers add adjunctive CMV immune globulin.	Weak, low (immune globulin)
		Duration: 3 mo	
		Preemptive therapy	Strong, moderate
		Weekly CMV QNAT (or pp65 antigenemia) for 12 wk after heart transplantation, and if a positive CMV threshold is reached, treat with (a) valganciclovir 900 mg[b] po BID (preferred), or (b) IV ganciclovir 5 mg/kg IV every 12 h until negative test	

Lung, heart-lung	D+/R−	Antiviral prophylaxis Drugs: valganciclovir or intravenous ganciclovir Duration: at least 6-12 mo. Some centers prolong prophylaxis beyond 12 mo. Some centers add CMV immune globulin.	Strong, high (12-month prophylaxis) Strong, low (6-month prophylaxis) Weak, low (>12 mo prophylaxis) Weak, low (immune globulin)
	R+	Antiviral prophylaxis Drugs: valganciclovir or intravenous ganciclovir Duration: 6-12 mo.	Strong, moderate
Intestinal	D+/R−, R+	Antiviral prophylaxis Drugs: valganciclovir or intravenous ganciclovir Duration: 3 mo for CMV R+; 6 mo for D+/R−.	Strong, low
Composite tissue allograft	D+/R−, R+	Antiviral prophylaxis Drugs: valganciclovir or intravenous ganciclovir Duration: 3 mo for CMV R+; 6 mo for D+/R−.	Strong, low

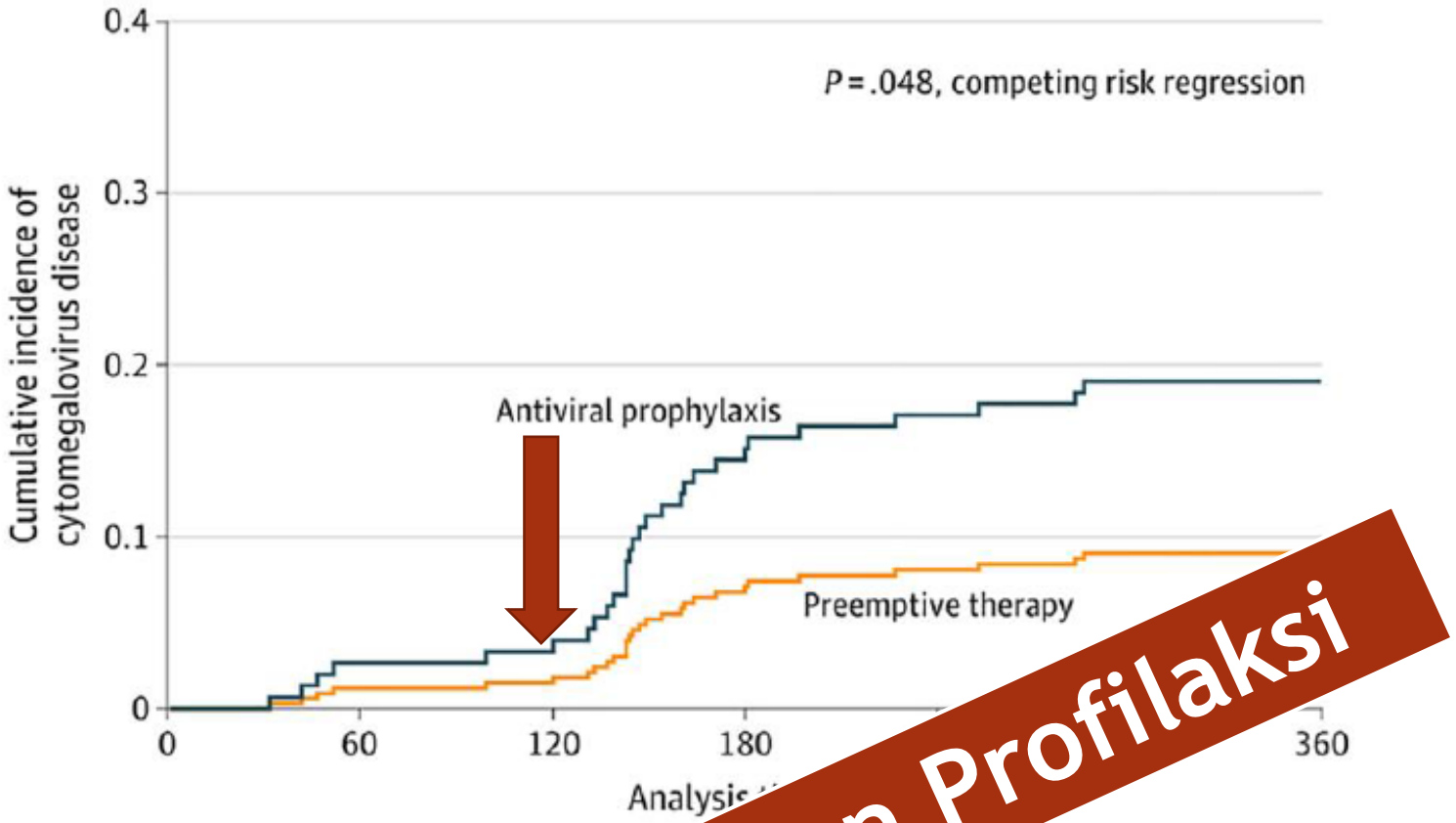
Profilaksi verilecekse 10. günde başlanmalı

Post-profilaksi Geç Başlangıçlı CMV Hastalığı

Korunma:

- Yakın takip
- Semptomlar oluşmaya başladığında erken tedavi
- Düşük bir QNAT eşik değeri
- Post profilaksi preemtif tedavi için takip
  - 3 ay süreyle haftada ≥1 QNAT ya da PP65 (???)

Akciğer Tx sonrası 12 ay hatta ömür boyu profilaksi



Neden Profilaksi

Figure 4. Cumulative incidence of CMV disease in CMV seronegative liver transplant recipients with CMV seropositive donors randomized to 3 months of preemptive therapy or prophylaxis. Adapted from Singh N, Winston DJ, Razonable RR, et al. JAMA **2020**; 323:1378–87. doi:10.1001/jama.2020.3138. Abbreviation: CMV, cytomegalovirus.

Preemptif Tedavi

- Yol gösterecek EŞİK değer???
  - Bölgeye özel
  - Teste özel
  - Kullanılan immünsüpresife özel

***Eşik değerler lokal olarak belirlenmeli

Kimler Uygun

Kime preemtif tedavi:

- R+ böbrek, karaciğer, [illegible] alıcılarında yapılabilir
- D+/R- QNAT böbre[illegible] aynı gün sonuç ve hast[illegible]
- D+/R- ye da D+/R+ Akciğer ve [illegible] emtif tedavi önerilmez

Sadece erken döneminde değil ayrıca

Rejeksiyon Tedavisi sırasında

ve sonrasında

preemptif tedavi kullanılabilir

CMI/ IGRA testleri bize yol göstermez mi???

Nakil Sonrası Takipte Hangisi, Nerede Kullanılır? (IGRA +PCR)

1.Profilaksi Sonu:

- Antiviral ilaç kesilmeden hemen önce test yapılır.
- Eğer test **pozitif** ise (bağışıklık oluşmuş), ilacı kesmek güvenlidir.
- Eğer **negatif** ise, ilaç kesildikten sonra virüsün geri gelme (rebound) riski çok yüksektir.

2.Risk Stratifikasyonu:

- Özellikle D+/R- (Donör pozitif, Alıcı negatif) gibi yüksek riskli hastalarda, bağışıklık gelişip gelişmediğini izlemek için kullanılır.

3.Tedavi Süresi Belirleme:

- Aktif CMV enfeksiyonu tedavisinde, sadece PCR'ın negatifleşmesi yetmeyebilir.
- IGRA testi pozitifleşene kadar tedaviye devam etmek, nüksleri (tekrarları) önlemede daha başarılı sonuçlar vermektedir.

Preemptif Tedavide başlama zamanı

- Ne zaman?
- Neye göre başlayalım?

INVITED ARTICLE

MEDICAL MICROBIOLOGY

L. Barth Reller and Melvin P. Weinstein, Section Editors

Interpreting Quantitative Cytomegalovirus DNA Testing: Understanding the Laboratory Perspective

Colleen S. Kraft,[1,2] Wendy S. Armstrong,[2] and Angela M. Caliendo[1,2]

[1]Department of Pathology and Laboratory Medicine, and [2]Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia

American Journal of Transplantation 2009; 9: 258–268
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2008.0251

Interlaboratory Comparison of Cytomegalovirus Viral Load Assays

[12]. Therefore, when detecting CMV viral load values of <1000 copies/mL, changes of <5-fold (0.7 $\log_{10}$) will rarely reflect clinically important changes in viral replication. For values >1000 copies/mL, 3-fold (0.5 $\log_{10}$) changes in viral load may be significant, although this may differ among LDTs. Some centers report viral loads as copies/mL and as $\log_{10}$ copies/mL because clinicians may be less likely to overinterpret small changes in viral load values when expressed as $\log_{10}$ values.

Viral yükteki artış izlenmeli

<1000 kopya/mL → 5 kat artış

>1000 kopya/mL → 3 kat artış önemli

- Tedavi başlanılan güne ait viral yük düzeyi bilinmeli, saptama sınırı üstündeyse dilusyonla gerçek değer belirlenmeli.

- Virusun plazmada yarılanma ömrü 3-8 gün.

Kraft CS, et al. Clin Infect Dis 2012

Preemptif Tedavi:

- Predefined viral yükü QNAT ya da PP65 bir kez geçerse

  2x900 valgansiklovir PO

  5mg/kg gansiklovir IV

  ➢süreye viral yüke göre karar verilir

  ➢2 kez bakılan haftalık QNAT negatif ise

  ya da

  ➢Sensitif QNAT 1 kez negatif ise tedavi kesilebilir

  ➢Toplamda en az 12 hafta izlem…

- Subklinik düzeylerde CMV replikasyonuna izin verilmeli mi?

- Preemptif tedavi alanlarda HSV-1 ve HSV-2 IgG (+) hastalara
    - Asiklovir
    - Valasiklovir
    - Famsiklovir

Clinical Infectious Diseases

REVIEW ARTICLE

Current and Future Strategies for the Prev and Treatment of Cytomegalovirus Infecti in Transplantation

Clinical Infe

Madeleine R. Heldman,[1] Michael J. Boeckh,[2,3,4] and Ajit P. Limaye[5]

[1]Division of Infectious Diseases, Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA; [2]Division of Alle Medicine, University of Washington, Seattle, Washington, USA; [3]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Center, Seattle Hutchinson Cancer Center, Seattle, Washington, USA; and [5]Division of Infectious Diseases, Department of Medicine, University of California

Table 1. Commonly Used Antivirals for the Prevention and Treatment of Cytomegalovirus Infection and Disease in Adult Solid Organ and Allogeneic Hematopoietic Cell Transplant Recipients

Drug (Route)	US FDA Approved Indication(s)	Other Applications and Common Uses	Major Toxicities and Limitations
Ganciclovir (IV)[a]	**Prevention:** SOT and HCT (5 mg/kg/day)	**Prevention:** See FDA approved indications	Myelosuppression (primarily leukopenia/ neutropenia).
	Treatment: CMV retinitis in SOT and HCT (5 mg/kg twice daily)	**Treatment:** CMV infection and non-retinitis disease in SOT and HCT (5 mg/kg twice daily)[1–3]	Requires dose adjustment for renal dysfunction.
Valganciclovir (PO)[a]	**Prevention:** kidney, kidney-pancreas, and heart transplant (900 mg/day)	**Prevention:** Lung, liver, and small bowel transplant (900 mg/day)[1,2]	Myelosuppression (primarily leukopenia/ neutropenia).
	Treatment: None	**Treatment**: First-line treatment of CMV infection and mild to moderate CMV disease in HCT and SOT (900 mg twice daily)[3,4]	Requires dose adjustment for renal dysfunction.
Foscarnet (IV)[a]	**Prevention:** None	**Prevention**: Maintenance or secondary prophylaxis in HCT (90 mg/kg daily)[3,4]	Nephrotoxicity, electrolyte wasting, gastrointestinal toxicity, mucosal ulceration, frequent lab monitoring.
	Treatment: None	**Treatment:** Second-line treatment for CMV infection in SOT[1,2]. First or second line for treatment of CMV infection and disease in HCT (90 mg/kg twice daily)	Difficult to administer in outpatient settings.
	Only approved for treatment of CMV retinitis in HIV/AIDS and for acyclovir resistant mucocutaneous HSV)	…	…
Letermovir (PO, IV)[b]	**Prevention:** R + HCTr through day +100 and through day +200 in those at high-risk for late CMV infection/disease (480 mg daily)[c]	**Prevention:** D + R– non-kidney SOT, R + SOT with leukopenia	Peripheral edema, headache. Not active against HSV or VZV.
	…	…	Not FDA approved for children < 18 years; phase 3 trial in pediatric HCT is currently underway (NCT05711667).
	D + R– kidney recipients (480 mg daily)	**Treatment:** When other antivirals are contraindicated (480mg–960 mg daily); in conjunction with other antivirals for R/R CMV disease[5,6]	Interactions with transplant medications through inhibition of CYP3A4 and induction of CYP2C19/2C9. Hepatic uptake is mediated by OATP1B1/B3, which is inhibited by cyclosporine.
	Treatment: None	…	
Maribavir (PO)	**Prevention:** None	**Prevention:** None	Dysgeusia. Increases tacrolimus exposure. Not active against HSV or VZV. Does not cross blood-brain or blood-eye barrier. Not available in intravenous form.
	Treatment: CMV infection or disease refractory to standard antivirals (with or without genotypic resistance) in SOT and HCT (400 mg twice daily)	**Treatment:** We consider maribavir for non-refractory/resistant CMV infection and/or disease with intolerance to other agents (400 mg twice daily)[7]	Inhibits UL97 dependent conversion of (val) ganciclovir to its active metabolite and should not be used concomitantly with (val) ganciclovir.
	…	…	Frequent treatment-emergent resistance. Limited clinical trial experience with CMV loads >10,000 IU/mL.

All citations refer to references in Supplementary Materials 2.

Antiviraller:

Drug	Treatment[a]	Prophylaxis	Comments on use and toxicity
Valganciclovir	900 mg[b] po twice daily	900 mg[b] po once daily	Ease of administration Leukopenia is major toxicity
IV ganciclovir	5 mg/kg IV every 12 h	5 mg/kg IV once daily	Intravenous access and its associated complications Leukopenia is major toxicity
Valacyclovir	NOT recommended	2 g po four times daily	For kidney transplant recipients only NOT recommended for heart, liver, pancreas, lung, intestinal, and composite tissue transplant recipients High pill burden Neurotoxicity NOT recommended for treatment of CMV disease or asymptomatic infection
Foscarnet	60 mg/kg IV every 8 h (or 90 mg/kg every 12 h)	NOT recommended	Second-line alternative agent for treatment Highly nephrotoxic Used for *UL97*-mutant ganciclovir-resistant CMV infection or disease NOT recommended for preemptive therapy
Cidofovir	5 mg/kg once weekly ×2, then every 2 wk thereafter	NOT recommended	Third-line agent Highly nephrotoxic May be used for *UL97*-mutant ganciclovir-resistant CMV infection or disease NOT recommended for preemptive therapy

Antiviraller:

- İlk seçenek:
  - Gansiklovir
  - Valgansiklovir
- Alternatif:
  - Foscarnet
  - Cidofovir
- SOT'ta off-label:
  - Letermovir
- Maribavir
  - Salvage

Orta-hafif şiddetli hastalık

Gansiklovir ile başla , switch açısından değerlendir

Nefrotoksik- second line

Etkinliği gösterilene kadar kullanılmamalı

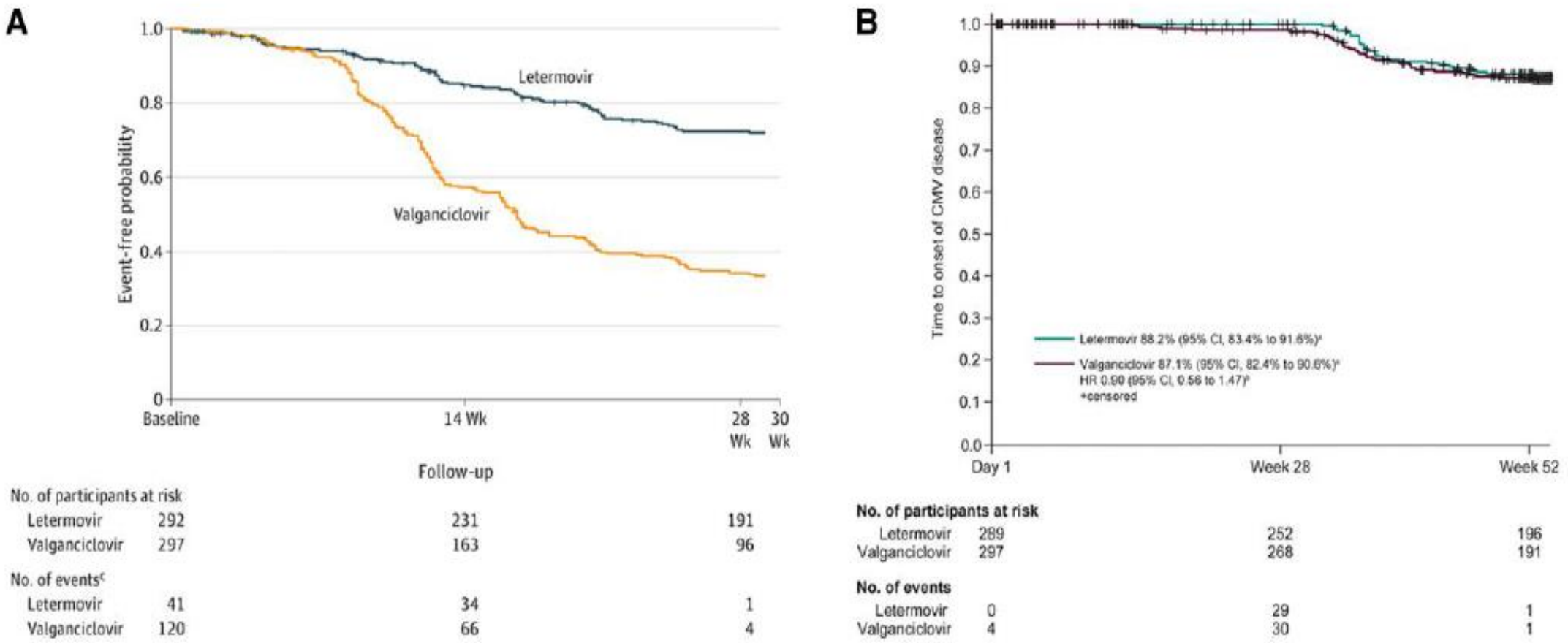


Figure 5. Probability of neutropenia or leukopenia (*A*) and endpoint committee-adjudicated CMV disease (*B*) in CMV seronegative kidney transplant recipients with CMV seropositive donors randomized to valganciclovir or letermovir as CMV prophylaxis. Adapted from Limaye AP, Budde K, Humar A, et al. JAMA **2023**. doi:10.1001/jama.2023.9106. Abbreviation: CMV, cytomegalovirus.

Tedavi

- Takip:
  - Haftada bir QNAT
  - Aynı tetkik
  - Aynı örnek materyal

  ***yan etki için haftada bir tam kan sayımı
- Süre:
  - Klinik düzelme
  - QNAT ya da pp65 Ag ile negatif (2 kez)

Direnç

- Tedavinin 2. haftasında > 1 log düşüş olmadıysa ???

➢Muhtemel direnç

- 2. haftada > 1 log artış: Direnç

- İmmünsüpresan fazlalığı
- Subterapötik ilaç düzeyi
  - Mini-dosing
- Gansiklovir direnci
- Akciğer transplantasyonu

Yanıtsız Hastalığın Sebepleri

Dirençli vaka yönetimi

- İmmünsüpresyonun dozunu azalt
- Direnç (genotipik) çalış
- Sirolimus içeren bir rejim ile değiştirilebilir
- Ampirik olarak Gansiklovir 10mg/kg

  Foskarnet
- CMV spesifik IgG ya da IVIG
- Gerekirse ilaç değişimi → Letermovir

  → Maribavir

Genotipik direnç:

UL-97 → gansiklovir

UL-54 → gansiklovir, foskarnet, cidofovir direnci

Aşı

Table 2. Investigational Vaccines and Monoclonal Antibodies for the Prevention of Cytomegalovirus Infection and Disease in Completed or Ongoing Clinical Trials

				Trials in Solid Organ Transplant			Trials in Hematopoietic Cell Transplant	
	Name	Platform	Epitope(s)	Population	Status		Population	Status
Vaccines	ASP0113	DNA	pp65, gB	Adult kidney transplant recipients	Phase 2 completed[9]	…	Adult recipients	Phase 3 completed[10]
	Triplex	Replication deficient viral vector (MVA)	pp65, IE-1, IE-2	Adult liver transplant candidates	Ongoing (NCT06075745)		Adult recipients	Phase 2 completed[11]
							Adult donors	Phase 2 ongoing (NCT03560752)
							Pediatric recipients	Phase 2 ongoing (NCT03354728)
	HB-101	Replication deficient viral vector (LCMV)	pp65, gB	Adult kidney transplant candidates	Phase 2 enrollment complete (NCT03629080)	…	None	N/A
	gB	Recombinant protein, MF-59 adjuvanted	gB	Adult kidney and liver transplant candidates	Phase 2 completed[12]	…	None	N/A
	Towne	Attenuated, replication competent CMV	Whole virus	Adult kidney transplant candidates	Completed[13]	…	None	N/A
	ALVAC-pp65	Replication competent viral vector (canarypox)	pp65	None	N/A		Adult donors	Phase 1 completed[14], Phase 2 completed (NCT00353977)
	Pepvax	Chimeric peptide[a]	pp65	None	N/A	…	Adult recipients	Phase 2 completed[15]
	mRNA-1647	mRNA	gB, PC	None	N/A	…	Adult recipients	Phase 2 ongoing (NCT05683457)
Monoclonal antibodies	MSL-109	Monoclonal antibody	gH	None	N/A	…	Adult HCT candidates	Completed[16]
	CSJ148	Two monoclonal antibodies	gB, PC	None	N/A	…	Adult HCT recipients	Phase 2 completed[17]
	RG7667	Two monoclonal antibodies	PC	Adult kidney transplant recipients	Phase 2 completed[18]	…	None	N/A
	Fiztasovimab	Monoclonal antibody	gB	Adult kidney transplant recipients	Phase 2 enrollment completed[19]	…	None	N/A

All citations refer to references in Supplementary Materials 2.

Abbreviations: gB, glycoprotein B; gH, glycoprotein H; IE-1, immediate early- 1; IE-2, immediate early-2; LCMV, lymphochoriomeningitis virus; MVA, modified vaccina Ankara; N/A, not applicable; PC, pentameric complex; pp65, phosphoprotein 65.

[a]Pepvax is human leukocyte antigen (HLA)-A*0201 restricted and PF-03512676 adjuvanted.

Gaziantep Üniversitesi Tıp Fakültesi Hastanesinde Böbrek Nakli Yapılan Hastalarda CMV Enfeksiyonunun 5 Yıllık Retrospektif Değerlendirilmesi

Uzm

Dr. Duran

Tez Danışmanı: Do

Gaziantep Üniversitesi, Enfeksiyon

Ocak 2019- Aralık 2024 tarihleri arasında

Gaziantep Üniversitesi Tıp Fakültesi Organ Nakli Hastanesinde

Böbrek nakli yapılan hastalarda

CMV enfeksiyonun sıklığı, risk faktörleri, nüks, greft kaybı ve mortalite üzerine etkisi değerlendirilmek amaçlandı.

- Çalışmamızda böbrek nakli alıcıları, CMV PCR negatif ve CMV PCR pozitif olmak üzere iki gruba ayrıldı.

- Nakilden sonra takipler boyunca bir kere **CMV PCR 80 copy/ml ve üzeri** olan hastalar **CMV PCR pozitif grup** olarak kabul edildi.

- Çalışmamızda 236 (% 47,68) CMV PCR negatif, **259 (% 52,32) CMV PCR pozitif hasta** mevcuttu.

CMV Enfeksiyonu Demografik Verilerin İlişkisi

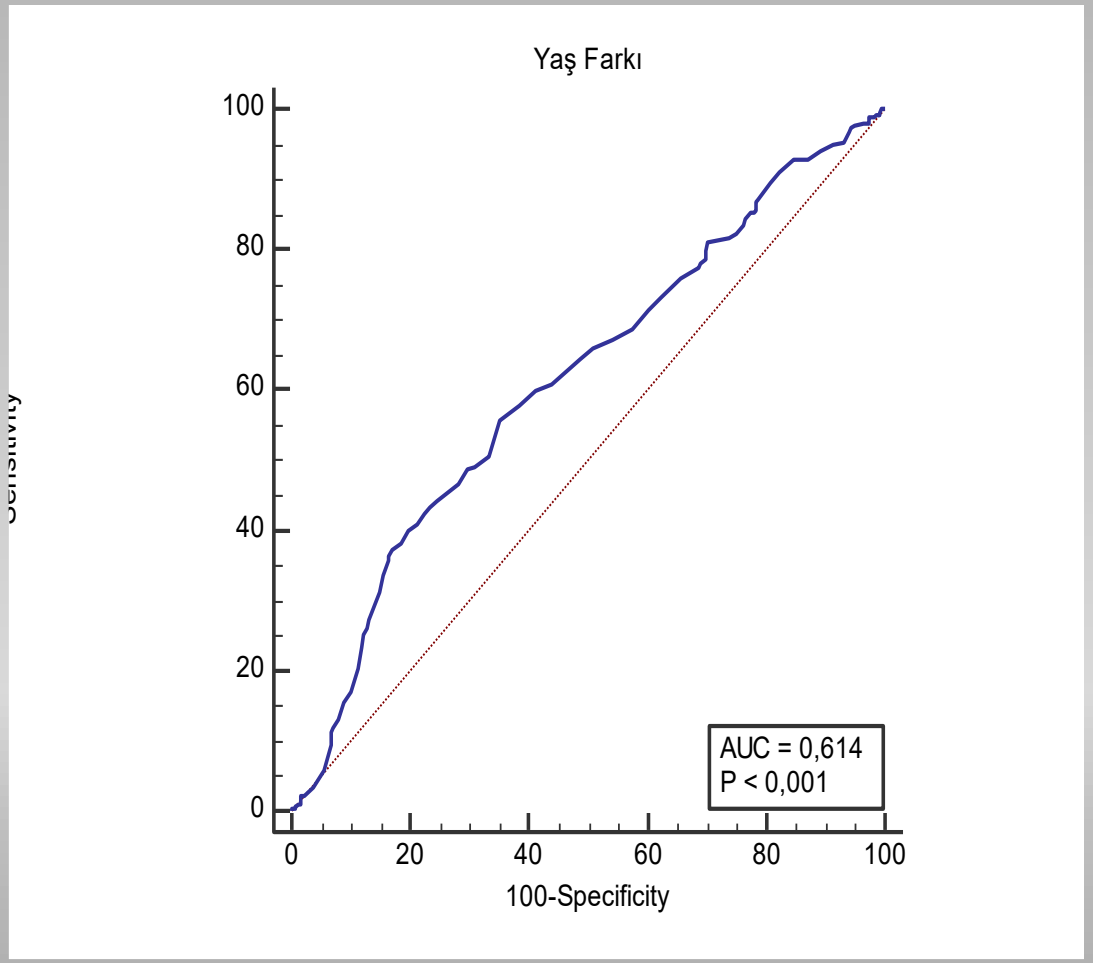
- Donör yaşının büyük olması CMV pozitifliği açısından istatistiksel olarak anlamlı bulundu

CMV PCR	Negatif	Pozitif	
	Ort.±SS	Ort.±SS	p
Alıcı Yaşı	43,60±13.37	42,68±13.86	0,463
Donör Yaşı	**41,89±13.88**	**48,41±13.87**	**0,001***

CMV Enfeksiyonu Yaş Farkı İlişkisi

CMV pozitifleşmesi açısından donör ile alıcı arasındaki yaş farkını değerlendirmek için yapılan ROC analizinde;

- Yaş farkının 15'ten fazla olması anlamlı bulundu.
- Testin spesifitesi % 83,05, sensivitesi % 37,45



Bulgular: CMV Enfeksiyonu Ek Hastalık İlişkisi

HT ve hiperlipidemi bulunan hastalarda CMV pozitif ile negatif grup arasında istatistiksel olarak anlamlı fark vardı

		CMV PCR Negatif	CMV PCR Pozitif	p
		Sayı (%)	Sayı (%)	
DM	Yok	143 (60,59)	156 (60,23)	0,935
	Var	93 (39,41)	103 (39,77)	
HT	Yok	17 (7,2)	5 (1,93)	**0,004***
	Var	**219 (92,8)**	**254 (98,07)**	
Hiperlipidemi	Yok	187 (79,24)	182 (70,27)	**0,022***
	Var	**49 (20,76)**	**77 (29,73)**	
KOAH	Yok	223 (94,49)	235 (90,73)	0,112
	Var	13 (5,51)	24 (9,27)	
Malignite	Yok	235 (99,58)	254 (98,07)	0,126
	Var	1 (0,42)	5 (1,93)	

CMV Enfeksiyonu Diyaliz ve Plazmaferez İlişkisi

Hastanın nakil öncesi diyaliz ve plazmaferez durumu ile CMV pozitif ve negatif grup arasında anlamlı fark bulunmadı.

		CMV PCR Negatif	CMV PCR Pozitif	p
		Sayı (%)	Sayı (%)	
Nakil Öncesi Diyaliz	Preemptif	80 (33,9)	96 (37,07)	0,153
	HD	146 (61,86)	143 (55,21)	
	PD	10 (4,24)	20 (7,72)	
Nakil Öncesi Plazmaferez	Yok	196 (83,05)	205 (79,15)	0,269
	Var	40 (16,95)	54 (20,85)	

Bulgular:
CMV Enfeksiyonu İndüksiyon Tedavi İlişkisi

İndüksiyon tedavisi olarak **ATG**+Prednisolon kullanımı ile CMV pozitif ve negatif grup arasındaki fark istatistiksel olarak **anlamlı bulundu.**

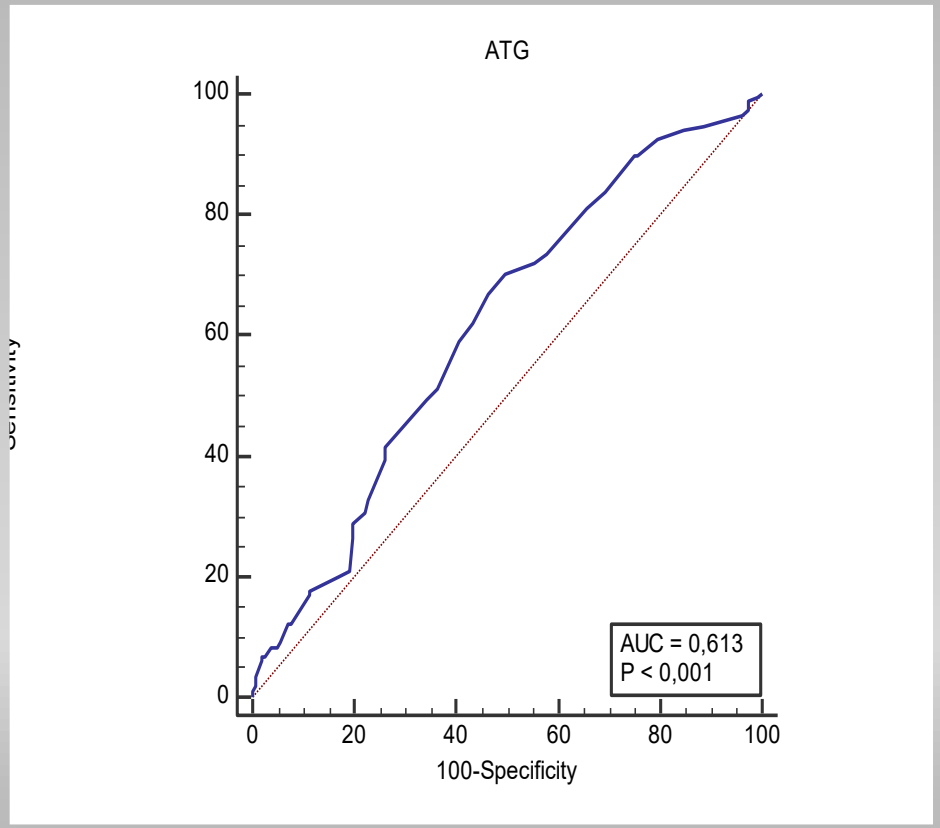
İndüksiyon tedavisi olarak ATG kullanan hastalarda ATG tedavi dozu ortalaması, CMV pozitif grupta **1008,61**±488,40 mg, CMV negatif grupta **830,06**±453,15 mg idi. **ATG tedavi dozu** CMV pozitif grupta istatiksel açıdan **anlamlı olarak daha yüksekti.**

		CMV PCR Negatif	CMV PCR Pozitif	p
İndüksiyon Tedavi	Basiliksimab+ATG+ Prednisolon	27 (11,59)	37 (14,34)	**0,014***
	Prednisolon	2 (0,86)	0 (0)	

CMV Enfeksiyonu ATG Dozu İlişkisi

ATG dozunun CMV PCR pozitifleşmesi ile ilişkisi açısından yapılan ROC analizinde;

- **ATG dozunun 700 mg'dan büyük** olması CMV pozitifleşmesi için istatiksel olarak **anlamlı bulundu.**
- Testin sensivitesi % 70,24, spesifitesi % 50,32



CMV Enfeksiyonu Greft Kaybı ve Mortalite İlişkisi

Greft kaybı ve mortalite ile CMV pozitif ve negatif grup arasında istatiksel olarak anlamlı fark bulunmadı.

		CMV PCR Negatif	CMV PCR Pozitif	p
		Sayı (%)	Sayı (%)	
Greft Kaybı	Yok	196 (83,05)	197 (76,06)	0,055
	Var	40 (16,95)	62 (23,94)	
Sonlanım	Eksitus	21 (8,9)	26 (10,04)	0,666
	Yaşıyor	215 (91,1)	233 (89,96)	

Tartışma

› Am J Physiol Renal Physiol. 2015 Dec 1;309(11):F925-32. doi: 10.1152/ajprenal.00317.2015. Epub 2015 Sep 9.

Long-term impact of CMV infection on allografts and on patient survival in renal transplant patients with protocol biopsies

U Erdbrügger [1], I Scheffner [2], M Mengel [3], A Schwarz [2], H Haller [2], W Gwinner [2]

- CMV enfeksiyonu **greft kaybı** ve **mortaliteye** neden olmaktadır.
- Erdbrügger ve ark.'larının 2015'de yaptığı transp sağkalı etkisin
  - CM ve bulunmuştur.
- Çalışmamızda ise CMV enfeksiyonu ile **greft kaybı ve mortalite arasında anlamlı ilişki bulunmadı.**

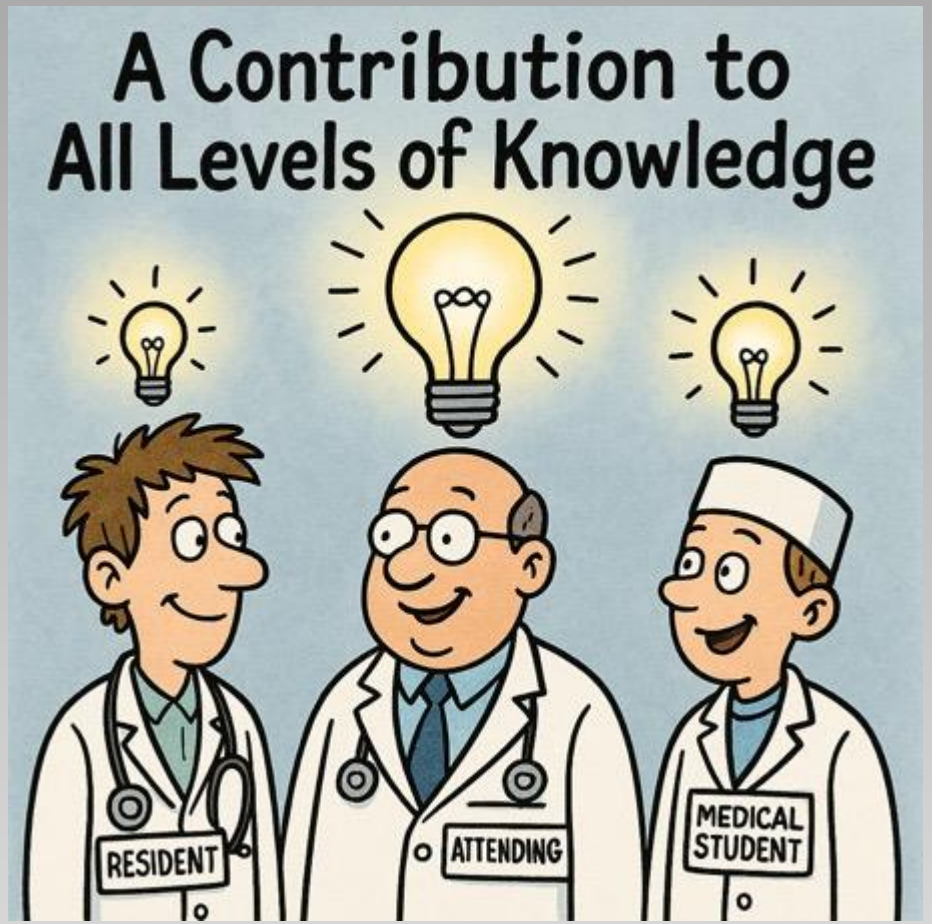
Çalışmamızın literatürden farklı olmasının sebebi;

- CMV proflaksinin ardından hibrid yaklaşım ile CMV enfeksiyonu yakın takip edildiğinden daha az greft kaybı ve mortaliteye neden olduğu düşünülmektedir.

Türkiyede

- QNAT…
- Quantiferon sınırlı
- Genotipik direnç (UL 54; UL97)
- Fenotipik direnç???
- Biyopsi (zor)

- Sekonder profilaksi??? (SUT)



Teşekkürler...