Corporació Sanitària CLÍNIC


# Maneig de la resistència en les infeccions per CMV

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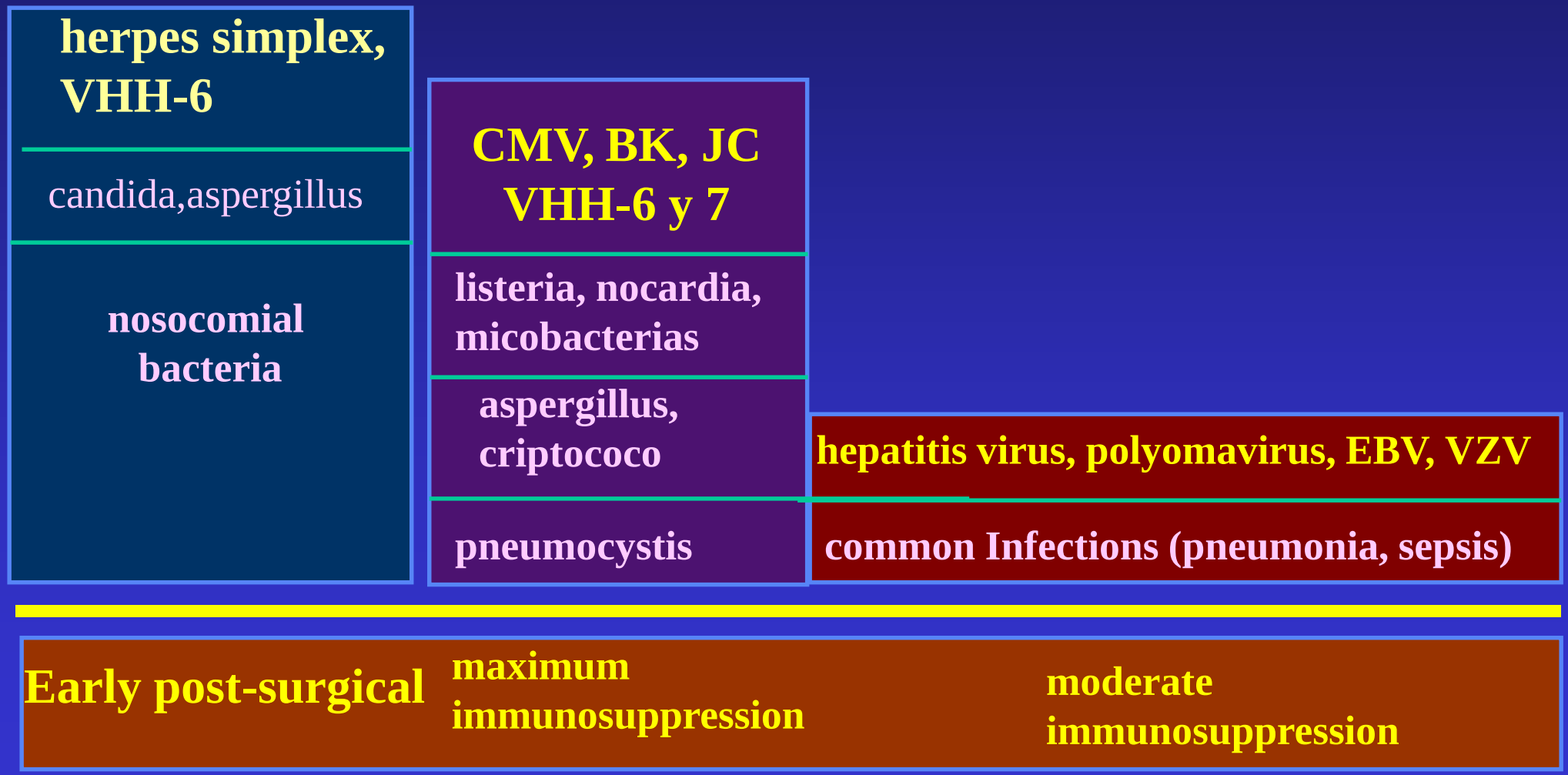
# Infection in the trasplanted patient (adapted from Rubin R.H., Am J Med 1978)



## El trasplante de órgano sólido predispone a la infección por virus adquiridos en el pos trasplante, transmitidos por el injerto y reactivados por la inmunosupresión.

- Efectos directos sobre el huesped: Clínica aguda
- Efectos indirectos: Rechazo agudo y/o crónico, acción inmunomoduladora, infecciones oportunistas asociadas.
  - Virus oportunistas:
    - Frecuentes: CMV, VEB, VHS, VVZ, VHH-6
    - Menos frecuentes: papilomavirus (VPH), poliomavirus (BKV y JCV) y eritrovirus B19.
  - Virus comunitarios: respiratorios (VRS, influenza, MPV, bocavirus..)
  - Virus neurotropos: VCML, VNL, …
  - Otros: Rotavirus, coronavirus, virus de las paperas..

# Efectos de la infección viral en el TOS

Efectos directos:

Fiebre, neutropenia, hepatitis

Colitis, nefritis, pancreatitis, retinitis

Efectos indirectos:

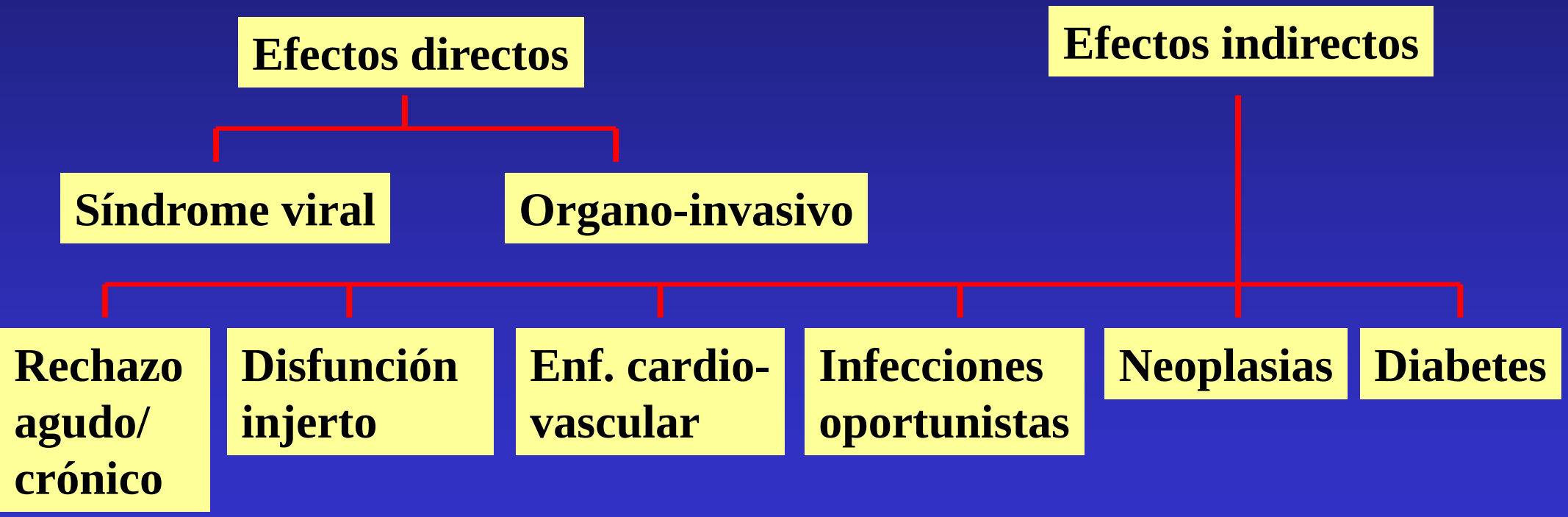
Oncogenesis

- Hepatitis B y C. Carcinoma hepatocelular y Linfoma esplénico
- Virus del Epstein Barr: Linfoma de Células B
- Papilomavirus: cancer anogenital y de células escamosas
- Virus del herpes 8: Sarcoma de Kaposi, linfoma

- Proliferación célular:
  - Aumento y aceleración de la aterogénesis
  - Obstrucción ureteral por el virus BK

# Citomegalovirus

## Efectos directos e indirectos de la ICMV tras el TOS




*Fishman. NEJM. 1998*
*Hjelmesaeth Diabetologia. 2004*
*Manez. J Infect Dis 1997*
*Hodson . Lancet 2005*
*Marcelin JR, Beam E, Razonable RR. World J Gastroenterol 2014*

# Citomegalovirus

**Efectos indirectos: Aumento de infecciones oportunistas**

- Bacteriemia: *Listeria monocytogenes*
- VHC: Riesgo de cirrosis, retrasplante y mortalidad
- Otros Virus: VEB, VHH8, VHH6
- Infecciones fúngicas (especialmente trasplantes intraabdominales)
    - •Candidemia e infecciones intra-abdominales (trasplante páncreas y hepático)
    - •*Aspergillus* sp (sobre todo en asociación con VHC)
    - •*Pneumocystis jirovecii*

# CMV infection/disease is a risk factor for developing post-transplant opportunistic infections

**Cytomegalovirus Infection Is a Risk Factor for Invasive Aspergillosis in Lung Transplant Recipients**

Rola N. Husni,* Steven M. Gordon, David L. Longworth, Alejandro Arroliga, Paul C. Stillwell, Robin K. Avery, Janet R. Maurer, Atul Mehta, and Thomas Kirby

*From the Departments of Infectious Diseases, Pulmonary Medicine and Critical Care and Cardiothoracic Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio*

**Rejection Treatment and Cytomegalovirus Infection as Risk Factors for *Pneumocystis carinii* Pneumonia in Renal Transplant Recipients**

S. M. Arend, R. G. J. Westendorp, F. P. Kroon, J. W. van't Wout, J. P. Vandenbroucke, L. A. van Es, and F. J. van der Woude

*From the Departments of Clinical Epidemiology, Infectious Diseases and Nephrology, University Hospital, Leiden, the Netherlands*

Risk Factors, Clinical Features, and Outcomes of Listeriosis in Solid-Organ Transplant Recipients: A Matched Case-Control Study

Núria Fernández-Sabé,[1] Carlos Cervera,[2] Francisco López-Medrano,[4] Miguel Lizasoain,[8] Elena Sáez,[5] Óscar Len,[3] Jesús Fortún,[4] Marino Blanes,[6] Rosa Laporta,[7] Julián Torre-Cisneros,[10] Joan Gavaldà,[3] Patricia Muñoz,[5] M. Carmen Fariñas,[9] José María Aguado,[4] Asunción Moreno,[2] and Jordi Carratalà[1]

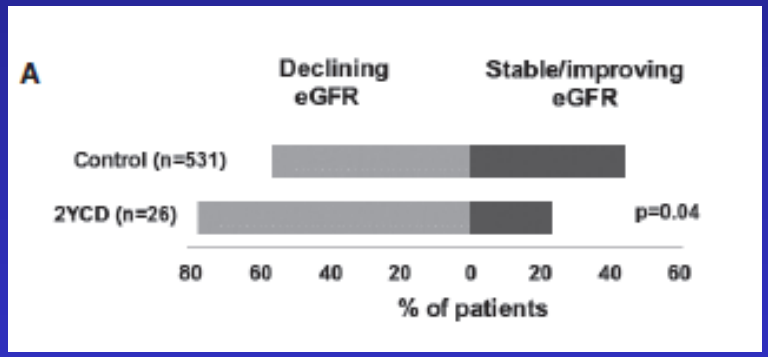
Risk Factors, Clinical Characteristics, and Outcome of *Nocardia* Infection in Organ Transplant Recipients: A Matched Case-Control Study

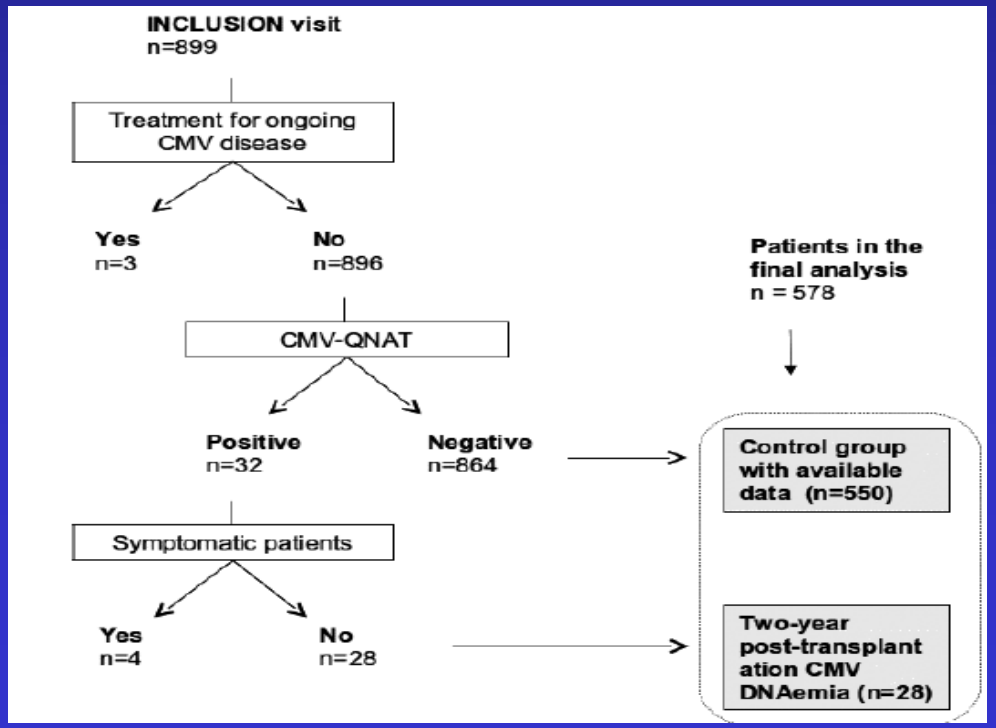
Anton Y. Peleg,[1] Shahid Husain,[2] Zubair A. Qureshi,[2] Fernanda P. Silveira,[2] Molade Sarumi,[2] Kathleen A. Shutt,[2] Eun J. Kwak,[2] and David L. Paterson[2]

# CMV infection/disease is a risk factor for developing post-transplant complications

**Risk factors of 2-year post-transplantation cytomegalovirus (CMV) DNAemia at the inclusion visit**

| Factor | Univariate analysis Odds ratio (95% confidence interval) | *P*-value | Multivariate analysis Odds ratio (95% confidence interval) | *P*-value |
|---|---|---|---|---|
| Female vs. male | 2.81 (1.30–6.30) | 0.008 | 2.57 (1.17–5.84) | 0.02 |
| Past history of *UL97/UL54* CMV mutation | 11.29 (2.86–38.59) | 0.001 | 8.73 (2.09–31.85) | 0.005 |
| Corticosteroid | 2.65 (1.17–5.82) | 0.01 | 2.37 (1.07–5.52) | 0.03 |




Viot B. et al. Two years post-transplantation CMV DNAemia in asymptomatic kidney transplant recipients: incidence, risk factors, and outcome. Transpl Infect Dis. 2015; 17: 497-509

# Citomegalovirus

**Factores de riesgo de ICMV:**

D+/R-, edad del donante, tto con CsA y/o Ac antilinfocítarios, episodios de rechazo, disfunción del injerto, linfopenia, hipogammaglobulinemia

**Estratégias preventivas**:

Terapia anticipada,

Profilaxis universal durante 3 a 6 meses o 1 a 3 meses tras tto con Ac antilinfocitarios

Tratamiento inmunosupresor (inhibidores de la rapamicina, …)

***Kristel De Keyzer, MD,*** **Human Cytomegalovirus and Kidney Transplantation: A Clinician's Update.** ***Am J Kidney Dis.*** **58(1):118-126. Marcelin JR, Beam E, Razonable RR. Citomegalovirus infection in liver transplant recipients: Updates on clinical management. World J Gastroenterol 2014; 20: 10658-67**

# Pre-transplant lymphocyte count predicts the incidence of infection during the first two years after liver transplantation

Fernández-Ruiz M, et al. Liver Transpl 2009;15:1209-16

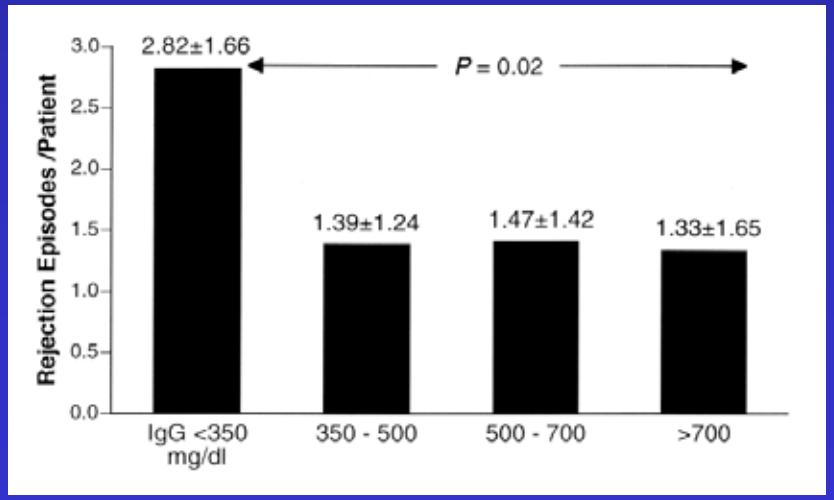
| Lymphocyte Subset ($10^3$/L) | No infection (n=28) | Any infection (n=35) | p |
|---|---|---|---|
| Total lymphocytes | 1.300 (0.97–1.70) | 0.870 (0.57–1.32) | 0.01 |
| $CD3^+$ T cells | 0.868 (0.70–1.22) | 0.557 (0.36–0.97) | 0.006 |
| $CD4^+$ T cells | 0.594 (0.47–0.83) | 0.364 (0.23–0.59) | 0.004 |
| $CD8^+$ T cells | 0.224 (0.12–0.39) | 0.138 (0.08–0.26) | NS |

| Variable | aOR | 95% CI |
|---|---|---|
| Peritransplant fresh frozen plasma requirements > 11 | 5.9 | 1.2–27.7 |
| Acute graft rejection | 4.8 | 0.9–25.0 |
| Pre-OLT total lymphocyte count <1.000 cells/$mm^3$ | 10.1 | 1.9–39.5 |

# Hypogammaglobulinaemia and opportunistic infection after transplantation

Yamani MH, et al. J Heart Lung Transplant 2001;20:425–430

| Event | <350 | 350-500 | 501-700 | >700 | p |
|---|---|---|---|---|---|
| n (%) | 11 (10%) | 18 (16%) | 34 (31%) | 48 (43%) | |
| Mean IgG level (mg/dl) | 217 | 414 | 599 | 908 | |
| CMV viremia | 7 (64%) | 5 (28%) | 7 (21%) | 22 (46%) | 0.02 |
| Clinically-relevant infection: | | | | | |
| § Opportunistic | 6 (55%) | 0 | 1 (3%) | 4 (8%) | <0.001 |
| § Non-opportunistic | 1 (9%) | 1 (6%) | 3 (9%) | 7 (15%) | 0.67 |



# Citomegalovirus

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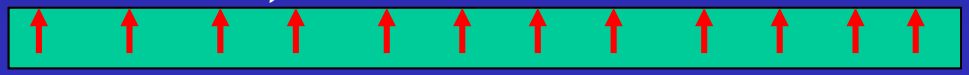
***Kristel De Keyzer, MD,*** **Human Cytomegalovirus and Kidney Transplantation: A Clinician's Update.** ***Am J Kidney Dis.*** **58(1):118-126. Marcelin JR, Beam E, Razonable RR. Citomegalovirus infection in liver transplant recipients: Updates on clinical management. World J Gastroenterol 2014; 20: 10658-67**

# Citomegalovirus

## Profilaxis, tratamiento anticipado , pauta secuencial

Profilaxis 90-100 días

Tratamiento anticipado tras monitorización semanal (CV o pp65Ag del CMV) durante 3 meses

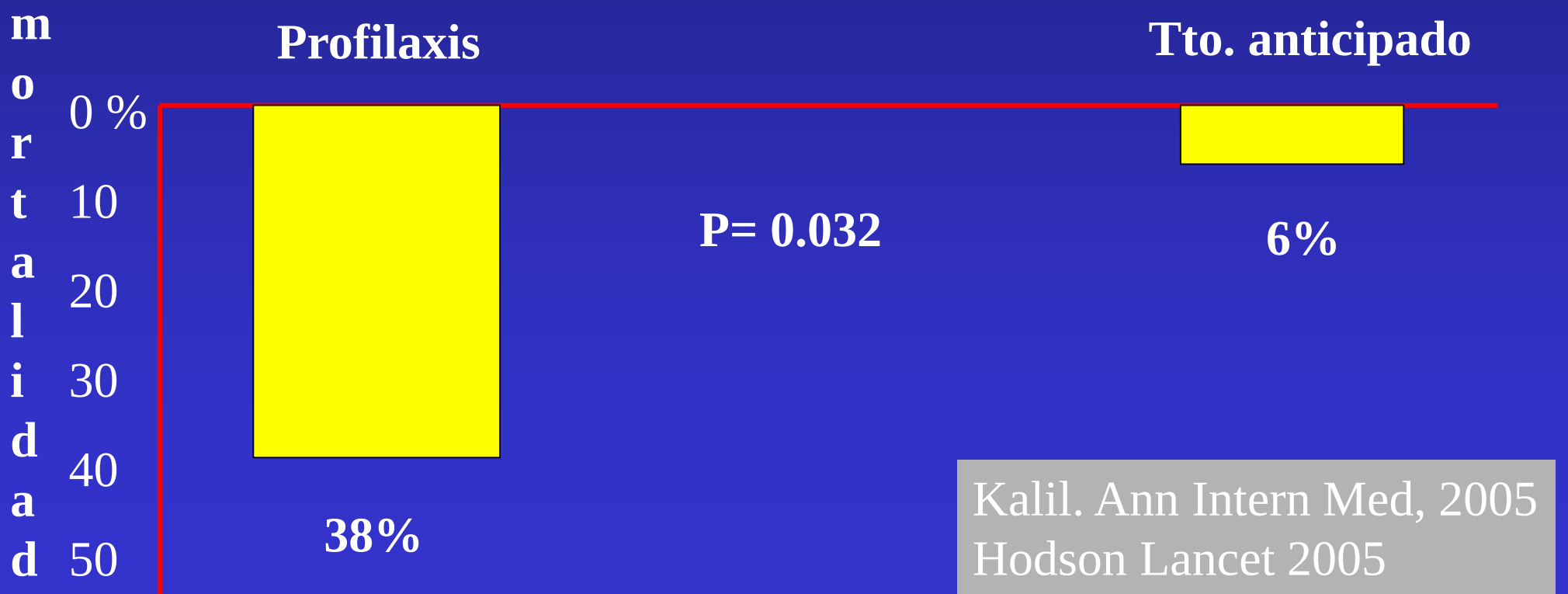


Profilaxis más monitorización

Trasplante 0 1 2 3 4 5 6 meses

# Citomegalovirus

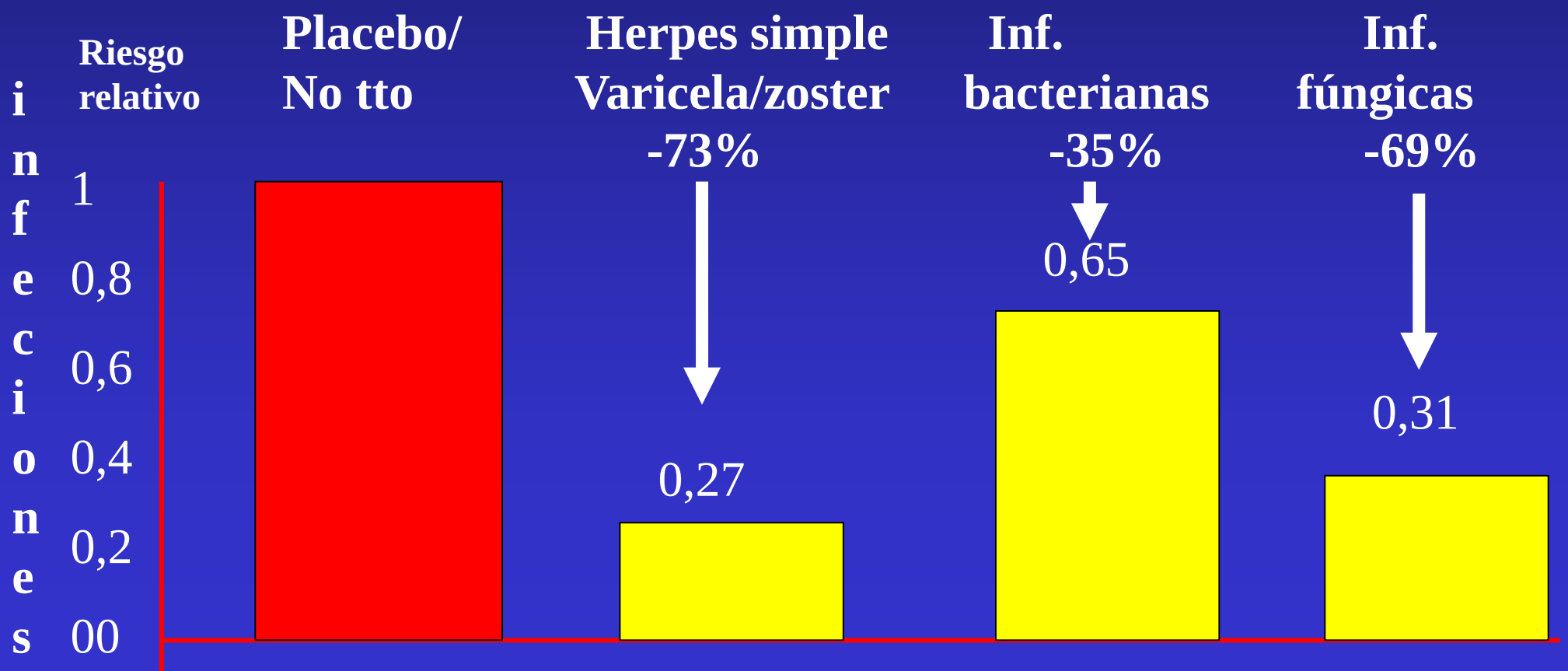
## Reducción de la mortalidad
## Profilaxis vs. Terapia anticipada




Kalil. Ann Intern Med, 2005
Hodson Lancet 2005

# Citomegalovirus

## Efecto de la profilaxis anti-CMV en infecciones concomitantes



# Citomegalovirus

**Efectos indirectos: Organo-específico**

- •Renal (disfunción aguda y crónica incrementada por VHH6 y VHH7)
  - •**Reducción (sobre todo la disfunción aguda) tras profilaxis para CMV**
- •Hepático (disfunción del injerto, cirrosis, retrasplante y muerte)
  - •Mayor agresividad de la recurrencia del VHC y la fibrosis (implicación del VHH6)
  - •**Reducción mediante profilaxis en recurrencia del VHC.**
- •Corazón (vasculopatía del injerto)
  - •**Prevención con profilaxis**
- •Pulmón (CMV y D+/R-) se asocia con bronquiolitis obliterante, infección y muerte.
  - •**Reducción mediante profilaxis**

# Citomegalovirus

**Relación con el tratamiento inmunosupresor**

**Coinfección viral**

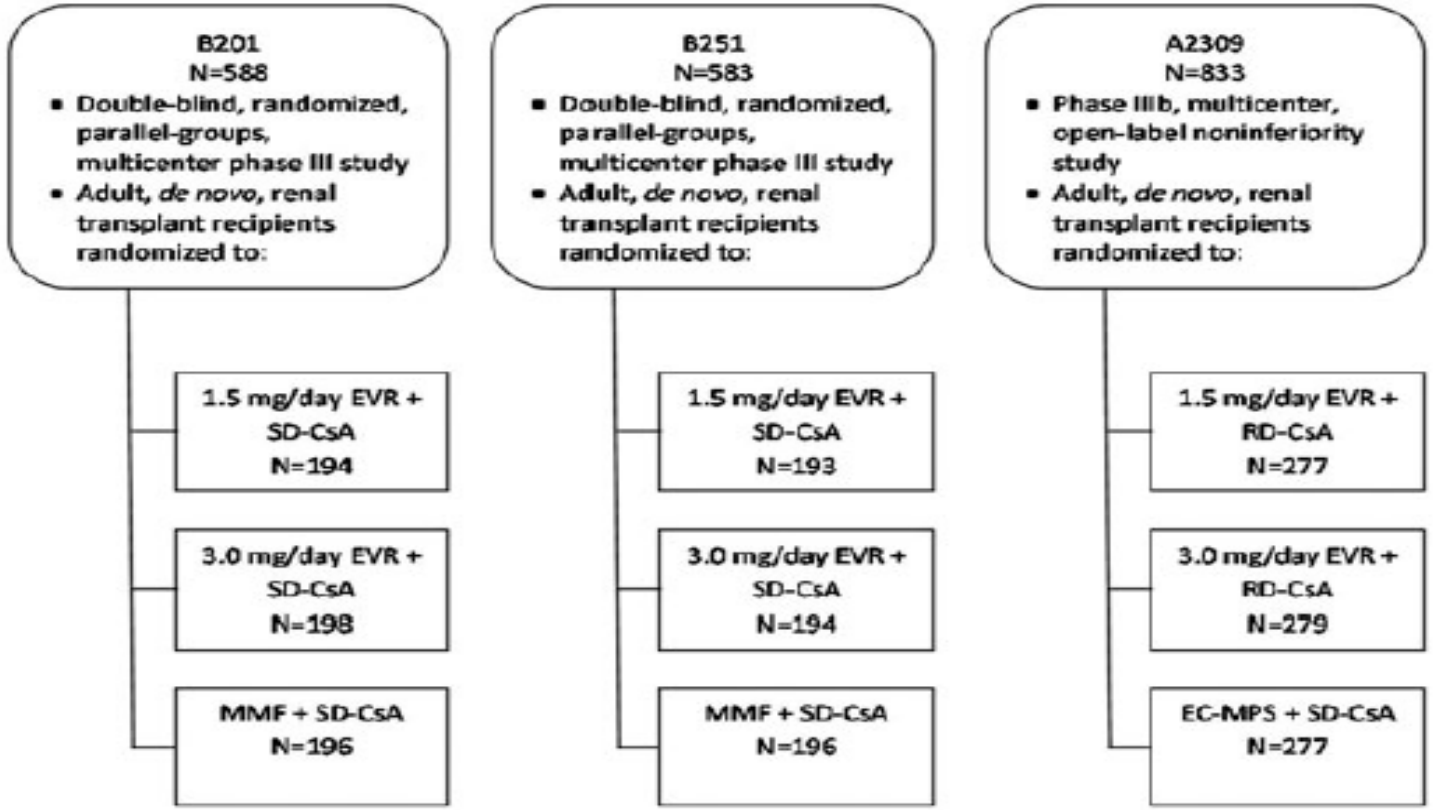
**Riesgo de mortalidad y pérdida del injerto**

**Profilaxis vs, tratamiento anticipado**

**Resistencias**

# Cytomegalovirus Incidence Between Everolimus Versus Mycophenolate in De Novo Renal Transplants: Pooled Analysis of Three Clinical Trials

***D. C. Brennan***, *American Journal of Transplantation 2011; 11: 2453–2462*




SD: Standard Dose; RD: Reduced Dose; EVR: Everolimus; CsA: Cyclosporine; MMF: Mycophenolate Mofetil; EC-MPS: Enteric Coated-Mycophenolate Sodium. Studies B201 & B251 employed fixed dose EVR, A2309 used concentration controlled EVR. In study A2309 all patients received basiliximab induction therapy. In all three studies, corticosteroids were administered according to local practice

**Figure 1: Description of the study designs of the three trials from which data were pooled for the present analysis.**

Nº total de pacientes incluidos: 2004

**Table 2:** Incidence of CMV events by 1 year post-transplantation by CMV prophylaxis

| | Everolimus 1.5 mg/day N = 319 | Everolimus 3.0 mg/day N = 323 | MPA N = 318 |
|---|---|---|---|
| No prophylaxis | | | |
| CMV infection/syndrome, n (%) | 16 (5.0)** | 14 (4.3)** | 44 (13.8) |
| CMV viremia, n (%) | 10 (3.1)# | 10 (3.1)# | 29 (9.1) |
| CMV with organ involvement, n (%) | 8 (2.5) | 3 (0.9) | 4 (1.3) |
| | **Everolimus 1.5 mg/day N = 345** | **Everolimus 3.0 mg/day N = 348** | **MPA N = 351** |
| Prophylaxis | | | |
| CMV infection/syndrome, n (%) | 21 (6.1)* | 21 (6.0)* | 37 (10.5) |
| CMV viremia, n (%) | 18 (5.2) | 9 (2.6)* | 23 (6.6) |
| CMV with organ involvement, n (%) | 3 (0.9)* | 7 (2.0) | 12 (3.4) |

**$p < 0.0001$ versus MPA; #$p \leq 0.0016$ versus MPA; *$p < 0.04$ versus MPA.

**Table 3:** Incidence of CMV infection or syndrome by D/R CMV serostatus

| Donor/recipient CMV serostatus | Everolimus 1.5 mg/day | Everolimus 3 mg/day | MPA |
|---|---|---|---|
| N | 105 | 105 | 107 |
| D+/R−, n (%) | 17 (16.2%) | 19 (18.1%) | 27 (25.2%) |
| N | 286 | 298 | 276 |
| D+/R+, n (%) | 14 (4.9%)^ | 10 (3.4%)* | 33 (12.0) |
| N | 101 | 119 | 119 |
| D−/R+, n (%) | 3 (3.0%) | 1 (0.8%)** | 8 (6.7%) |
| N | 143 | 116 | 139 |
| D−/R−, n (%) | 1 (0.7%) | 2 (1.7%) | 6 (4.3%) |

^$p = 0.0034$ versus MPA; *$p < 0.001$ versus MPA; **$p = 0.036$ versus MPA.

**Estos tres estudios demuestran una reducción en la incidencia de la infección y enfermedad por CMV en trasplantados renales en tratamiento inmunosupresor con EVEROLIMUS vs. ACIDO MICOFENOLICO, fundamentalmente en el grupo que no recibieron profilaxis para CMV**

*D. C. Brennan, American Journal of Transplantation 2011; 11: 2453–2462*

Transplant Infectious Disease. ISSN 1398-2273

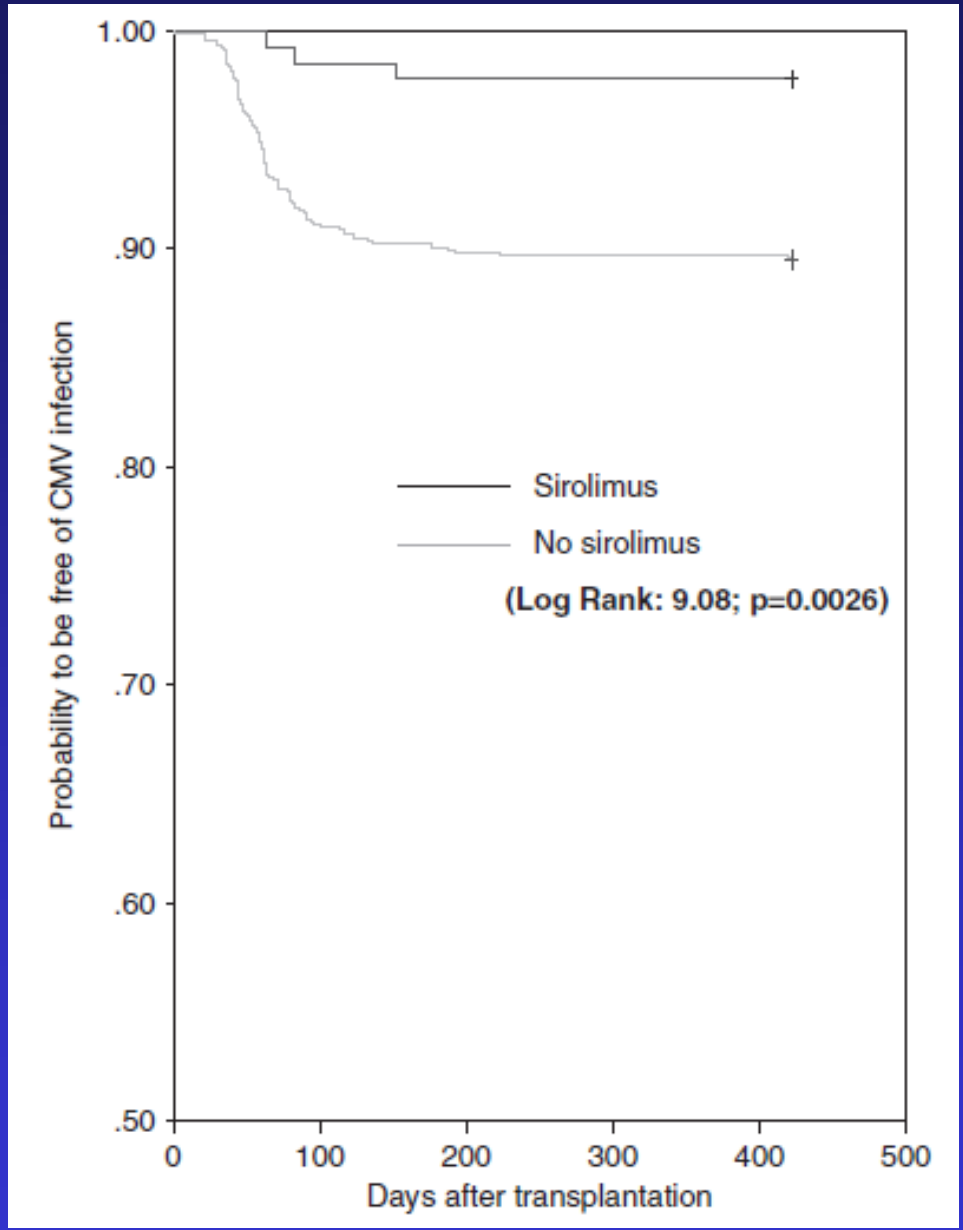
# Immunosuppressive therapy and infection after kidney transplantation

J. Fortun, P. Martin-Davila, J. Pascual, C. Cervera, A. Moreno, J. Gavalda, J.M. Aguado, P. Pereira, M. Gurguí, J. Carratala, M. Fogueda, M. Montejo, F. Blasco, G. Bou, J. Torre-Cisneros; RESITRA Transplant Network. Immunosuppressive therapy and infection after kidney transplantation.
Transpl Infect Dis 2010. 

J. Fortun[1], P. Martin-Davila[1], J. Pascual[1], C. Cervera[2], A. Moreno[2], J. Gavalda[3], J.M. Aguado[4], P. Pereira[5], M. Gurguí[6], J. Carratala[7], M. Fogueda[8], M. Montejo[9], F. Blasco[10], G. Bou[11], J. Torre-Cisneros[12], RESITRA Transplant Network

**Frequency of infections and pathogens observed in kidney recipients**

| Infection | Number (%) (Total number of patients = 1398) |
|---|---|
| Cytomegalovirus infection | 134 (9.6) |
| Cytomegalovirus disease | 85 (6.1) |
| Bacteria | |
| Bacteremia | 110 (7.9) |
| Urinary infections | 64 (4.6) |
| Pneumonia | 45 (3.2) |
| Surgical site infection | 36 (2.6) |
| Other | 26 (1.8) |
| *Candida* species | 5 (0.4) |
| Herpes simplex virus | 4 (0.3) |
| Parvovirus B-19 | 2 (0.1) |
| *Mycobacterium tuberculosis* | 2 (0.1) |



**Principal differences between patients receiving and not receiving sirolimus (univariate analysis; $n = 946$)[1]**

| | No sirolimus ($n = 813$), % | Sirolimus ($n = 133$), % | *P* |
|---|---|---|---|
| Thymoglobulin induction | 4.1 | 14.3 | **<0.01** |
| Basiliximab/daclizumab induction | 15.3 | 27.8 | **<0.01** |
| Donor age >50 years | 45.9 | 69.6 | **<0.01** |
| Recipient age >60 years | 21.8 | 47.4 | **<0.01** |
| CMV recipient −/donor + | 9.8 | 7.8 | NS |
| Acute rejection | 34 | 38 | NS |
| Diabetes | 11.6 | 9.8 | NS |
| Prophylaxis CMV (primary or preemptive) | 18.9 | 22.6 | NS |
| CMV infection | 10.6 | 2.3 | **<0.01** |
| CMV disease | 5.7 | 3.0 | NS |
| Bacteremia | 7.1 | 7.5 | NS |
| Urinary infection | 4.7 | 4.5 | NS |
| Pneumonia | 2.7 | 3.0 | NS |
| Surgical site infection | 1.8 | 5.3 | **0.02** |

[1]Patients receiving an investigational new drug for maintenance were excluded.
NS, not significant; CMV, cytomegalovirus. Boldface indicates statistical significance.

# Citomegalovirus

**Relación con el tratamiento inmunosupresor**

**Coinfección viral**

**Riesgo de mortalidad y pérdida del injerto**

**Profilaxis vs, tratamiento anticipado**

**Resistencias**

# Association of Cytomegalovirus Infection and Disease With Recurrent Hepatitis C After Liver Transplantation

***Wendelyn Bosch**, Transplantation* 2012;93: 723–728

**Pacientes incluidos con trasplante hepático : 347**

**D+/R- CMV: 78 (22%). Profilaxis VALG: 94%**
**ICMV: 111 (32%) (38% D+/R-)**
**ECMV: 24 (7%) (18% D+/R-)**

**Biopsia hepática**
**Inflamación ≥ 2: 221 (64%)**
**Fibrosis ≥ 2: 140 (40%)**

**TABLE 3.** Evaluation of associations of CMV infection and CMV disease with outcomes

| Association | Single variable analysis RR (95% CI) | *P* | Multivariable analysis RR (95% CI) | *P* |
|---|---|---|---|---|
| CMV infection with | | | | |
| Grade ≥2 inflammation | 1.28 (0.94–1.73) | 0.12 | 1.12 (0.80–1.58) | 0.50 |
| Stage ≥2 fibrosis | 1.49 (1.05–2.13) | 0.027 | 1.52 (1.03–2.24) | 0.033 |
| Graft loss or death | 1.68 (1.08–2.61) | 0.023 | 1.46 (0.90–2.37) | 0.13 |
| CMV disease with | | | | |
| Grade ≥2 inflammation | 2.17 (1.24–3.82) | 0.007 | 3.40 (1.83–6.30) | <0.001 |
| Stage ≥2 fibrosis | 1.52 (0.77–3.01) | 0.23 | 2.03 (0.99–4.14) | 0.052 |
| Graft loss or death | 2.69 (1.34–5.41) | 0.005 | 1.91 (0.91–4.03) | 0.087 |

**Estudio con 347 trasplantados hepáticos por VHC seropositivos para CMV. Se demuestra progresión de la recurrencia del VHC postrasplante por la ECMV y un aumento de la gravedad (grado de fibrosis por la ICMV y ECMV)**

# Citomegalovirus

**Relación con el tratamiento inmunosupresor**

**Coinfección viral**

**Riesgo de mortalidad y pérdida del injerto**

**Profilaxis vs, tratamiento anticipado**

**Resistencias**

# Association of Cytomegalovirus Infection and Disease With Death and Graft Loss After Liver Transplant in High-Risk Recipients

***W. Bosch**. American Journal of Transplantation 2011; 11: 2181–2189*

**227 pacientes con Tx hepático D+/R- CMV**
**Profilaxis con GAN/VALG durante 100 días**
**ICMV: 91 (40%)  ECMV: 43 (19%).**
**48 (21%) fallecen**
**10 (5%) pérdida del injerto**
**58 (26%) exitus o pérdida injerto**

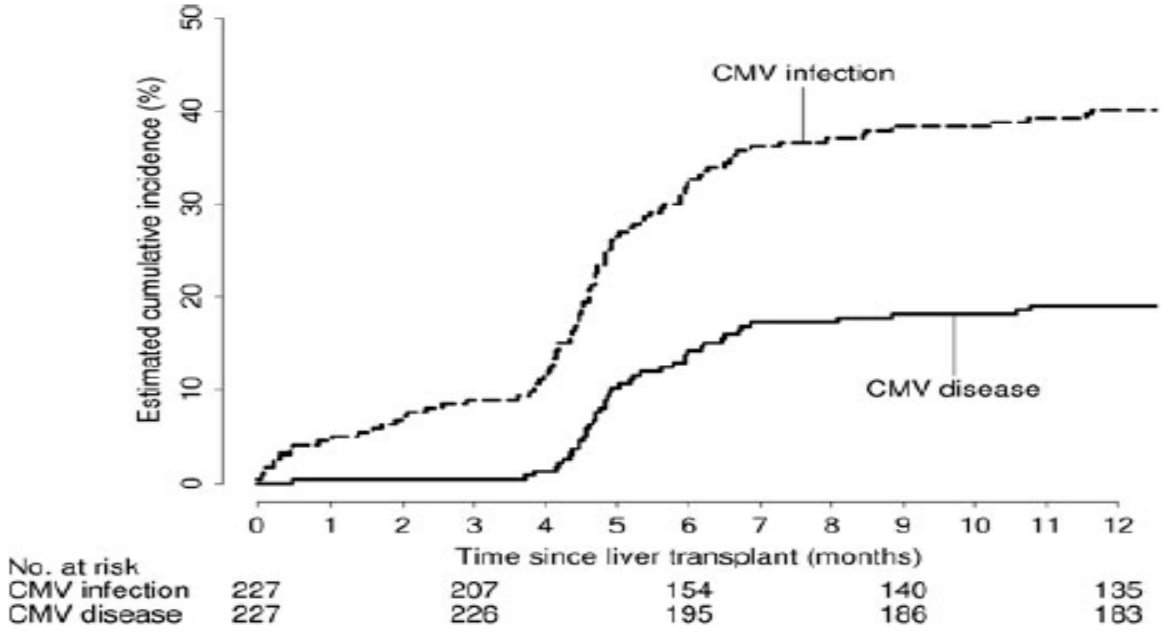



**Figure 1: Estimated cumulative incidence of CMV infection and CMV disease after liver transplant.**

# Association of Cytomegalovirus Infection and Disease With Death and Graft Loss After Liver Transplant in High-Risk Recipients

***W. Bosch**. American Journal of Transplantation 2011; 11: 2181–2189*

**Table 3**: Associations of CMV infection and CMV disease within 1 year of liver transplant with death and graft loss or death occurring at any time after liver transplant.

| | Single variable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| Association | RR (95% CI) | p-Value | RR (95% CI) | p-Value |
| CMV infection with: | | | | |
| Death | 2.42 (1.34, 4.39) | 0.004 | 2.24 (1.24, 4.05) | 0.008 |
| Graft loss or death | 2.92 (1.64, 5.18) | <0.001 | 2.85 (1.62, 5.01) | <0.001 |
| CMV disease with: | | | | |
| Death | 2.60 (1.34, 5.05) | 0.005 | 2.73 (1.40, 5.34) | 0.003 |
| Graft loss or death | 2.91 (1.52, 5.59) | 0.001 | 3.04 (1.56, 5.92) | 0.001 |

Relative risks and p-values result from the Cox proportional hazards models

**La infección tardía por CMV en pacientes de riesgo (D+/R-) cursa con aumento de la mortalidad y pérdida del injerto hepático (sobre todo entre el 3º y 6º mes postrasplante) . Los autores consideran que debería prolongarse la profilaxis hasta el 6º mes en pacientes de riesgo**

# Citomegalovirus

**Relación con el tratamiento inmunosupresor**

**Coinfección viral**

**Riesgo de mortalidad y pérdida del injerto**

**Profilaxis vs, tratamiento anticipado**

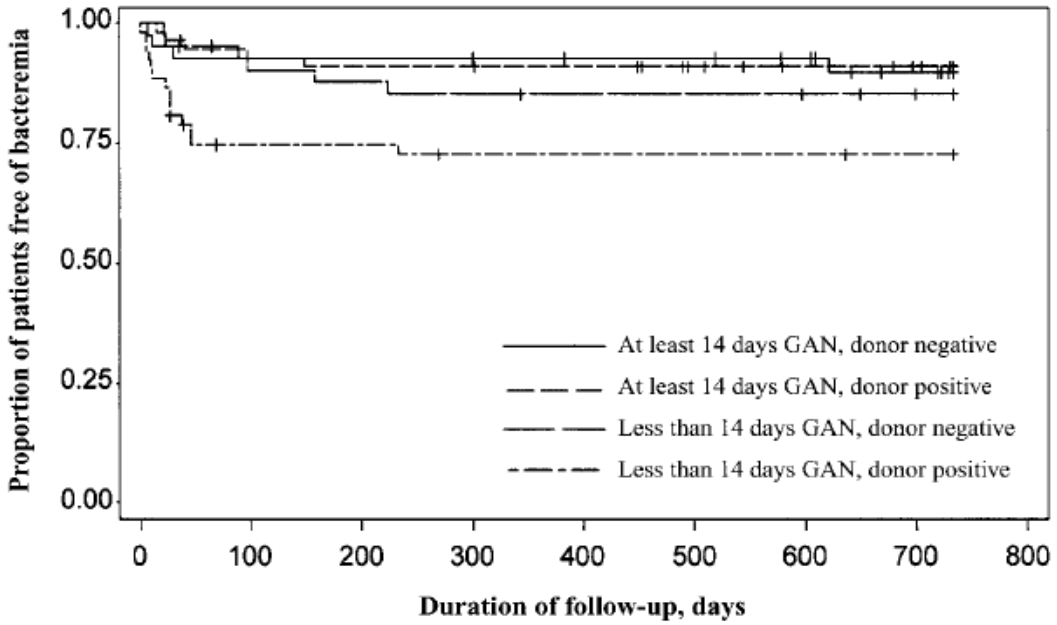
**Resistencias**

# Studies on GCV and bacteremia in liver transplant

## The Clinical Impact of Ganciclovir Prophylaxis on the Occurrence of Bacteremia in Orthotopic Liver Transplant Recipients

**L. Silvia Munoz-Price,[1,4] Michelle Slifkin,[1,4] Robin Ruthazer,[3] Debra D. Poutsiaka,[1,4] Susan Hadley,[1,4] Richard Freeman,[2,5] Richard Rohrer,[2,5] Michael Angelis,[2,5] Jeffrey Cooper,[2,5] Ralph Fairchild,[1] Laurie Barefoot,[1] Judy Bloom,[2] Susan Fitzmaurice,[2] and David R. Snydman[1,4]**

Divisions of [1]Geographic Medicine and Infectious Diseases and [2]Transplantation, [3]Institute for Clinical Research and Health Policy Studies, and Departments of [4]Medicine and [5]Surgery, Tufts–New England Medical Center and Tufts University, Boston, Massachusetts

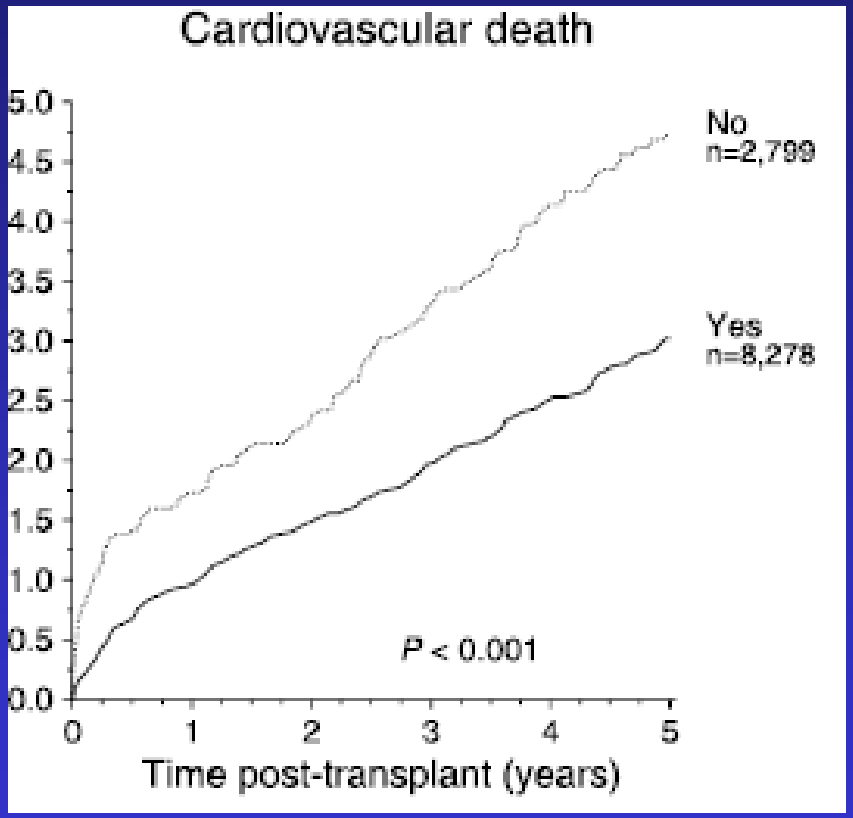


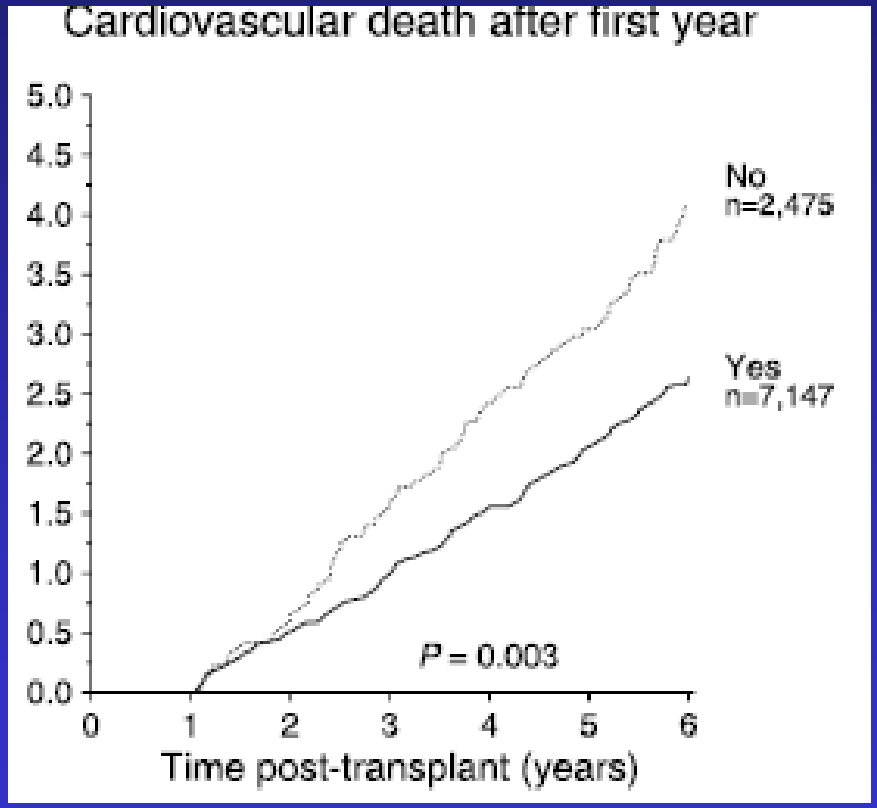

Clinical Infectious Diseases 2004;39:1293-9

# Reduced Rate of Cardiovascular Death After Cytomegalovirus Prophylaxis in Renal Transplant Recipients

Gerhard Opelz and Bernd Döhler

(*Transplantation* 2015;99: 1197–1202)



# Updated International Consensus Guidelines on the Management of Cytomegalovirus in Solid-Organ Transplantation

*Camille N. Kotton,[1,8] Deepali Kumar,[2] Angela M. Caliendo,[3] Anders Åsberg,[4] Sunwen Chou,[5] Lara Danziger-Isakov,[6] and Atul Humar,[7] on behalf of The Transplantation Society International CMV Consensus Group*

*Transplantation* 2013;96: 00–00

**TABLE 5.** Comparison of prophylaxis versus preemptive therapy

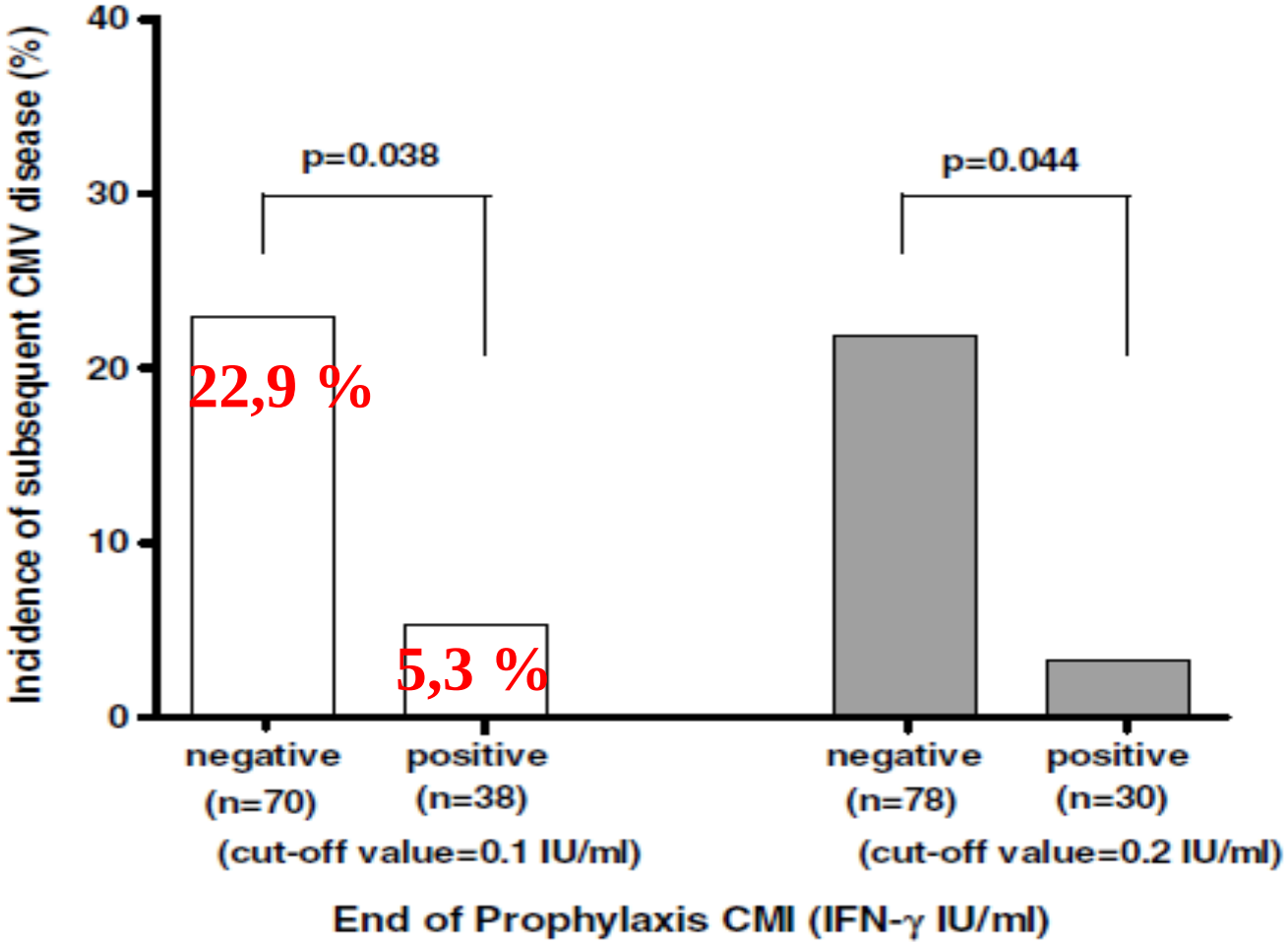
| | Prophylaxis | Preemptive therapy |
|---|---|---|
| Early CMV DNAemia | Rare | Common |
| Prevention of CMV disease | Good efficacy | Good efficacy (less optimal in high-risk populations) |
| Late CMV (infection/disease) | Common | Rare |
| Resistance | Uncommon | Uncommon |
| Ease of implementation | Relatively easy | More difficult |
| Other herpes viruses | Prevents HSV, VZV | Does not prevent |
| Other opportunistic infections | May prevent | Unknown |
| Cost | Drug costs | Monitoring costs |
| Safety | Drug side effects | Less drug toxicity |
| Prevention of rejection | May prevent | Unknown |
| Graft survival | May improve | May improve |

American Journal of Transplantation 2009; 9: 1214–1222
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2009.02618.x

# Kumar et al. AJT 2009

## Cell-Mediated Immunity to Predict Cytomegalovirus Disease in High-Risk Solid Organ Transplant Recipients




**CD8 + CMI se analizó usando QuantiFERON -CMV**

**Figure 3: Cell-mediated immunity (CMI) at the end of prophylaxis and the prediction of subsequent CMV disease** (the time point closest to discontinuation of prophylaxis was used to analyze predictive value; in patients on indefinite prophylaxis, the 3-month time point was used).



Oriol Manuel. . Clin Infect Dis 2013; 56:817-24

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*Transplantation* 2013;96: 00–00

**TABLE 4.** Potential clinical scenarios for the use of immune-based assays

| Clinical scenarios | Assays studied | Potential clinical management[a] |
|---|---|---|
| CMV D+/R- and R+ at the end of prophylaxis | QFT, ELISpot, ICS | For negative assay, prolong prophylaxis; for positive assay, no further prophylaxis |
| CMV D+/R- and R+ during preemptive strategy | QFT, ELISpot, ICS | Result may help guide frequency of viral load monitoring and thresholds for initiating antiviral therapy |
| Posttherapy for acute rejection | ICS (small number, not predictive) | For negative assay, restart prophylaxis or viral load monitoring; for positive assay, no further intervention |
| Recent completion of therapy for CMV disease or viremia (prediction of relapse) | No studies | For negative assay, secondary prophylaxis; for positive assay, no further therapy |
| Risk stratification in patients before transplantation | ICS, QFT | For positive assay, assume true positive CMV status |

[a] No formal studies of clinical management have been published to date.
QFT, QuantiFERON-CMV.

# Citomegalovirus

**Relación con el tratamiento inmunosupresor**

**Coinfección viral**

**Riesgo de mortalidad y pérdida del injerto**

**Profilaxis vs, tratamiento anticipado**

**Resistencias**

# Citomegalovirus

## Profilaxis vs. tratamiento anticipado en D+/R-

| CMV | Profilaxis N=32 | Tto.anticipado N=80 | p |
|---|---|---|---|
| Infección CMV | 11 (34%) | 40 (50%) | 0.02 |
| ECMV | 5 (16%) | 21 (26%) | 0.3 |
| Infección tardía | 9 (28%) | 6 (8%) | 0.003 |
| CV (log 10 copias/ml) | 4.2 ±1.1 | 5 ± 1 | 0.06 |
| Resistencia CMV | 1 (3%) | 13 (16%) | 0.05 |
| Recurrencia CMV | 3 (9%) | 18 (23%) | 0.1 |

Couzi. AJT 2011

# High Incidence of Anticytomegalovirus Drug Resistance Among D+R- Kidney Transplant Recipients Receiving Preemptive Therapy

***L. Couzi*** *American Journal of Transplantation 2012; 12: 202–209*

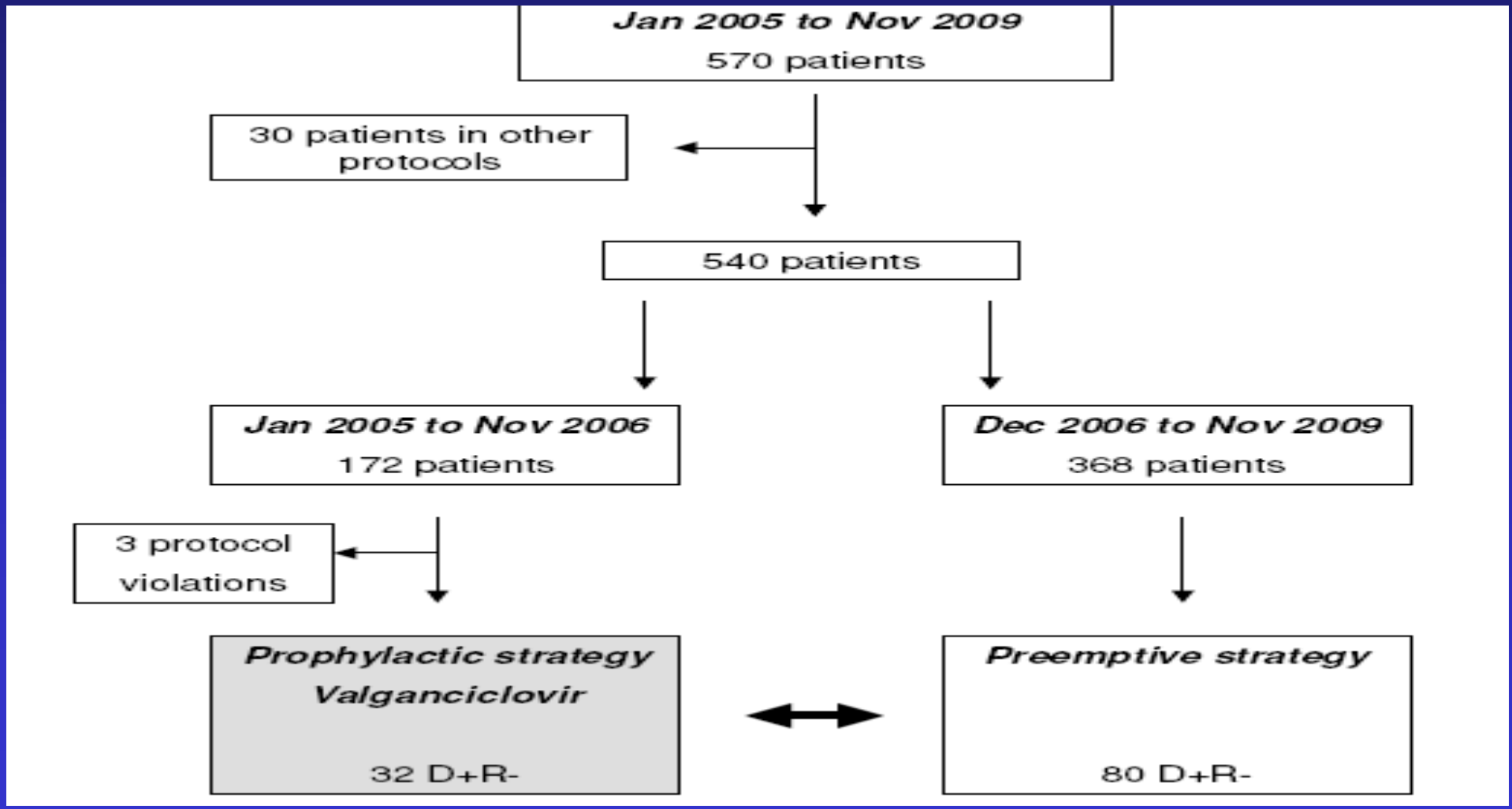


**Table 2:** Direct effects of CMV and anti-CMV treatment

| | D+R− | | |
|---|---|---|---|
| | Prophylactic (n = 32) | Preemptive (n = 80) | p-Value |
| CMV infection (%) | 11 (34) | 48 (60) | 0.02 |
| CMV disease (%) | 5 (16) | 21 (26) | 0.3 |
| Time of CMV infection (median, days) | 132 [56–206] | 33 [16–256] | 0.002 |
| Late-onset infection (%) | 9 (28) | 6 (8) | 0.003 |
| Baseline viral load (mean, $log_{10}$ copies/mL) | 4.3 ± 1.6 | 3.7 ± 1.1 | 0.5 |
| Peak viral load (mean, $log_{10}$ copies/mL) | 4.2 ± 1.1 | 5.0 ± 1.0 | 0.06 |
| Prophylaxis: valganciclovir for 3 months | 32 (100) | 0 (0) | |
| Initial anti-CMV therapy for CMV infection (curative not prophylactic) | | | |
| Valganciclovir (%) | 1 (3) | 31 (39) | 0.0002 |
| IV ganciclovir (%) | 7 (22) | 17 (21) | 0.9 |
| Agranulocytosis (%) | 6 (18) | 16 (20) | 0.9 |
| Treatment failure (%) | 1 (3) | 25 (31) | 0.001 |
| Anti-CMV drug resistance (%) | 1 (3) | 13 (16) | 0.05 |
| Recurrent CMV (%) | 3 (9) | 18 (23) | 0.1 |

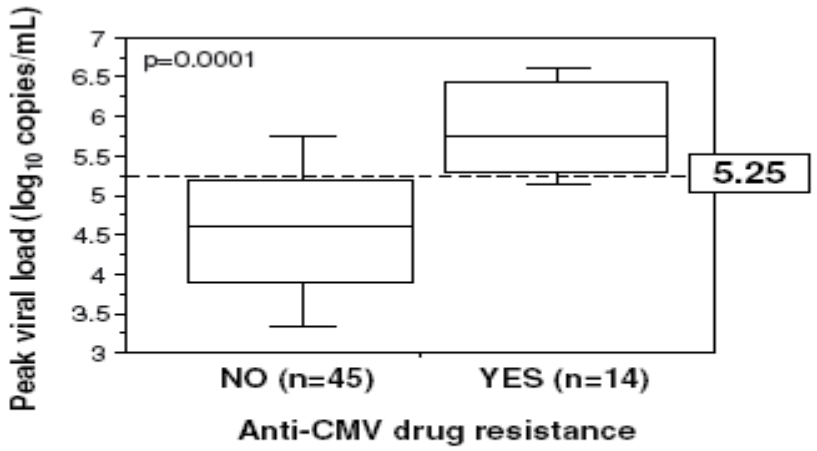



**Figure 3: Peak viral load and occurrence of anti-CMV drug resistance in the 59 D+R− kidney transplant recipients with a CMV infection/disease.**

**La terapia anticipada se asocia con una mayor incidencia de cepas resistentes de CMV en trasplantados renales D+/R-. Los pacientes con CV elevada (superior a 5,25 log) tienen un riesgo elevado de desarrollar resistencias (OR= 16,91, p=0.0008) y ocurre en pacientes que no responden al tratamiento antiviral (62% vs.23%, p=0.0001)**

*L. Couzi American Journal of Transplantation 2012; 12: 202–209*

# Citomegalovirus. Diagnóstico

**Table 1.** Summary of the clinical utility of quantitative cytomegalovirus nucleic acid tests

| Clinical utility | |
|---|---|
| Rapid diagnosis | |
| | Rapid turn-around time |
| | High sensitivity and specificity |
| | Allows early initiation of antiviral therapy |
| Preemptive therapy | |
| | Routine monitoring to guide the initiation of antiviral drugs for preemptive treatment of subclinical CMV infection |
| Prognosis | |
| | Higher viral loads correlates with symptomatic and more severe disease |
| Treatment response | |
| | Viral load decline correlates with clinical response to antiviral therapy |
| Disease recurrence | |
| | Failure to achieve an undetectable viral load, and suboptimal or slow decline in viral load correlates with a higher risk for disease relapse |
| Resistance | |
| | Lack of viral clearance or an increase in viral load during antiviral therapy should raise concerns for drug-resistant CMV disease |

CMV, cytomegalovirus.

Dioverti M.V., Razonable R.R. Clinical utility of citomegalovirus viral load in solid organ transplant recipients.Curr Opin Infect Dis. 2015; 28: 317-322

# What technique is recommended to perform genotypic studies about antiviral drug resistance? (DOC de CONSENSO)

- When resistance to antiviral drugs is suspected (in presence of progressive or stable viral loads or if clinical symptoms persist, despite adequate antiviral treatment at least after 2 weeks)

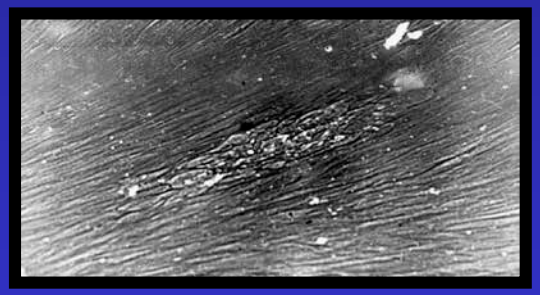
  The presence of resistance must be confirmed by phenotypic or genotypic methods .
- Clinical resistance is not necessarily accompanied by virological resistance
- In the first 2 weeks of treatment, are not recommended
- Genotypic testing has become the usual means, gen UL97 + UL54.

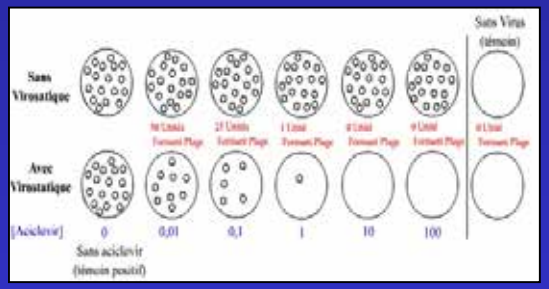
  Sample of choice is the plasma
- Interpretation of results from genotypic tests requires confirmation by phenotypic methods

# MÉTODOS MICROBIOLÓGICOS

1.- MET. FENOTÍPICOS (Método de reducción en placas)

- Cultivo de CMV. Laborioso, largo, falta estandarización.
- Concentraciones crecientes de antiviral-suspensión titulada CMV
- Miden la concentración antiviral necesaria para inhibir el 50% del crecimiento del virus . $CI_{50}$






Estudiar la sensibilidad “in vitro” a un antiviral

Caracterizar mutaciones no descritas

# MÉTODOS MICROBIOLÓGICOS

## 2.- MÉTODOS GENOTÍPICOS

- Detección de mutaciones genéticas asociadas a resistencia
  - UL97 k (400-670)
  - UL54 pol (300-1000)
- Método de elección.


- A partir de muestra directa. Mayor rapidez
- Es necesario diferenciar polimorfismos de mutaciones-resistencia
- Requiere caracterización fenotípica previa en mutaciones nuevas

*Lurain NS, Chou S. Clin Microb Rev 2010*

# Mutaciones de CMV en el HCB

| PACIEN -TE | ORGANO | PROFILAXIS | SEROLOGIA D/R | SOSPECHA | MUTACIÓN | Tiempo de trasplante | CARGA VIRAL | ESTRATEGIA | resolución |
|---|---|---|---|---|---|---|---|---|---|
| 29 | cardiaco | 3M | D+/R- | enfermedad | L595S (UL97) | 13 meses | 154.486 c/ml | aumento GCV | Si(OK) |
| 19 | riñón | 1M | D+/R+ | enfermedad | del 601-603(UL97) | 5 m | 11.234 c/ml | aumento GCV +POS+ everolimus | Si(OK) |
| 34 | pulmón | 12M | D+/R- | Profilaxis | H520Q(UL97) | 7 m | 33.772 C/ML | FOS+SIROLIMUS + dism.de inmunosupres | Si(OK) |
| 35 | pulmón | 12M | D+/R- | tto anticip | M460V(UL97)/ P522A (UL54) | 7m | 68.494 C/ML | FOS+SIROLIMUS+ dism.de inmunosupres | SI (OK) |
| 10 | hígado | NO | D+/R- | tto anticip | A594V | 2m | 9.300 c/ml | aumento GCV+ dism.de inmunosupres | rechazo |
| 30 | riñón | 3M | D+/R- | enfermedad | C592G(UL97) | 3 m | 11.605 C/ML | GCV + SIROLIMUS+ dism.de inmunosupres | SI (OK) |
| 36 | pulmón | 6M | D+/R- | tto anticip | L595S (UL97) | 7m | 38.700 C/ML | aumento GCV +FOS+ dism.de inmunosupres+EVEROLIMUS | Si(OK) |
| 38 | hígado | NO | D+/R- | enfermedad | M460V | 19m | 11.375 C/ML | aumento GCV. FOS | MUERTE |
| 41 | pulmón | 12M | D+/R- | tto anticip | M460I (UL97) D413N (UL54) | 21m | 2.800 C/ML | aumento GCV.FOS.Leflunomida | rechazo |

**FIS PI12/02131**
**“Emergencia de variantes de citomegalovirus portadoras de mutaciones asociadas a resistencia en trasplantados de órgano sólido”**
**De 35 pacientes con sospecha analizados, 9 presentaron mutaciones asociadas a resistencia.**

IP: Dra. Marcos

# Tratamiento de la infección/enfermedad por CMV resistente

**Sospecha de R:**

**1/ No evidencia por genotipado: mantener dosis de GAN o VAL (si leucopenia cambiar a FOS) + optimizar factores del huesped (disminuir tto inmunosupresor o cambiar a inhibidores del m-TOR).**

**2/ UL97 o UL54 +: Con bajos niveles de R, aumentar dosis de GAN o VAL. Con alta R a GAN, cambiar a FOS.**

**3/ Si persistencia de la CV (refractaria al tto), varias estrategias:**

- **Añadir CMV Ig .**
- **Maribavir (inhibidor benzimidazol L-ribosido del CMV UL97 kinasa) a dosis altas.**
- **Leflunomida o artesunato (poca experiencia)**
- **Otras opciones en fase II: Letermovir (inhibidor del CMV-UL54), CMX001 (derivado del Cidofovir)**


Kotton CN. Updated international Consensus Guidelines on the management of Cytomegalovirus in Solid Organ Transplantation. Transplantation 2013: 96:1-28

Chon WJ. et al. Use of Leflunomide in renal transplant recipients with ganciclovir resistant /refractory Citomegalovirus infection: A case series from the University of Chicago. Nephrology and Dialysis 2015; 5: 96-105

American Journal of Transplantation 2015; 15: 827–832
Wiley Periodicals Inc.



doi: 10.1111/ajt.13023

Case Report

# Adoptive T Cell Immunotherapy for Treatment of Ganciclovir-Resistant Cytomegalovirus Disease in a Renal Transplant Recipient

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**Cytomegalovirus (CMV) is a significant cause of morbidity, mortality and graft loss in solid organ transplantation (SOT). Treatment options for ganciclovir-resistant CMV are limited. We describe a case of ganciclovir-resistant CMV disease in a renal transplant recipient manifested by thrombotic microangiopathy-associated glomerulopathy. Adoptive T cell immunotherapy using CMV-specific T cells from a donor bank was used as salvage therapy. This report is a proof-of-concept of the clinical and logistical feasibility of this therapy in SOT recipients.**

include cidofovir and foscarnet but are limited due to possible cross-resistance in the case of cidofovir and issues of nephrotoxicity with both agents (1). In renal transplantation, this is particularly concerning due to the possibility of graft loss.

In summary, we have shown that ACT from a donor bank can be safely used to treat resistant CMV disease in an SOT recipient. The use of multiple therapeutic agents makes it difficult to attribute the observed response to ACT alone but disease progression was reversed only after its commencement. No significant toxic effects from ACT were observed. These findings suggest that novel techniques for generating virus-specific CTLs and the development of donor banks may make this a feasible future therapeutic option in SOT recipients and warrants further investigation.

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