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8° Congreso Argentino de Infectología Pediátrica
Sociedad Argentina de Pediatría

Terapia preventiva en el paciente con trasplante de órgano sólido(TOS)

Dr. Enrique V. Casanueva.
Jefe Sección Infectología Infantil
Hospital Universitario Austral

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Siglo IV y V a.C. Ganesha

300 dC
San Cosme y San Damian

París del siglo XIII

1954	• primer trasplante renal entre gemelos univitelinos
1958	• Boston, utilización de inmunosupresores en trasplante renal. La paciente murió a causa de las infecciones provocadas por la inmunosupresión....
1963	• Guy Alexandre en Lovaina :primer trasplante renal a partir de un cadáver en situación de "muerte cerebral" y con corazón latiente. El receptor falleció un mes más tarde por una septicemia.
1967	• Ciudad del Cabo, Christian Barnard realizó el primer trasplante cardíaco en el ser humano. Una neumonía bilateral provocará la muerte del receptor 14 días más tarde

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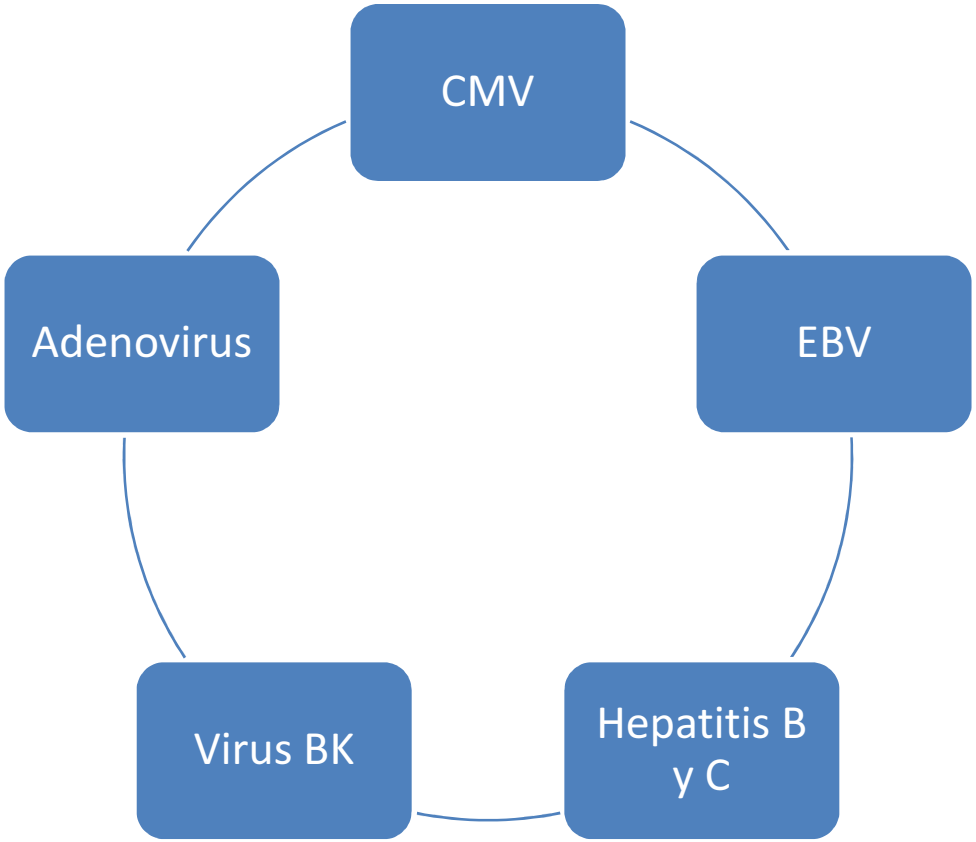
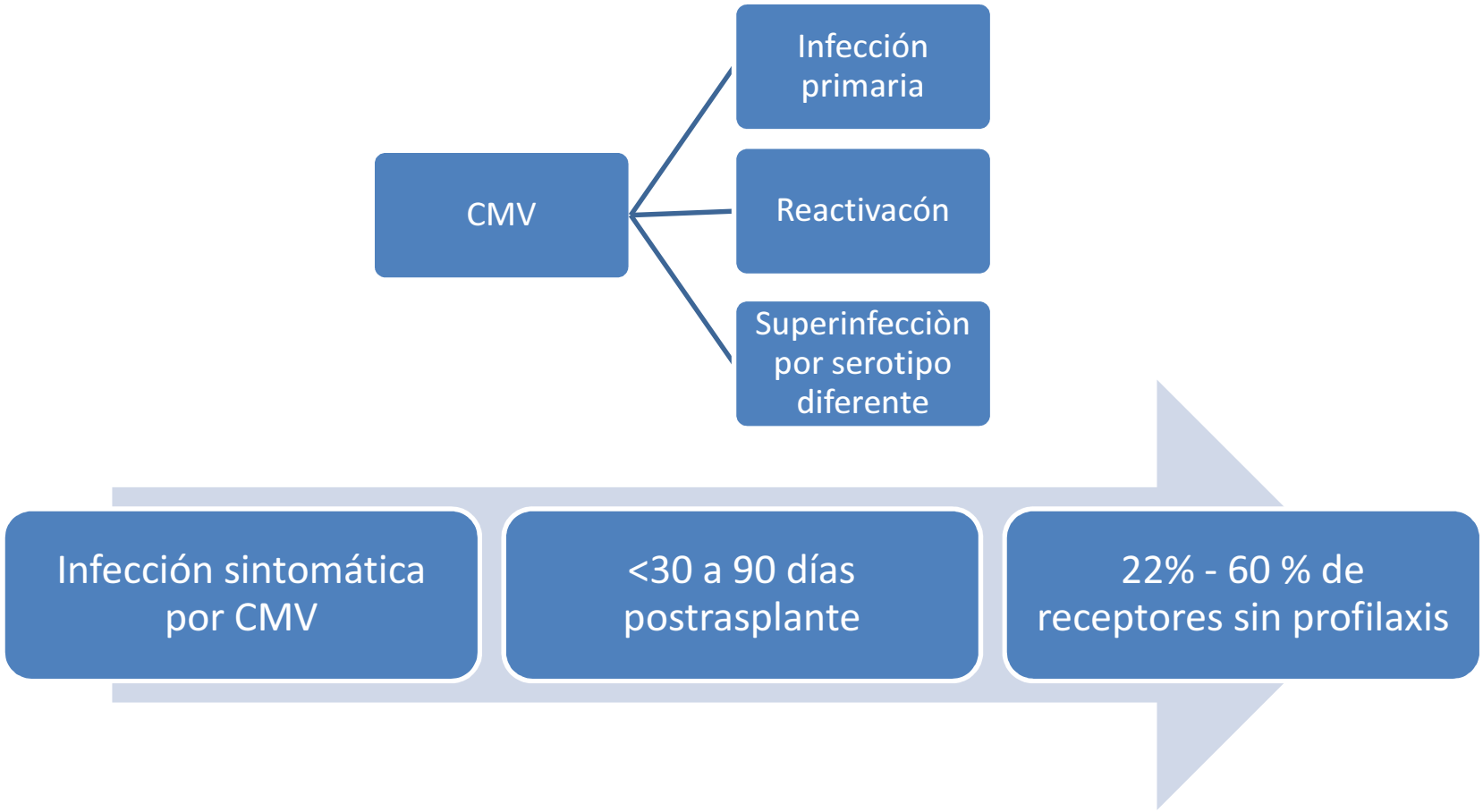
inmunosupresión

Infección

Trasplante

- Cuales son las infecciones más frecuentes de acuerdo a TOS?
- En que infecciones tengo métodos diagnósticos que me permiten evaluar con precisión una infección nueva o una reactivación?
- Cual es la evidencia científica que existe para la terapia preventiva
- Cual es la ventaja de la terapia preventiva?


CMV
EBV
Hepatitis B y C
Virus BK
Adenovirus



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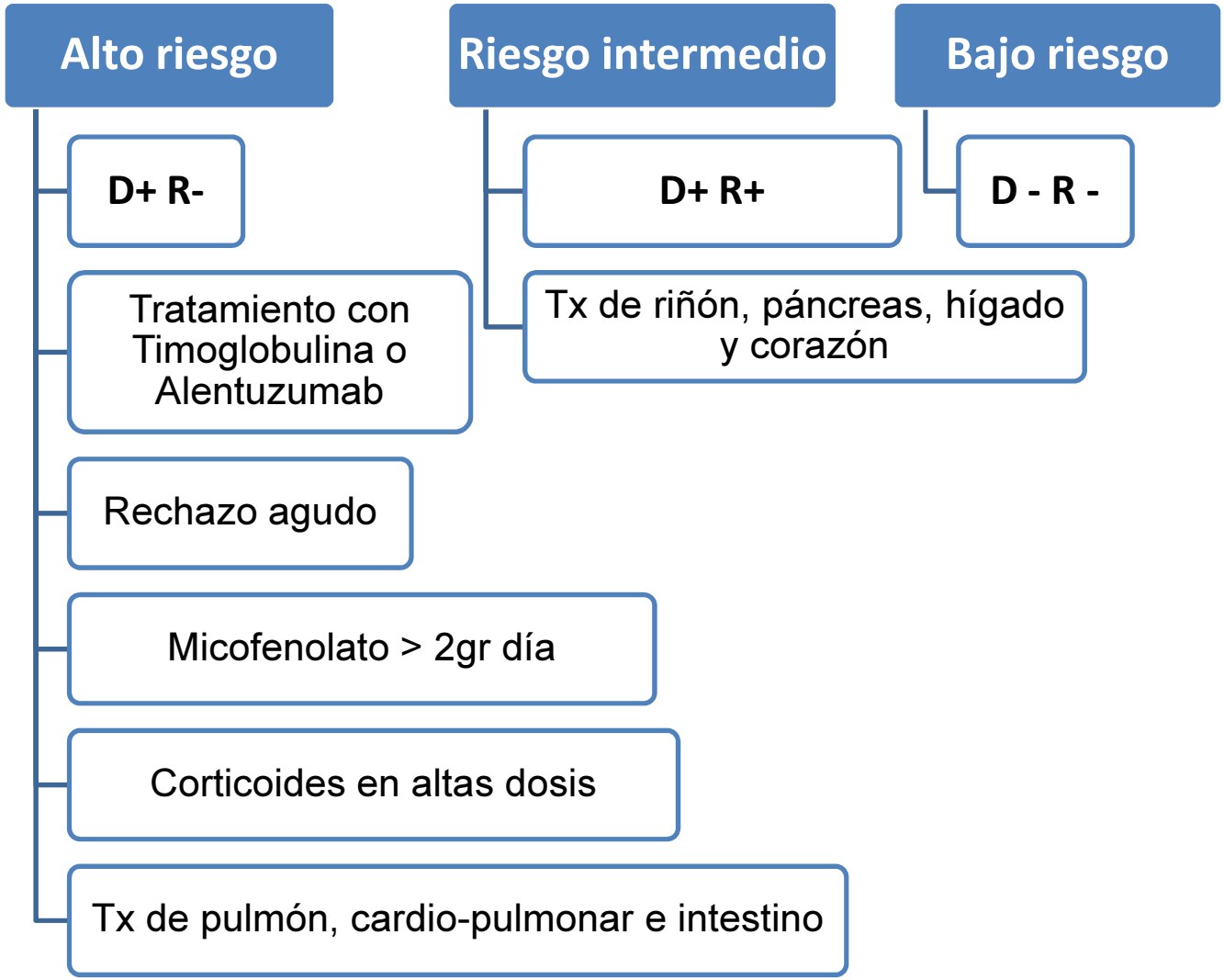
Riesgo de infección CMV en pacientes con TOS



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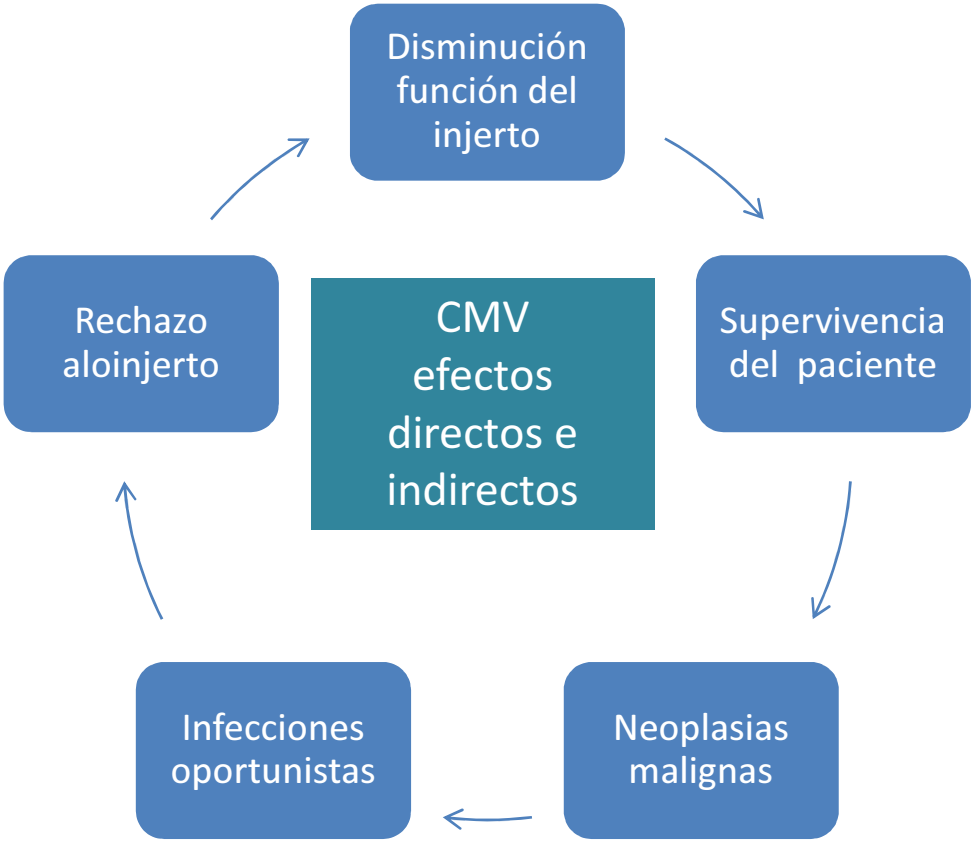
CMV Trasplante de órganos sólidos (TOS)



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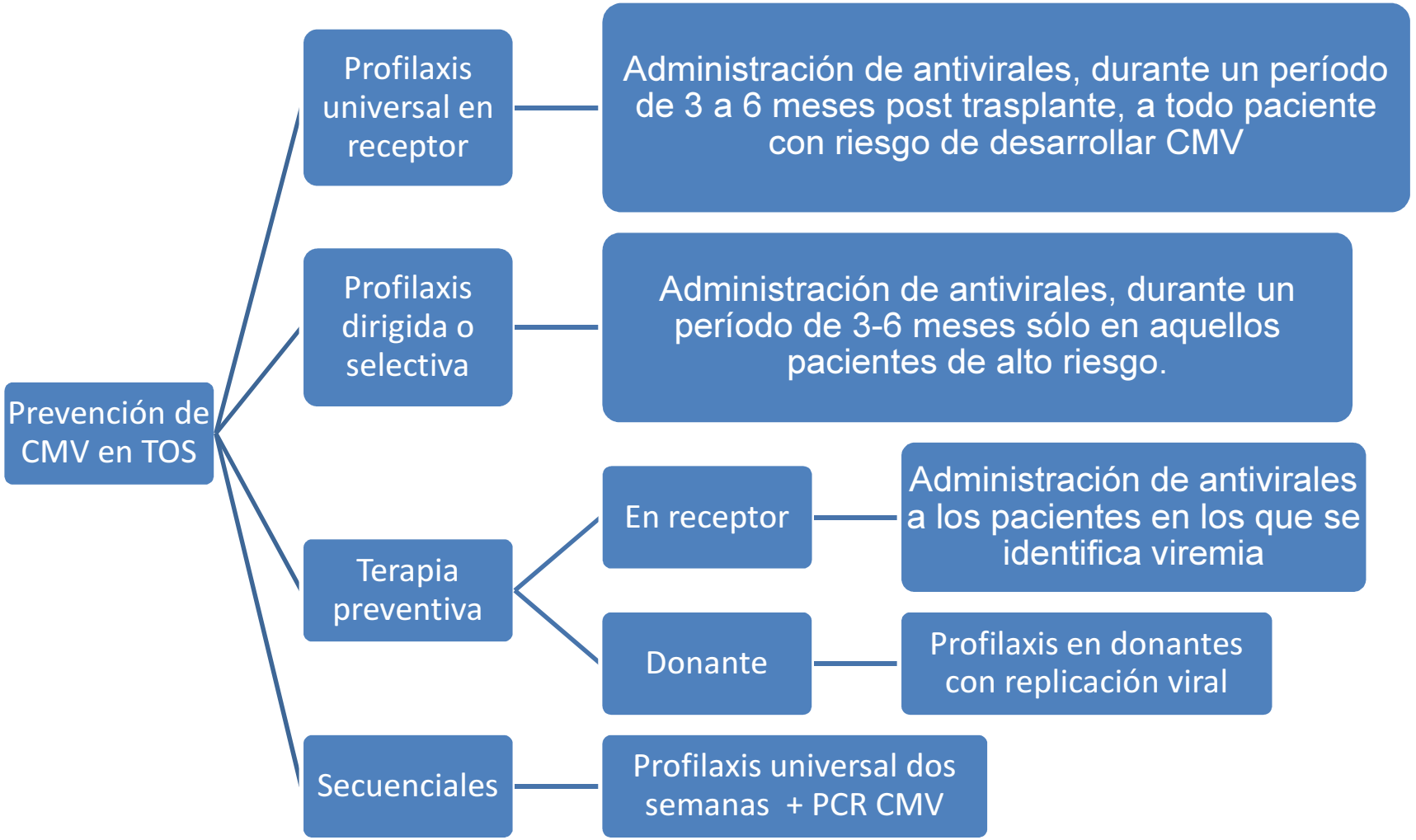
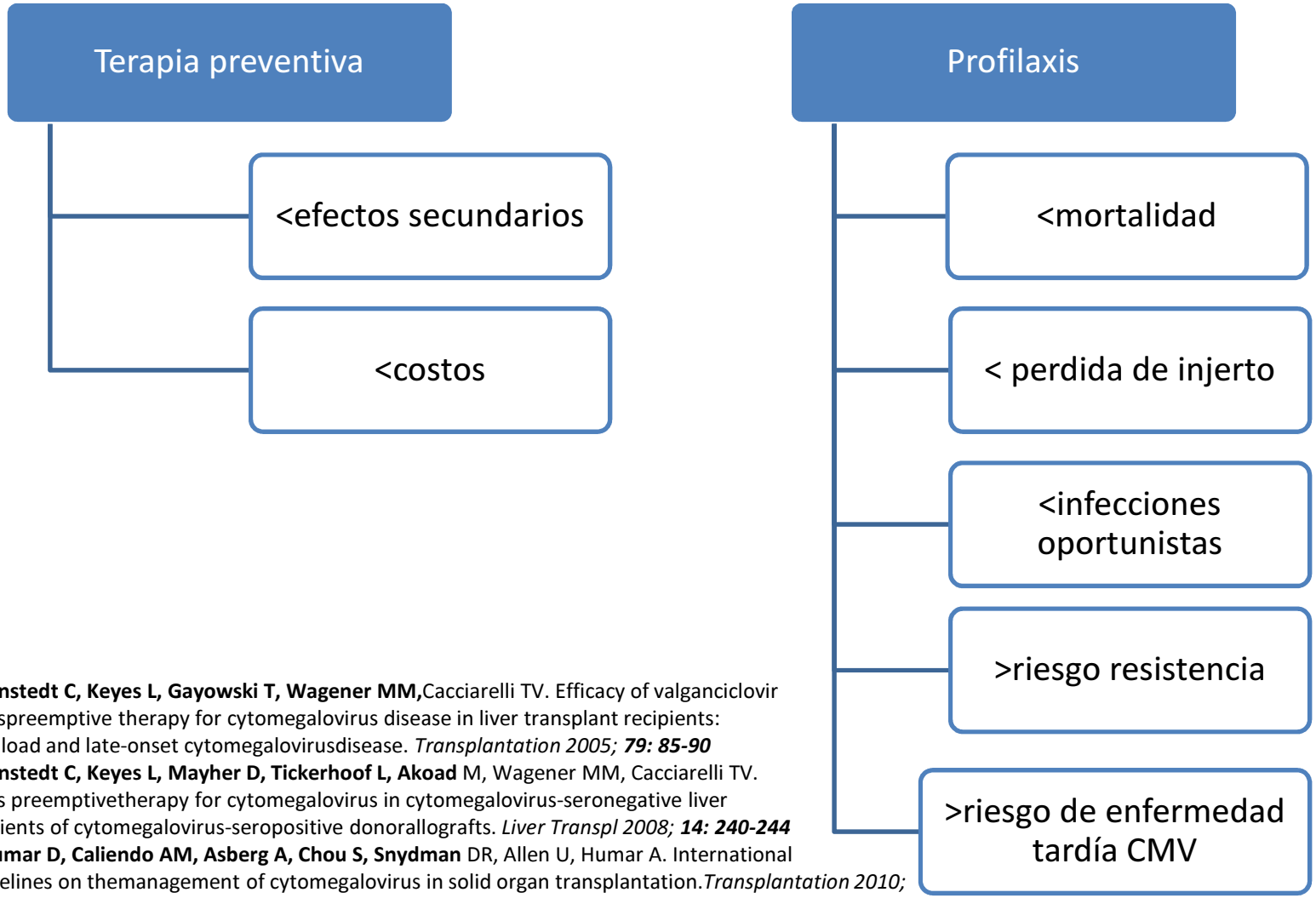
Estrategias de prevención de infección por citomegalovirus (CMV) en Trasplante de Órgano Solido (TOS)





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World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i12.3412

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ORIGINAL ARTICLE

Retrospective Study

Two strategies for prevention of cytomegalovirus infections after liver transplantation

Michael Bartels, Udo X Kaisers, Sven Bercker

Table 1 Patient demographics *n* (%)

	All (*n* = 128)	Prophylaxis (*n* = 60)	Preemptive therapy (*n* = 68)	*P* value
Age (yr)	54 ± 10	52 ± 12	56 ± 8.5	0.04
Sex				
Male	90 (70)	42 (70)	48 (71)	1.00
Female	38 (30)	18 (30)	20 (29)	
Weight (kg)	80 ± 16	81 ± 13	79 ± 19	0.52
SOFA	9.1 ± 4.0	8.8 ± 3.8	9.4 ± 4.3	0.34
APACHE II	14.2 ± 6.7	13.3 ± 5.5	15.0 ± 7.5	0.13
Lab. MELD at Transplantation	18.5 ± 9.4	18.8 ± 8.8	18.2 ± 9.9	0.73
CMV-status D/R				0.24
-/-	19 (17)	5 (10)	14 (22)	
-/+	33 (29)	16 (33)	17 (27)	
+/+	60 (54)	28 (57)	32 (51)	
+/-	Excluded			

Data are expressed as mean ± SD or *n* (%). Complete CMV-status was unavailable for 16 patients, but was known not to be +/-. D/R: Donor/receptor; CMV: Cytomegalovirus; Lab.MELD: Model of end stage liver disease.

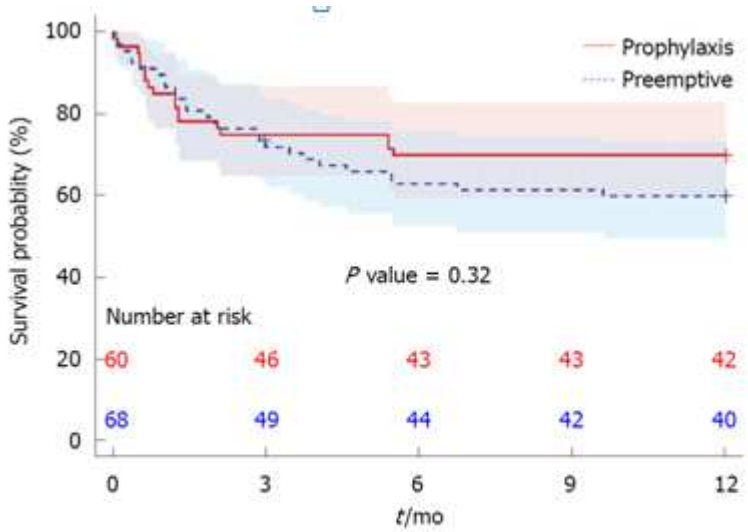

Figure 1 Survival curve. Mortality did not differ significantly between the groups.

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ORIGINAL ARTICLE

Retrospective Study

Two strategies for prevention of cytomegalovirus infections after liver transplantation

...hael Bartels, Udo X Kaisers, Sven Bercker

Table 2 Infection/blood count abnormalities *n* (%)

	All (*n* = 128)	Prophylaxis (*n* = 60)	Preemptive therapy (*n* = 68)	*P* value
Re - LTx	17 (13)	10 (17)	7 (10)	0.31
Infection	86 (71)	40 (69)	46 (72)	0.84
Sepsis	63 (52)	30 (52)	33 (52)	1.00
Thrombocytopenia (PLT < 50 Gpt/L; > 72 h post-LTx	69 (57)	32 (55)	37 (58)	0.86
Leukocytopenia (WBC < 4 Gpt/L; > 72 h post-LTx)	38 (31)	15 (26)	23 (36)	0.25
Anaemia (Hct < 30%; > 72 h post-LTx)	114 (93)	54 (93)	60 (94)	1.00

GPT: Giga particles; LTx: Liver transplantation; PLT: Platelet count; WBC: White blood cells; Hct: Haematocrit.

Patients who were treated according to the preemptive algorithm had a significantly higher rate risk of therapeutic intervention with ganciclovir [*n* = 16 (24%) *vs n = 3 (5%), P = 0.005].*
From these 19* patients 16 patients (84.0%) had clinical symptoms allegeable by CMV in context of the viremia [prophylaxis *n = 2 (12.5%), preemptive therapy n = 14 (87.5%)].
Patients who were treated according to the preemptive algorithm had a significantly higher rate risk of therapeutic intervention with ganciclovir [n = 16 (23.5%) vs n = 3 (4.9%), P = 0.003)].

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Resultados de terapia preventiva para infección por Citomegalovirus en trasplante hepático pediátrico

Autores: Malla, I, Selzer E, Uranga M, Ávila Diez M, Cheang Y, Panatteri N, Silva M, Casanueva E

Hospital Universitario Austral

Objetivo: Comparar la evolución de pacientes pediátricos receptores de trasplante hepático mismatch CMV (R-/D+) vs receptores pre-trasplante CMV positivos, con terapia preventiva.

Material y métodos: Análisis retrospectivo de historias clínicas digitales de pacientes pediátricos con trasplante hepático en nuestro hospital en el período 12/2007 – 10/2016.

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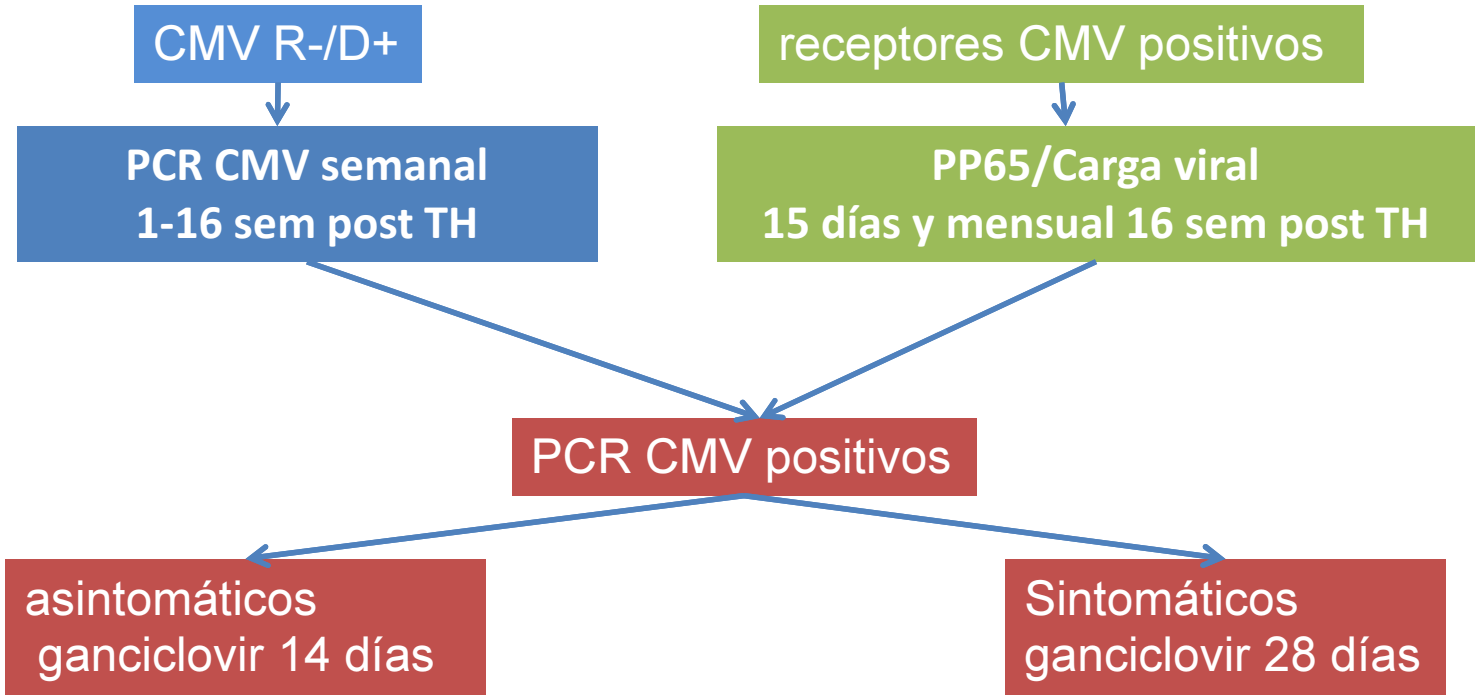

Carga Viral CMV mediante PCR en tiempo real con sondas específicas LightCycler Rango lineal: 200 a 500.000.000 copias / ml

Detección de CMV por PCR en tiempo real con sondas específicas LightCycler Límite de detección: 20 copias / reacción

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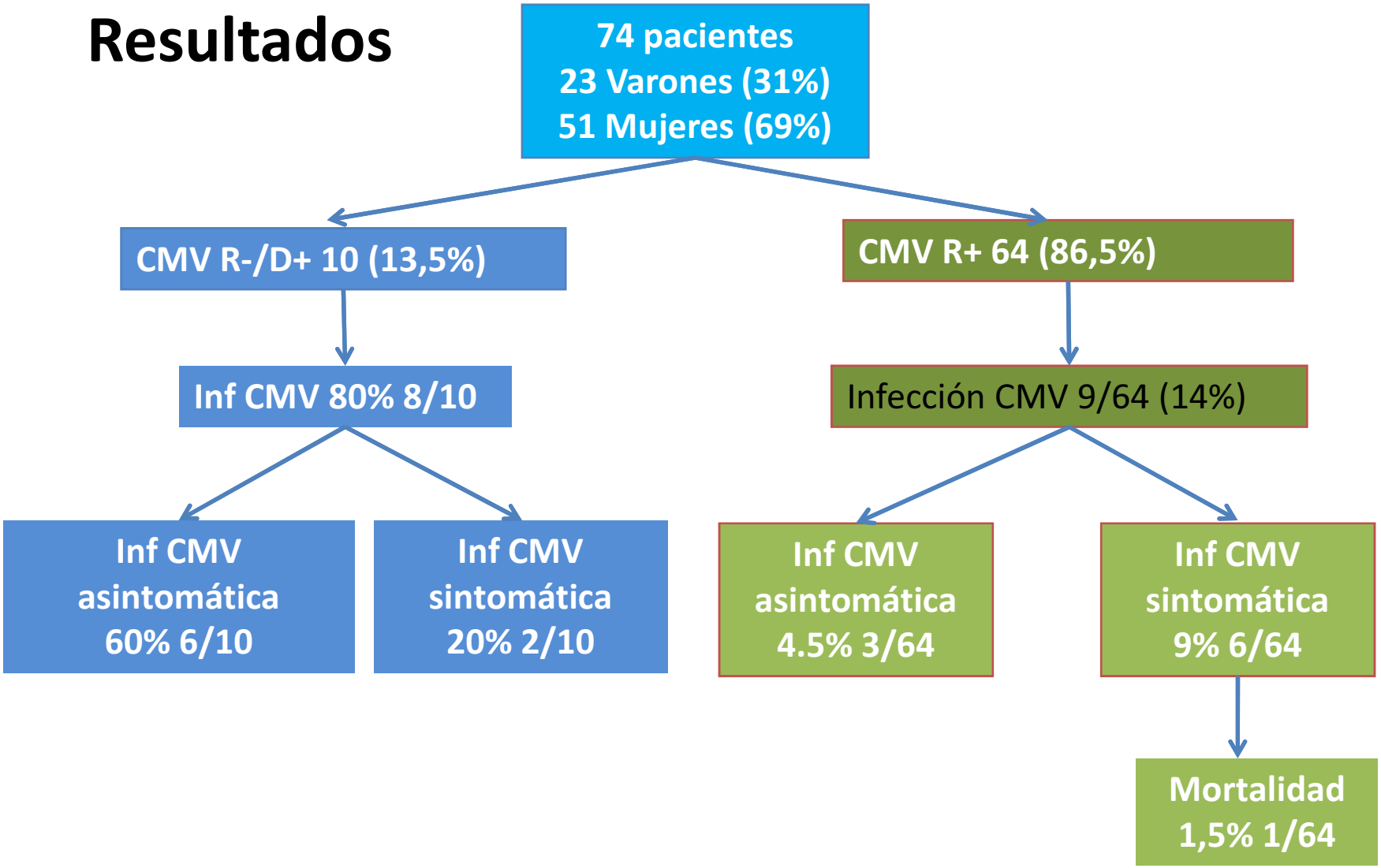
Resultados



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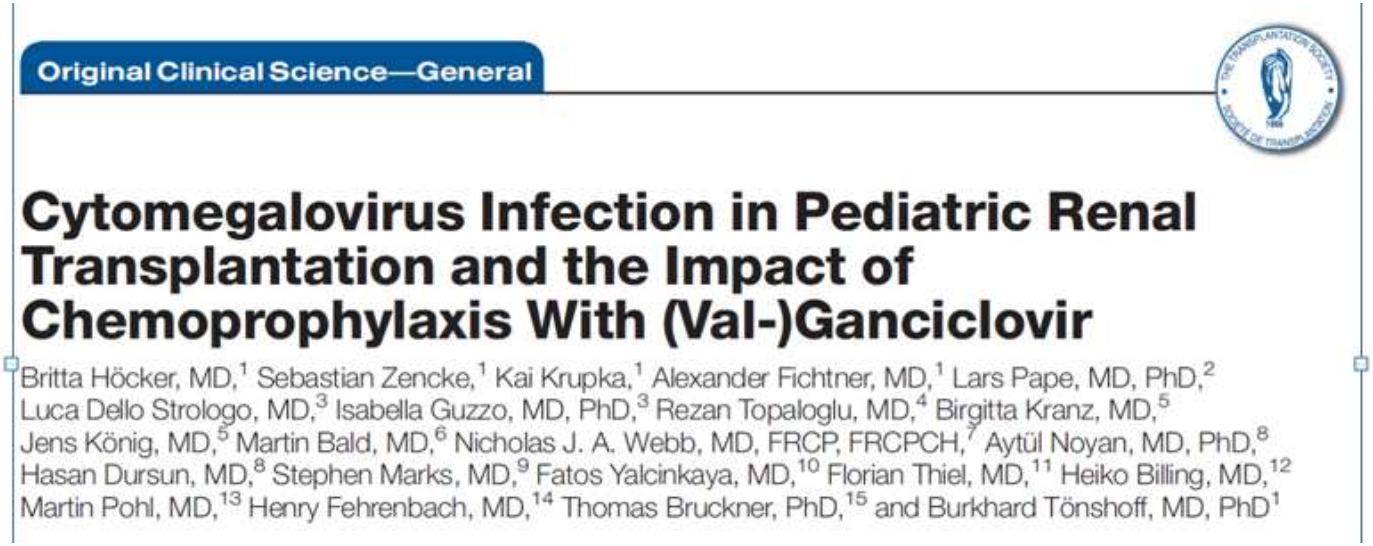


Original Clinical Science—General

Cytomegalovirus Infection in Pediatric Renal Transplantation and the Impact of Chemoprophylaxis With (Val-)Ganciclovir

Britta Höcker, MD,[1] Sebastian Zencke,[1] Kai Krupka,[1] Alexander Fichtner, MD,[1] Lars Pape, MD, PhD,[2] Luca Dello Strologo, MD,[3] Isabella Guzzo, MD, PhD,[3] Rezan Topaloglu, MD,[4] Birgitta Kranz, MD,[5] Jens König, MD,[5] Martin Bald, MD,[6] Nicholas J. A. Webb, MD, FRCP, FRCPCH,[7] Aytül Noyan, MD, PhD,[8] Hasan Dursun, MD,[8] Stephen Marks, MD,[9] Fatos Yalcinkaya, MD,[10] Florian Thiel, MD,[11] Heiko Billing, MD,[12] Martin Pohl, MD,[13] Henry Fehrenbach, MD,[14] Thomas Bruckner, PhD,[15] and Burkhard Tönshoff, MD, PhD[1]

The study is a retrospective cohort analysis of data reported to the **Cooperative European Paediatric Renal Transplant Initiative (CERTAIN) Registry** (www.certain-registry.eu)

Transplantation ■ April 2016 ■ Volume 100 ■ Number 4

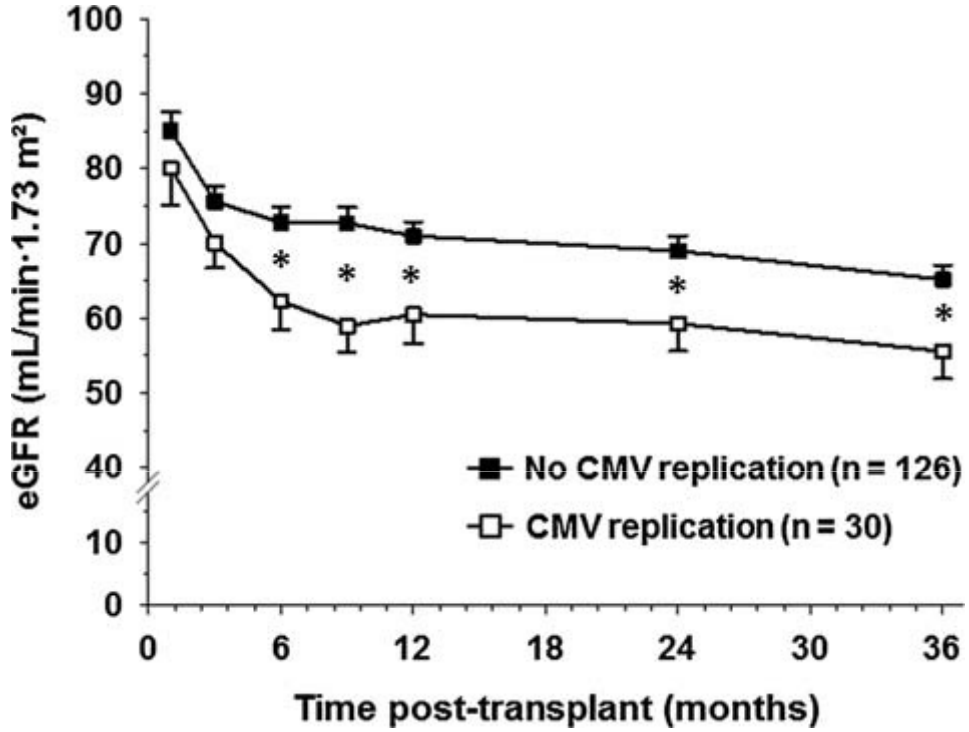


FIGURE 1. Transplant function. eGFR during the first 3 years after transplantation in patients with a complete 3-year data set (n = 156), with (n = 30) and without CMVreplication (n = 126). Data are depicte as mean ± standard error of the mean. Statistical method: repeated measures analysis of variance. *P < 0.05

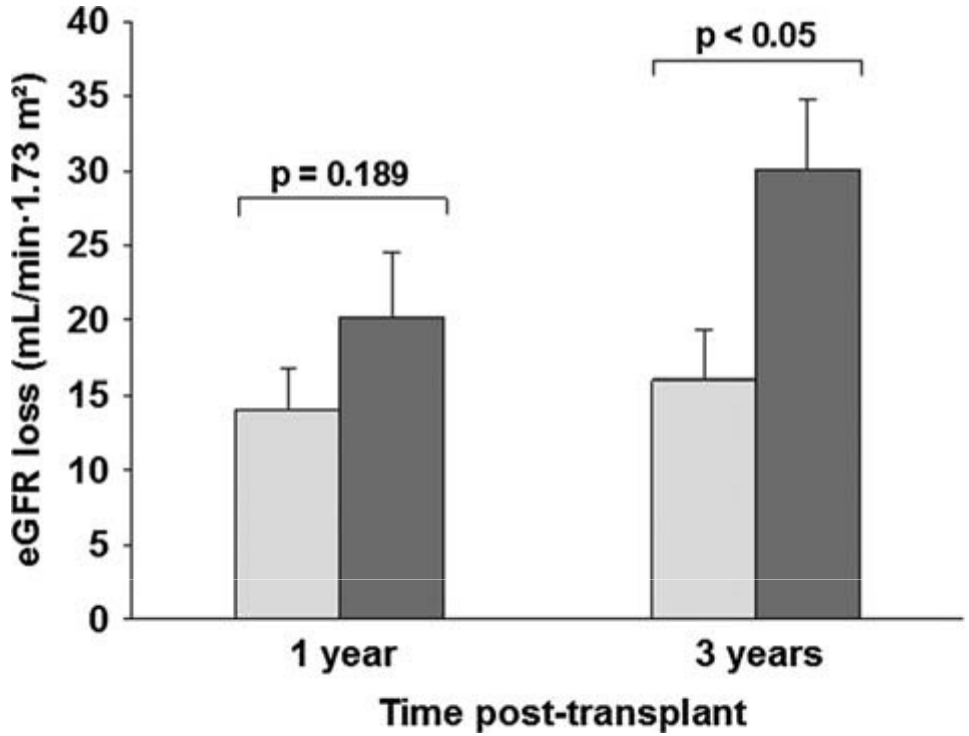


FIGURE 2. Transplant function. eGFR loss 1 year and 3 years after transplantation in patients with a high (D+/R−) or intermediate (D+/R+) CMV risk, who received antiviral chemoprophylaxis (light gray bars) or preemptive therapy (dark gray bars). 1-year data: n = 129 patients (antiviral chemoprophylaxis, n = 82; preemptive therapy, n = 47); 3-year data: n = 87 (antiviral chemoprophylaxis, n = 59; preemptive therapy, n = 28). Data are depicted as mean ± standard error of the mean. Statistical method: Mann-Whitney rank-sum test.

TABLE 3.

Patient and transplant characteristics of CMV D+/R– and D+/R+ recipients (n = 129)

Characteristics	Entire cohort (n = 129)	Prophylaxis cohort (n = 82)	Preemptive therapy cohort (n = 47)	*P*
Age at transplantation, y	10.9 ± 5.6	11.5 ± 5.9	9.8 ± 5.0	0.139
Male sex, n (%)	72 (55.8)	46 (56.1)	26 (55.3)	0.932
White, n (%)	116 (89.9)	74 (90.2)	42 (89.4)	0.873
Living-related donation, n (%)	67 (51.9)	37 (45.1)	30 (63.8)	0.041
Cold ischemia time: median (range), h	10 (0 – 29)	12 (0 – 29)	8 (0 – 26)	0.104
HLA mismatch, n	2.2 ± 1.2	2.2 ± 1.2	2.2 ± 1.4	0.867
CMV status, n (%)				0.004
D+/R–	63 (48.8)	48 (58.5)	15 (31.9)	
D+/R+	66 (51.2)	34 (41.5)	32 (68.1)	
Initial immunosuppressive regimen, n (%)				
IL-2 receptor antagonist	41 (31.8)	19 (23.2)	22 (46.8)	0.006
Thymoglobulin	4 (3.1)	3 (3.7)	1 (2.1)	0.629
TAC	78 (60.5)	50 (61.0)	28 (59.6)	0.876
CSA	51 (39.5)	32 (39.0)	19 (40.4)	0.876
MMF	115 (89.1)	77 (93.9)	38 (80.9)	0.022
AZA	10 (7.8)	4 (4.9)	6 (12.8)	0.107
Corticosteroids	125 (96.9)	78 (95.1)	47 (100.0)	0.124
Immunosuppressive score[a]	14.3 ± 5.4	13.8 ± 5.0	15.1 ± 6.1	0.145
Baseline eGFR, mL/min per 1.73 m^2[b]	86.0 ± 23.9	79.8 ± 29.6	96.6 ± 35.4	0.008
Number of patients with treated acute rejection episodes, n (%)[c]	32 (24.4)	20 (24.4)	12 (25.5)	0.885
No. patients with BPAR, n (%)[c,d]	28 (21.7)	18 (22.0)	10 (21.3)	0.929
No. patients with CMV replication during the first year after transplantation, n (%)	30 (23.3)	14 (17.1)	16 (34.0)	0.028

[a] As described in Hocker et al.[21]
[b] Defined as eGFR[MDRD] at 30 days after transplantation.
[c] Within first year of transplantation.
[d] Including borderline changes (Banff 97 '09 update[22,23]).

TABLE 4.

Hematological data in CMV D+/R– and D+/R+ recipients (n = 129) receiving GCV/VGCV chemoprophylaxis or preemptive therapy

Parameter	Prophylaxis cohort (n = 82)	Preemptive therapy cohort (n = 47)	*P*
Anemia (hemoglobin < 8 g/dL), n (%)			
During chemoprophylaxis[a]	12/82 (14.6%)	4/47 (8.5%)	0.310
Within first year of transplantation	19/82 (23.2%)	8/47 (17.0%)	0.409
Leukocytopenia (leukocytes <4000/μL), n (%)			
During chemoprophylaxis[a]	23/82 (28.0%)	5/47 (10.6%)	0.021
Within first year of transplantation	32/82 (39.0%)	11/47 (23.4%)	0.070
Neutropenia (neutrophils < 1000/μL), n (%)			
During chemoprophylaxis[a]	8/50 (16.0%)	1/28 (3.6%)	0.099
Within first year of transplantation	11/46 (23.9%)	4/25 (16.0)	0.435
Agranulocytosis (granulocytes < 500/μL), n (%)			
During chemoprophylaxis[a]	3/50 (6.0%)	0/28 (0.0%)	0.186
Within first year of transplantation	5/45 (11.1%)	0/25 (0.0%)	0.084
Thrombocytopenia (thrombocytes < 100/μL), n (%)			
During chemoprophylaxis[a]	2/82 (2.4%)	2/47 (4.3%)	0.567
Within first year of transplantation	5/82 (6.1%)	2/47 (4.3%)	0.657

[a] Up to 100 days after transplantation in patients of the preemptive therapy cohort.

TABLE 5.

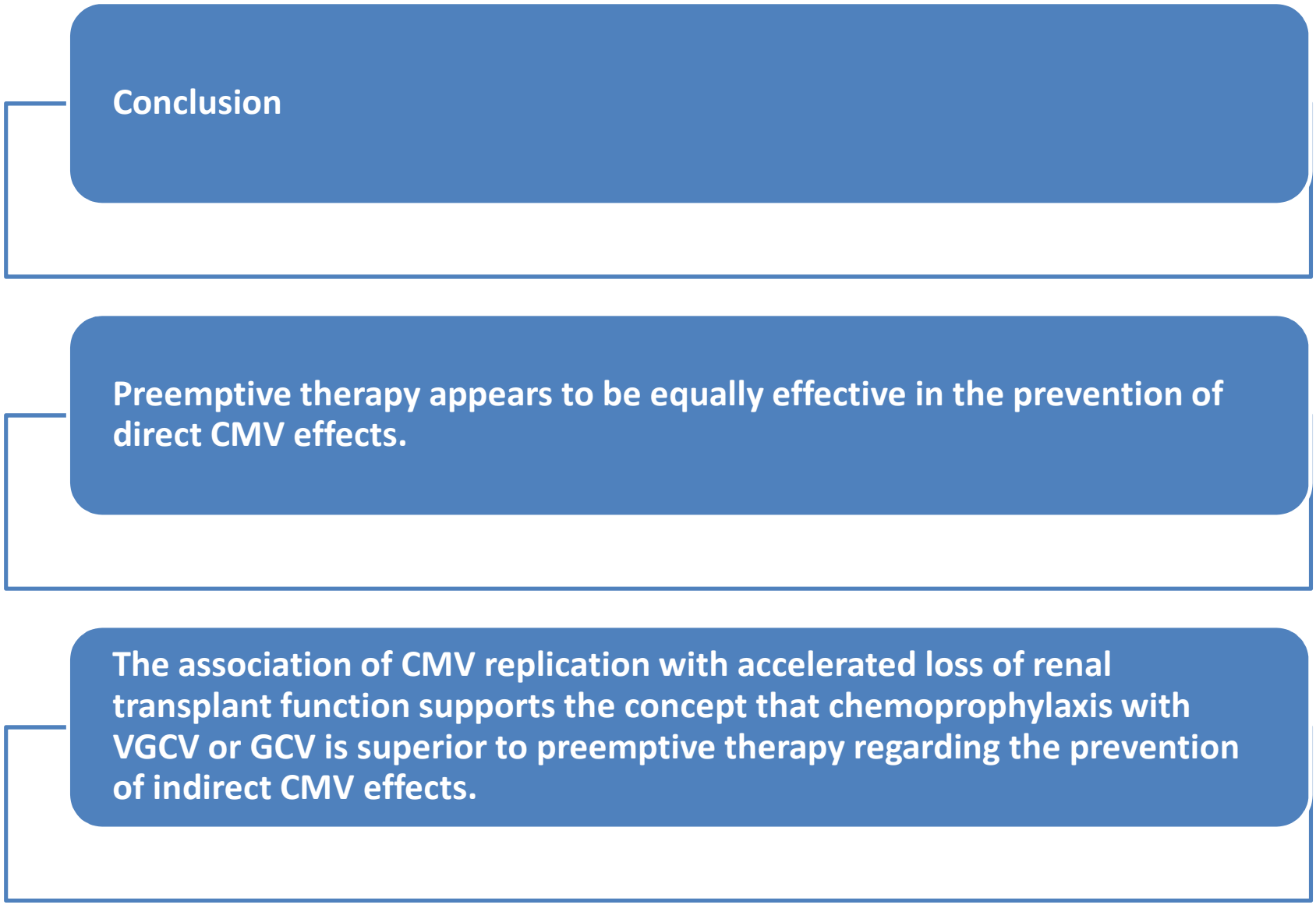
Risk factors for developing CMV replication

Risk factors	OR	95% CI	*P*
IL-2 receptor antagonist	1.77	0.80-3.92	0.159
TAC vs CSA	0.56	0.26-1.22	0.146
Immunosuppressive score[a]	0.94	0.78-1.12	0.478
AR before CMV replication	0.34	0.14-1.18	0.098
CMV high risk (D+/R–)	9.71	3.62-26.10	<0.001
Prophylaxis vs preemptive therapy	0.36	0.12-0.93	0.036

[a] As described in Hocker et al.[21]

D, donor; R, recipient, defined as both treated and biopsy-proven acute rejection episodes, according to Banff.[22,23]

Patients receiving antiviral chemoprophylaxis carried a by 64% lower risk of CMV replication than patients receiving preemptive therapy


Conclusion
Preemptive therapy appears to be equally effective in the prevention of direct CMV effects.
The association of CMV replication with accelerated loss of renal transplant function supports the concept that chemoprophylaxis with VGCV or GCV is superior to preemptive therapy regarding the prevention of indirect CMV effects.

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The Impact of Donor Viral Replication at Transplant on Recipient Infections Posttransplant: A Prospective Study

Priya S. Verghese[1], **David O. Schmeling**[3], **Jennifer A. Knight**[3], **Arthur J. Matas**[2], and **Henry H. Balfour Jr**[1,3]

[1]University of Minnesota, Department of Pediatrics, 2450 Riverside Avenue, East Building, MB680, Minneapolis, MN 55454

[2]University of Minnesota, Department of Surgery, 420 Delaware Street, Minneapolis, MN 55455

[3]University of Minnesota, Department of Lab Medicine and Pathology, 420 Delaware Street, Minneapolis, MN 55455

Results

The 98 donor-recipient (15 liver and 83 kidney transplants, 18 of whom were children).

No donor had detectable CMV replication

Donor EBV replication occurred in 22%, mostly in the oral wash and had no impact on posttransplant recipient EBV replication (p 0.9) or EBV viremia (p 0.6) in kidney or liver recipients.

Donor BKV replication occurred in 17%, mostly in the urine and although not associated with posttransplant recipient urinary BKV replication in recipients, it was associated with BKV viremia (p 0.02), and a significantly shorter time to BKV viremia (p 0.01) in kidney recipients.

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Original Clinical Science

Valganciclovir Administration to Kidney Donors to Reduce the Burden of Cytomegalovirus and Epstein-Barr Virus Transmission During Transplantation

Priya S. Verghese,[1] David O. Schmeling,[2] Jennifer A. Knight,[2] Arthur J. Matas,[3] and Henry H. Balfour, Jr.[1,2]

1 Department of Pediatrics, University of Minnesota, Minneapolis, MN. 2 Department of Lab Medicine and Pathology, University of Minnesota, Minneapolis, MN. 3 Department of Surgery, University of Minnesota, Minneapolis, MN.

We postulated that in transplantation, donor pretreatment in D+R− donor-recipient pairs might reduce the burden or quantity of viral transmission of CMV and EBV to the recipient, making posttransplant recipient prophylaxis more effective in the prevention of disease posttransplant.

Transplantation ■ June 2015 ■ Volume 99 ■ Number 6

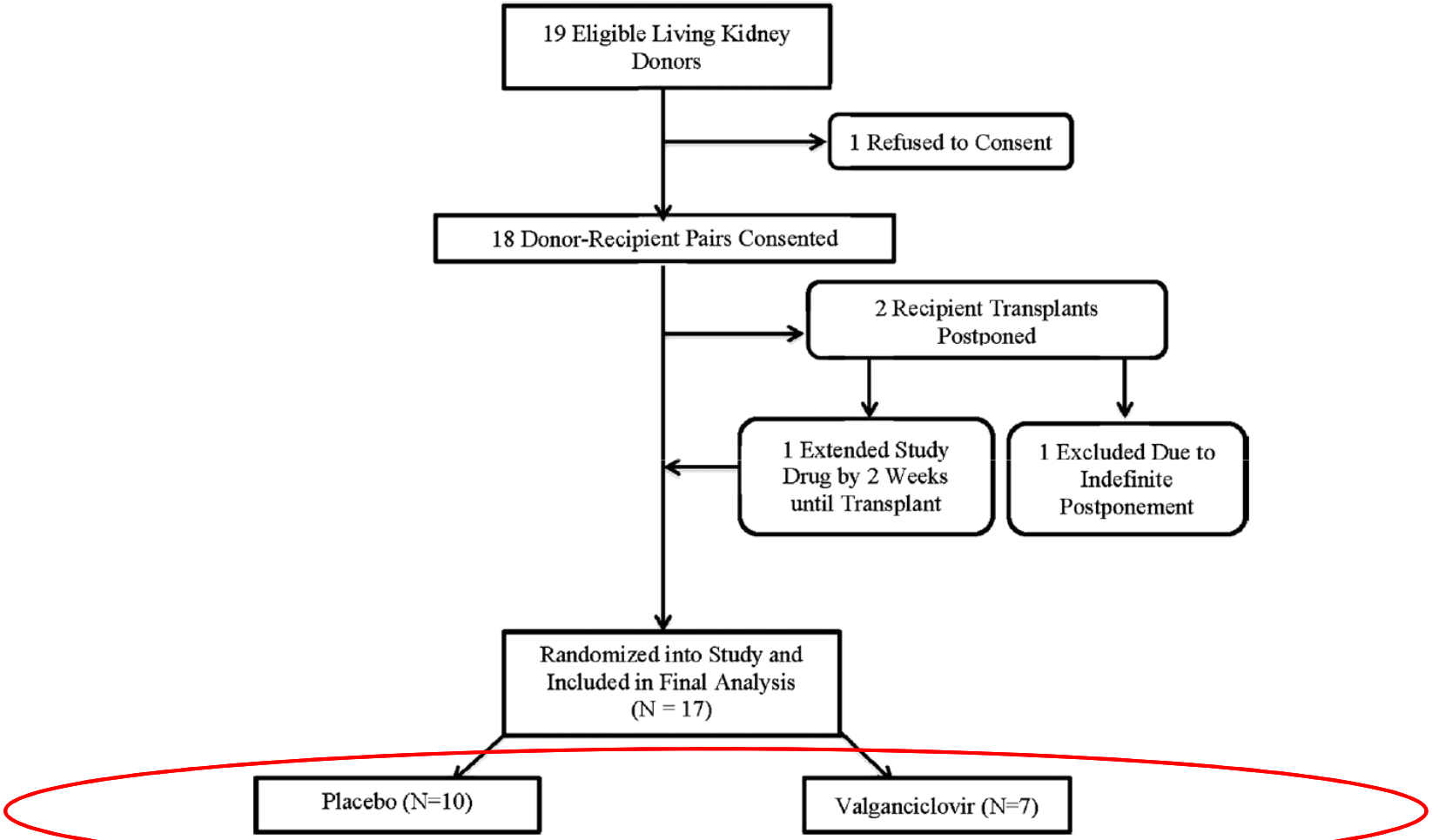

FIGURE 1. Flow diagram of donor enrollment

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TABLE 2.

Number of enrolled kidney donors with detectable viral replication receiving valG or placebo

	At evaluation	After 1 week of study drug	At Tx (after 2 weeks of study drug)	Post-Tx
Valganciclovir arm				
CMV wb[a]	0	0	0	0
EBV oral[b]	2	0	0	2
EBV wb[a]	0	0	0	0
Placebo arm				
CMV wb[a]	0	0	0	0
EBV oral[b]	3	0	3	3
EBV wb[a]	0	0	0	0

[a] wb, whole blood specimen.
[b] oral, oral wash specimen.
CMV, cytomegalovirus; EBV, Epstein-Barr virus; valG, valganciclovir; Tx, transplantation.

In our prospective, randomized pilot trial, there was not a **single case of CMV or EBV disease in D+R− recipients when the donors received 14 days of valG before donation**.

All recipients received standard posttransplant valG prophylaxis.

In contrast, in the **placebo treated D+R− group, one recipient developed CMV disease, and a second had EBV-related PTLD that was EBER+.**
Sequencing the variable region of LMP-1 of the EBV strains from donor and recipient suggested that the PTLD was caused by the donor's EBV and might have been prevented if the donor had been given valG pretransplant.

Conclusiones

- La terapia preventiva contra CMV puede traer beneficios en trasplante hepático.
- La evidencia en el resto de TOS es limitada y no recomendada de inicio- Puede considerarse las estrategias “hibridas y secuenciales”
- La interpretación de las cargas virales y antigenemia es problemática y difiere entre los diferentes Kits. Cada centro debe entonces validar los valores del “cutoff” que permitan inducir que valor esta relacionado con riesgo de desarrollar enfermedad
- La terapia preventiva en los donantes no es posible por ahora ya que no se detectan adecuadamente quienes serán mayores transmisores. Profilaxis universal?

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Departamento Materno Infantil
Servicio de Pediatría-Servicio de Terapia Intensiva- Equipo de trasplante Hepático – Equipo de Trasplante Renal- Equipo de trasplante de Medula Ósea-Laboratorio de Bacteriología-Laboratorio de Virología-Departamento de Enfermería-
Sección de Infectología Infantil

HOSPITAL UNIVERSITARIO AUSTRAL

Gracias por su atención