Sobreinmunosupresión e infección oportunista

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Introducción

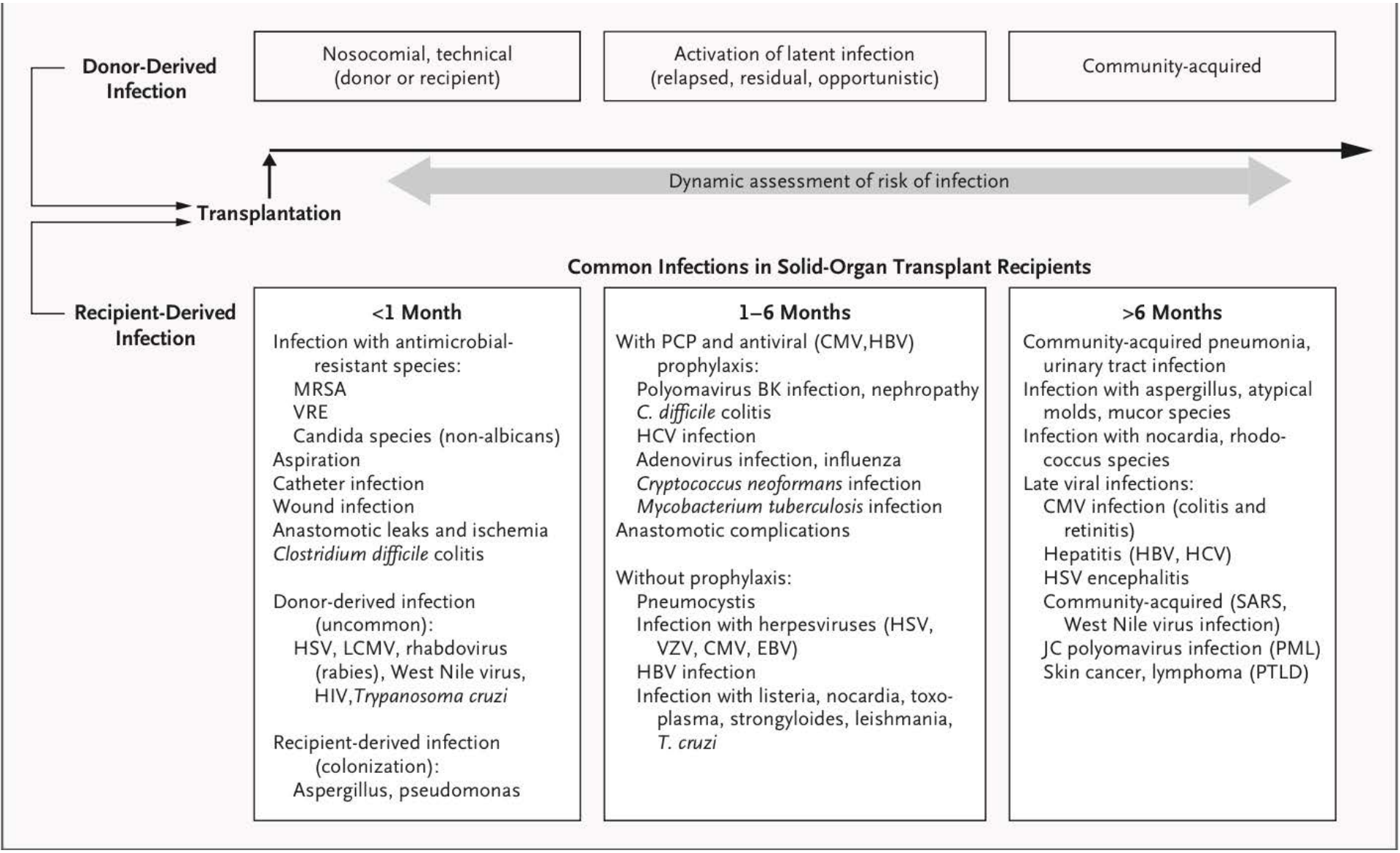
Las infecciones oportunistas y el cáncer son causa frecuente de mortalidad post-trasplante como consecuencia obvia de la sobre-inmunosupresión

En teoría, una ventana terapéutica separa la excesiva inmunosupresión de la inmunosupresión insuficiente, pero en la práctica clínica no siempre es así. Conocer cuál debería ser el grado adecuado de inmunosupresión es difícil.

Desde un punto de vista práctico, sobreinmunosupresión se define en términos de la frecuencia y severidad de las infecciones, infecciones oportunistas y neoplasias en un paciente que recibe tratamiento inmunosupresor

Budde, K. et al, Clin Pharmacol Ther 2011 Aug;90(2):316-22

Changing Timeline of Infection after Organ Transplantation



Fishman JA, N Engl J Med 2007;357:2601-14

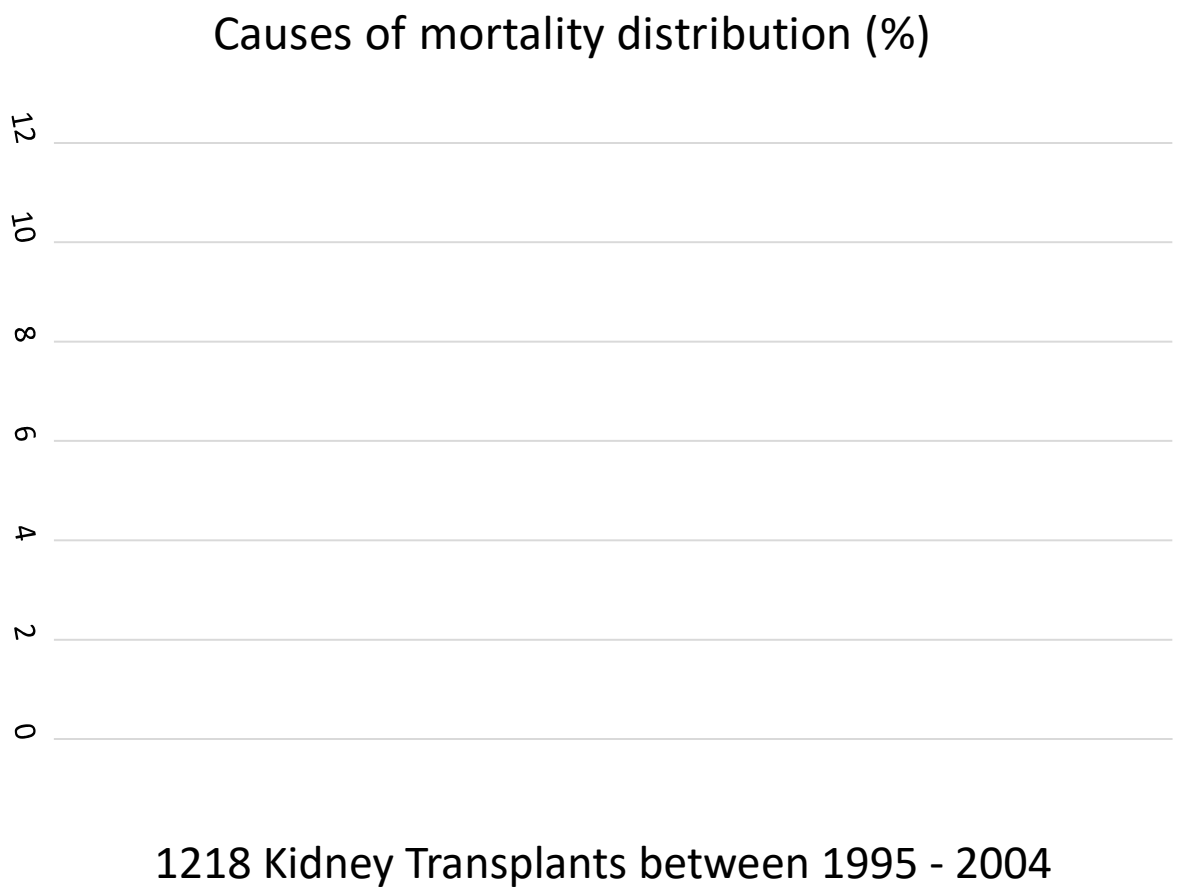
Causas de muerte post trasplante

Cause of death	Percentage of total deaths					
	USRDS [2] (1988–97) (7040 deaths)	ERA–EDTA[a] [3] (1991–99) (1969 deaths)	Glasgow [4]			Leiden [5] (1966–94) (163 deaths)
			(1969–82) (30 deaths)	(1983–96) (151 deaths)	(1969–96) (181 deaths)	
Cardiovascular	42	47	23	61	55	40
Malignancy	9	15	10	16	15	14
Infection	18	15	40	12	16	46
Other/unknown	31	23	27	11	14	

[a]Unpublished data from six European national registries.

Briggs JD. Nephrol Dial Transplant 2001, 16: 1545±1549

Causes of mortality in a large cohort of renal transplant recipients



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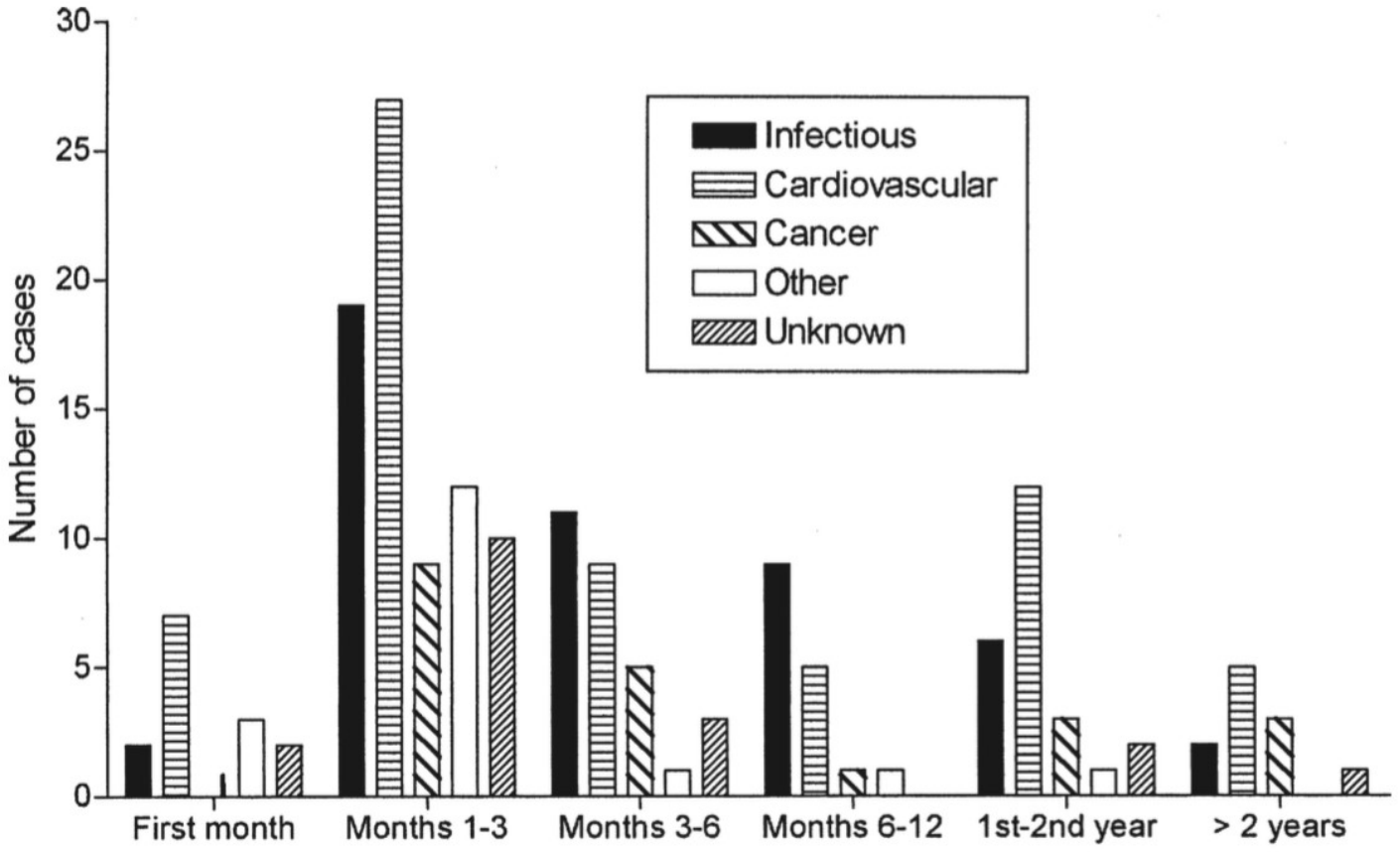
Linares L. et al Transplant Proc. 2007, 39: 2225–2227

Episodes of death according to the posttransplant timeline



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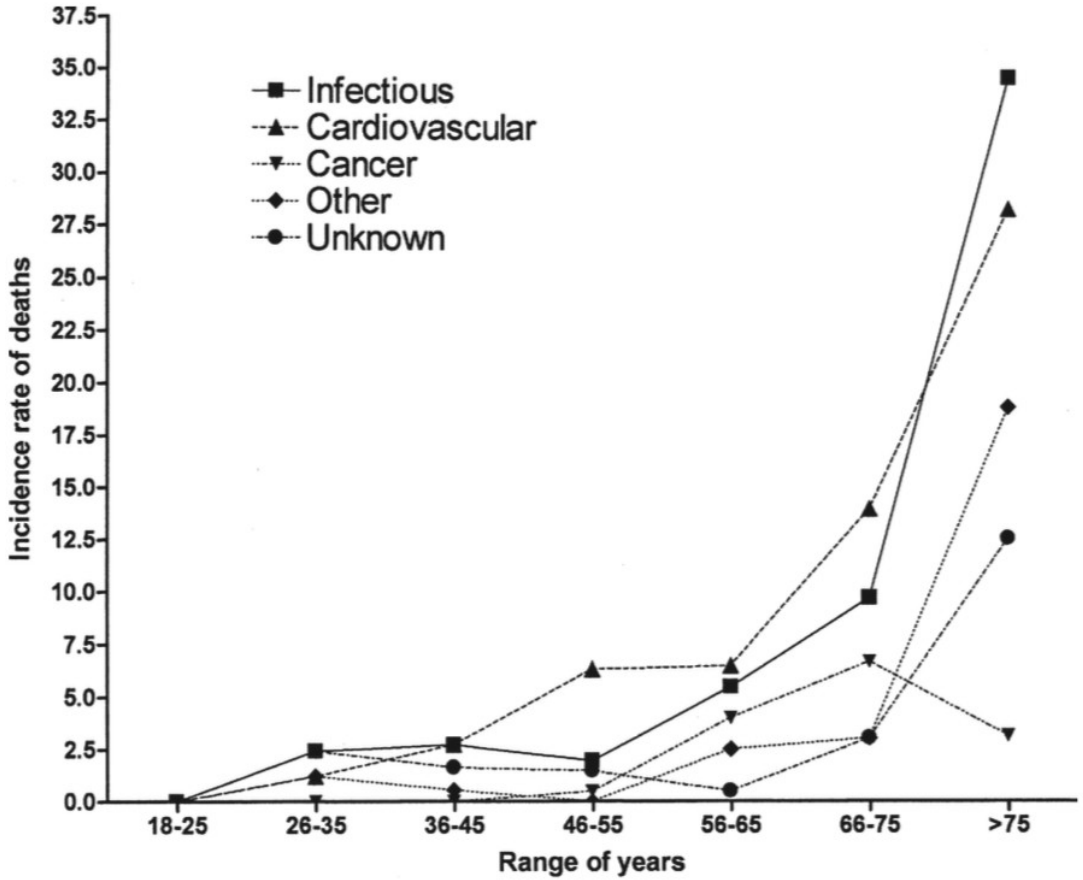
Linares L. et al Transplant Proc. 2007, 39: 2225–2227

Incidence rate of mortality according to the range of age



Incidence rate is expressed as deaths per 10,000 transplant- months

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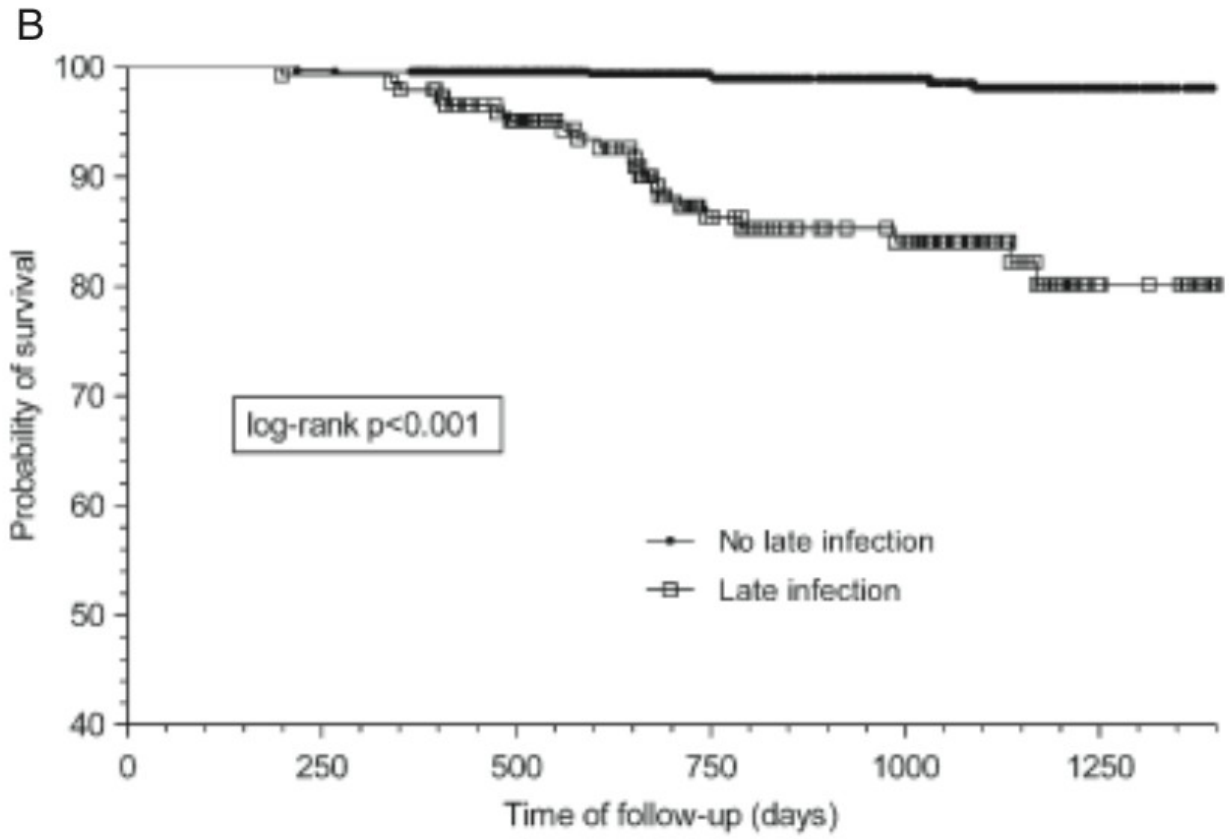
Linares L. et al Transplant Proc. 2007, 39: 2225–2227

Late infection (88% bacterial) in solid organ transplant recipients and risk of death



Number at risk:

No late infection	642	484	318	167	49
Late infection	126	101	71	46	16

Cervera C et al, Transpl Infect Dis 2011: 13: 598-607

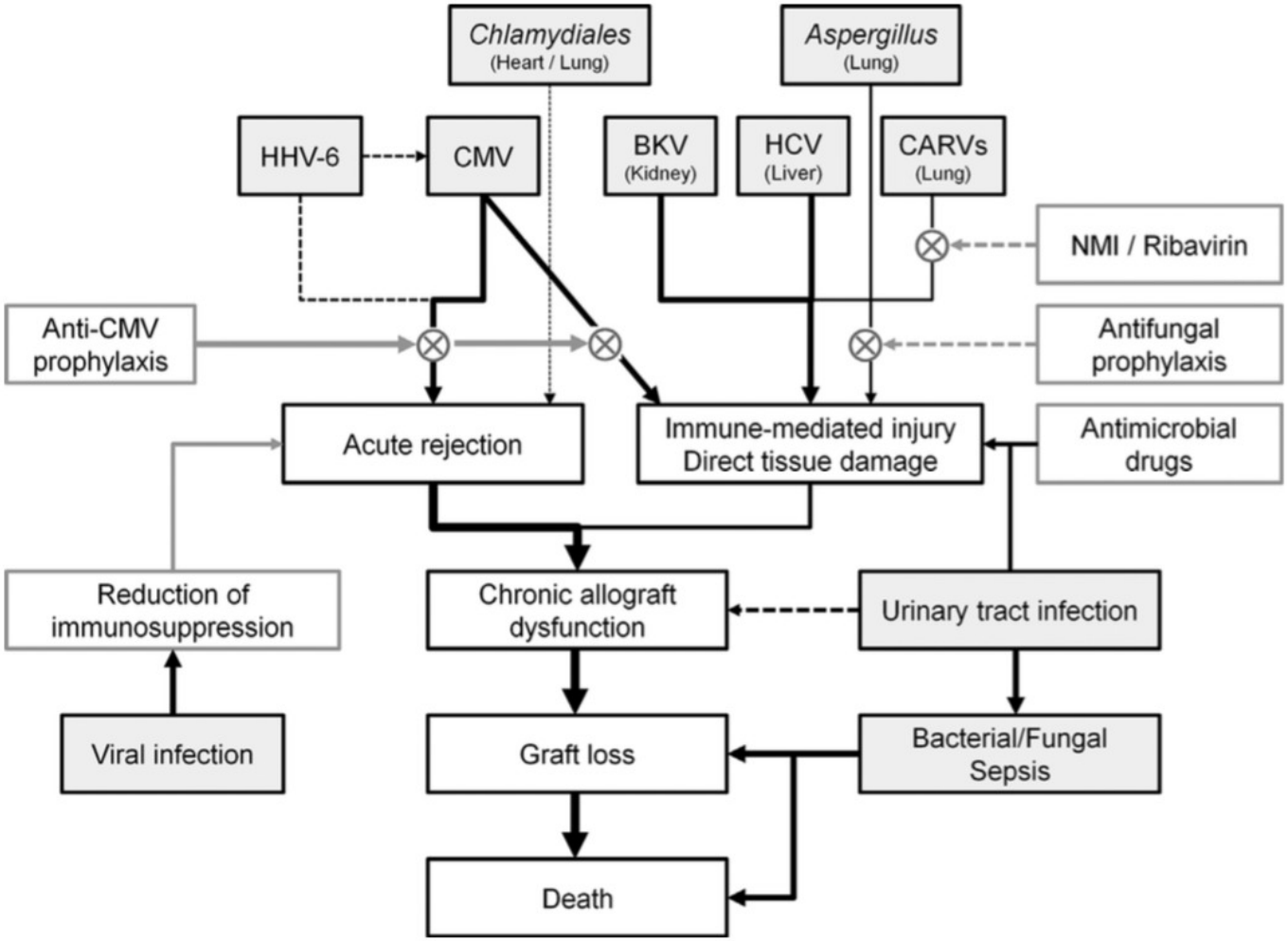
Analysis of risk factors associated with late bacterial infection in solid organ transplant recipients

	Univariate analysis			Multivariate model	
Variable [*N* (%)]	Late bacterial infection (*N* = 123)	No late bacterial infection (*N* = 819)	*P*-value	HR (95% CI)	*P*-value[1]
Mean age, *y* (mean ± SD)[2]	53.7 ± 12.9	49.8 ± 12.6	0.001	1.0 (1.0–1.0)	0.023
Female gender	58 (47.2)	283 (34.6)	0.007	1.7 (1.1–2.6)	0.015
Pre-transplant diabetes	29 (23.8)	187 (23.0)	0.845	1.1 (0.6–2.0)	NS
Anti-HCV positive serostatus	43 (35.2)	180 (22.4)	0.002	1.8 (1.1–3.0)	0.009
CMV mismatch serology (D + /R −)	12 (9.8)	84 (10.3)	0.864	1.1 (0.5–2.2)	NS
Type of transplantation					
Kidney	67 (54.5)	424 (51.8)	0.025	1.1 (0.5–2.8)	NS
Liver	43 (35.0)	237 (28.9)			
Heart	1 (0.8)	64 (7.8)			
Double organ	12 (9.8)	94 (11.5)			
mTOR inhibitor-based regimen	35 (28.5)	136 (16.6)	0.001	1.6 (0.9–2.7)	0.072
Use of MMF	91 (74.6)	612 (75.7)	0.782	1.0 (0.6–1.8)	NS
Need for post-transplant dialysis	25 (21.6)	103 (14.2)	0.040	1.3 (0.7–2.2)	NS
Acute rejection	35 (30.2)	151 (19.6)	0.009	1.3 (0.8–2.1)	NS
Chronic allograft dysfunction	19 (15.4)	35 (4.3)	<0.001	3.2 (1.7–6.1)	<0.001
Surgical reoperation	41 (35.0)	175 (22.3)	0.003	1.1 (0.7–1.9)	NS
CMV disease in the early period	22 (17.9)	51 (6.2)	<0.001	2.2 (1.2–4.1)	0.012
Bacterial infection in the early period	79 (64.2)	286 (34.9)	<0.001	2.5 (1.6–3.8)	<0.001

[1]Only *P*-values ≤0.09 are detailed.
[2]Per unitary increment.
SD, standard deviation; *y*, years; HR, hazard ratio; CI, confidence interval; HCV, hepatitis C virus; CMV, cytomegalovirus; NS, not significant; D/R, donor/recipient; mTOR, mammalian target of rapamycin; MMF, mycophenolate mofetil.

Cervera C et al, Transpl Infect Dis 2011: 13: 598-607

The Impact of Infection on Chronic Allograft Dysfunction and Allograft Survival After Solid Organ Transplantation



Martin-Gandul et al. Am J Transplant 2015; 15: 3024–3040

Infectius risk assessment in transplantation

- Greater infectious risk
  - Critical illness entering transplantation
  - Prior colonization with antimicrobial-resistant pathogens
  - Induction therapy—lymphocyte depletion
  - High-dose corticosteroids
  - Plasmapheresis (not well studied)
  - High rejection risk (HLA mismatch desensitization)
  - Early graft rejection
  - Graft dysfunction
  - Technical complications
    - Anastamotic leak
    - Bleeding
    - Wound infection/poor wound healing
    - Prolonged intubation/intensive unit care
    - Surgical, vascular or urinary catheters
- Lower infectious risk
  - Immunological tolerance
  - Good HLA match
  - Technically successful surgery
  - Good graft function
  - Appropriate surgical prophylaxis
  - Effective antiviral prophylaxis
  - PCP prophylaxis
  - Appropriate vaccination

Fishman JA, CMI, 2014, 20 (Suppl. 7), 4–9

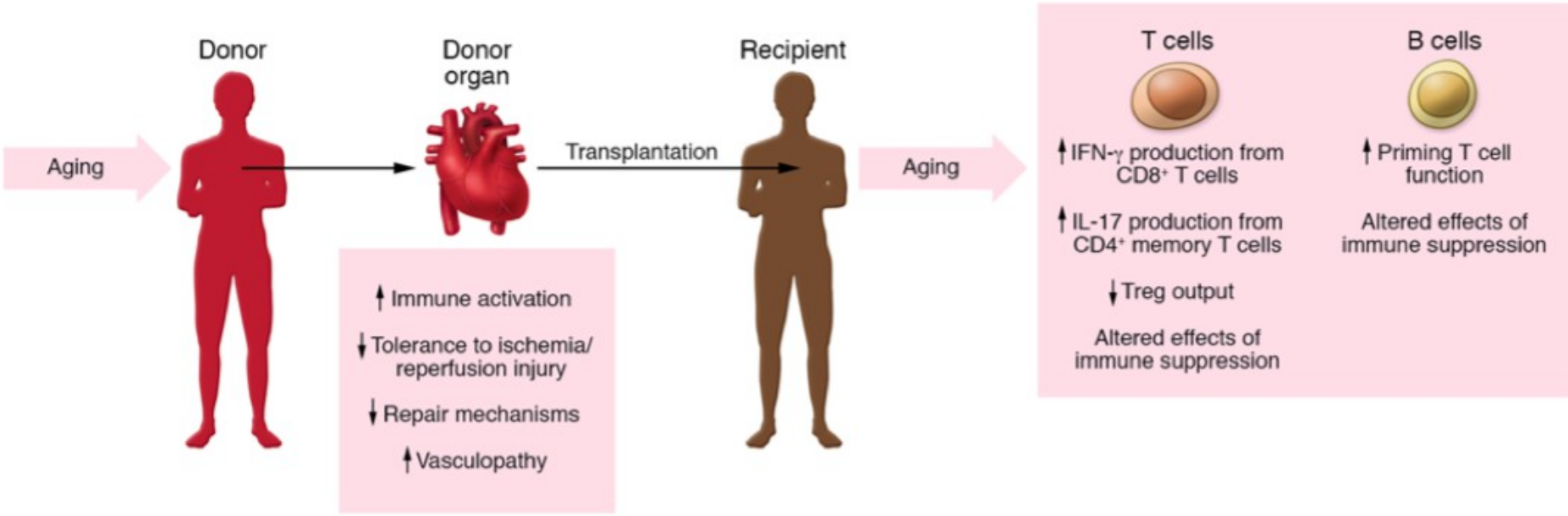
The ‘net state of immune deficiency”

Preexisting immune deficits
- Critical illness
- Malnutrition
- Organ dysfunction (uraemia, cirrhosis, COPD/cystic fibrosis, heart failure)
- Diabetes

Colonization with antimicrobial-resistant pathogens, hospitalization
Immunosuppressive therapies (current and past)
Acquired immune deficiencies (e.g. hypogammaglobulinaemia)
Prior therapies (chemotherapy, antimicrobials)
Mucocutaneous barrier integrity (catheters, lines, drains)
Fluid collections (blood, lymph, urine, bile, pus)
Neutropenia, lymphopenia
Viral co-infection (e.g. CMV, EBV, HCV, HBV, HIV)

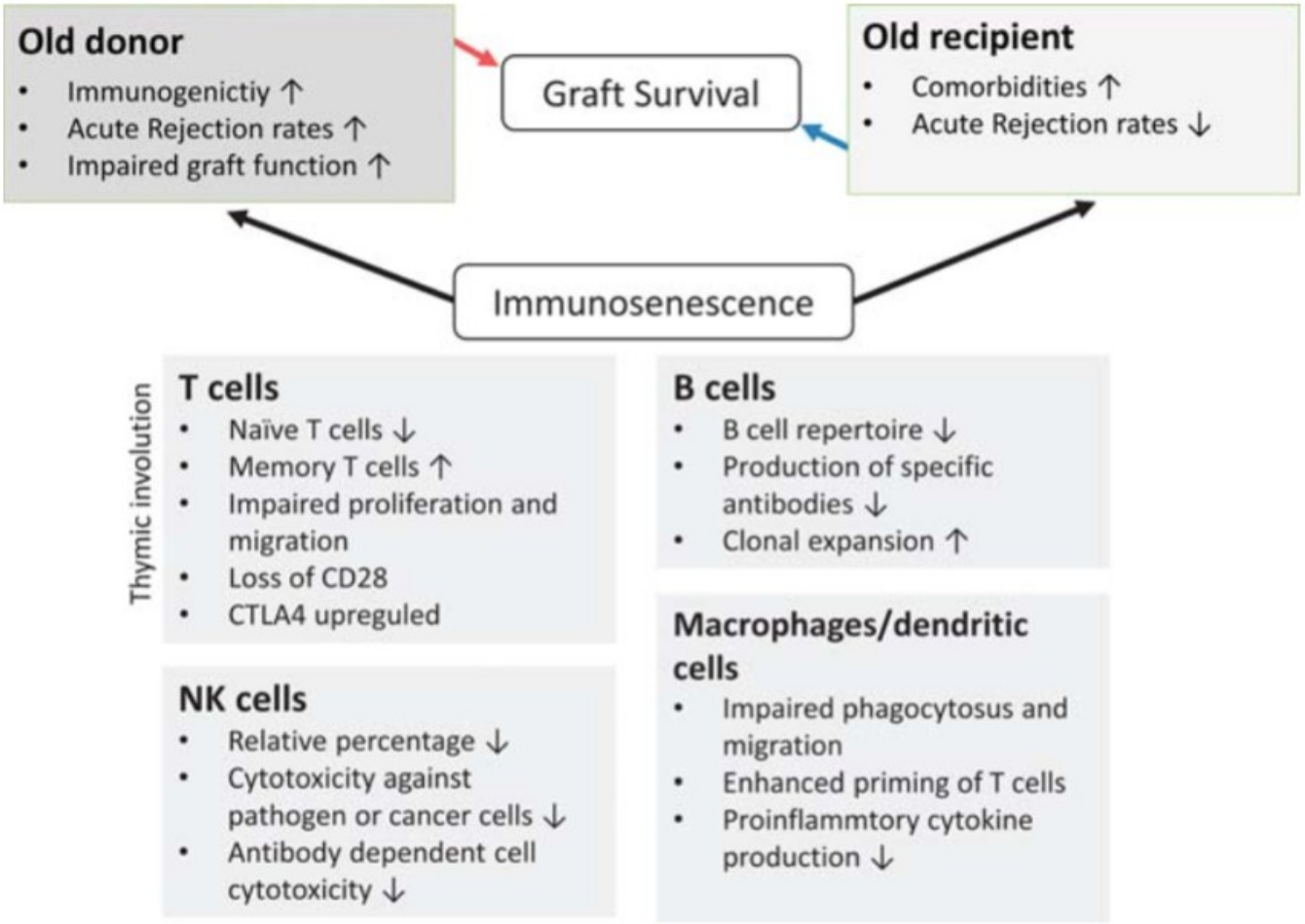
Fishman JA, CMI, 2014, 20 (Suppl. 7), 4–9

Impacto del envejecimiento en el órgano del donante y en la respuesta inmune del receptor durante el trasplante de órganos



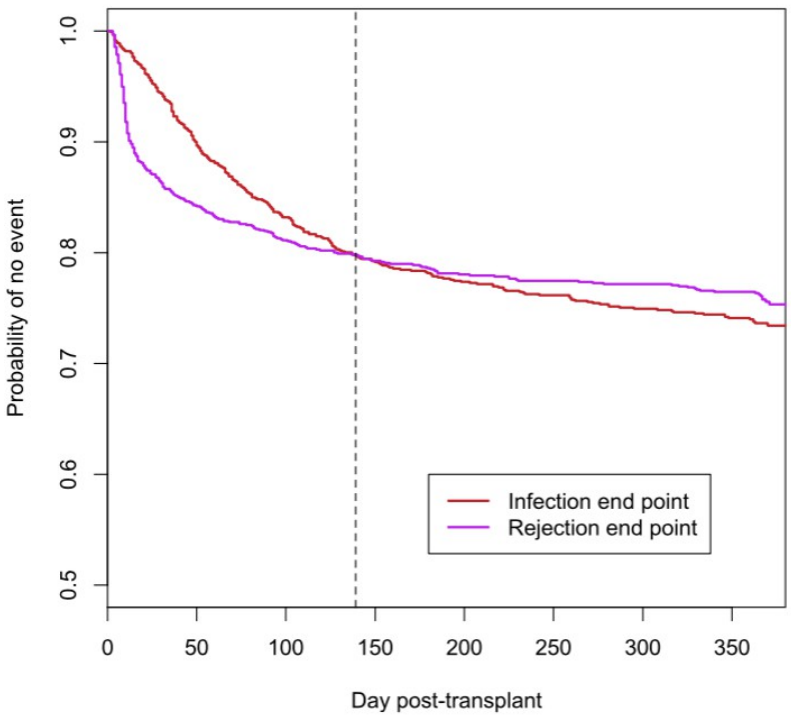
Colvin MM et al. J Clin Invest. 2017;127(7):2523–2529

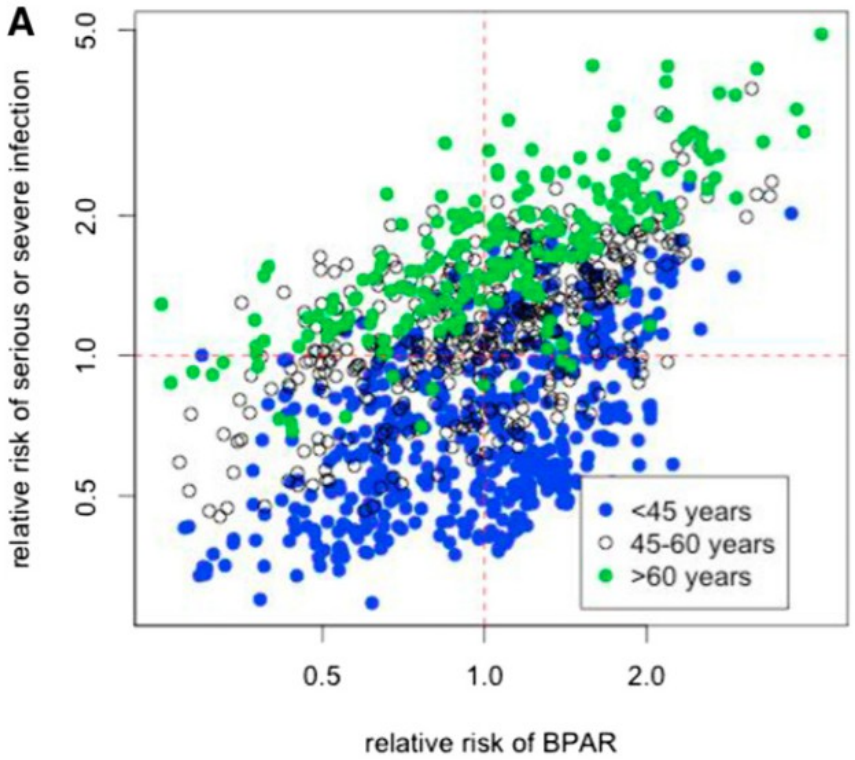
La inmunosupresión debe individualizarse en función de la edad del donante y del receptor



Krenizien F et al. Transplantation 2015;99: 2258–2268

Edad, infección grave y rechazo

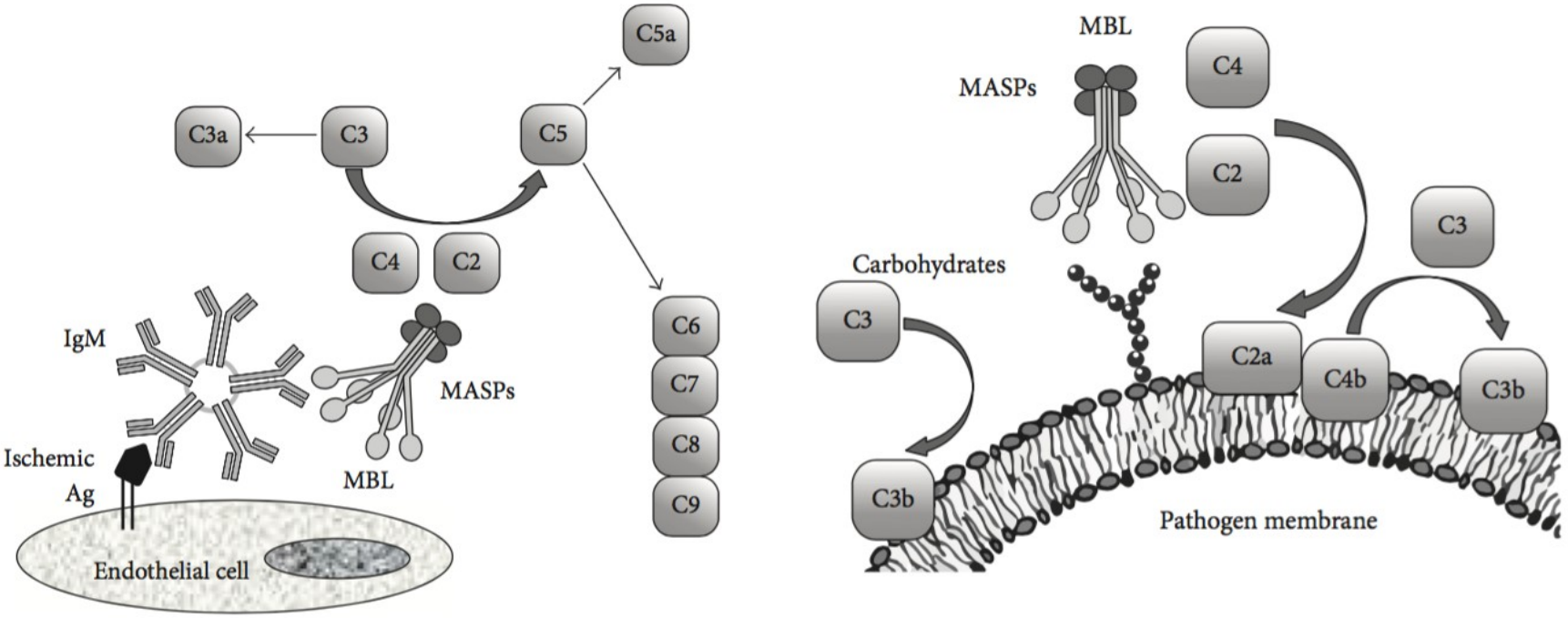




58% presentaron primero la infección y luego el rechazo
37% presentaron primero el rechazo y luego la infección
5% presentaron rechazo e infección simultáneamente

Cippà P et al. Clin J Am Soc Nephrol 2015, 10: 2213–2220

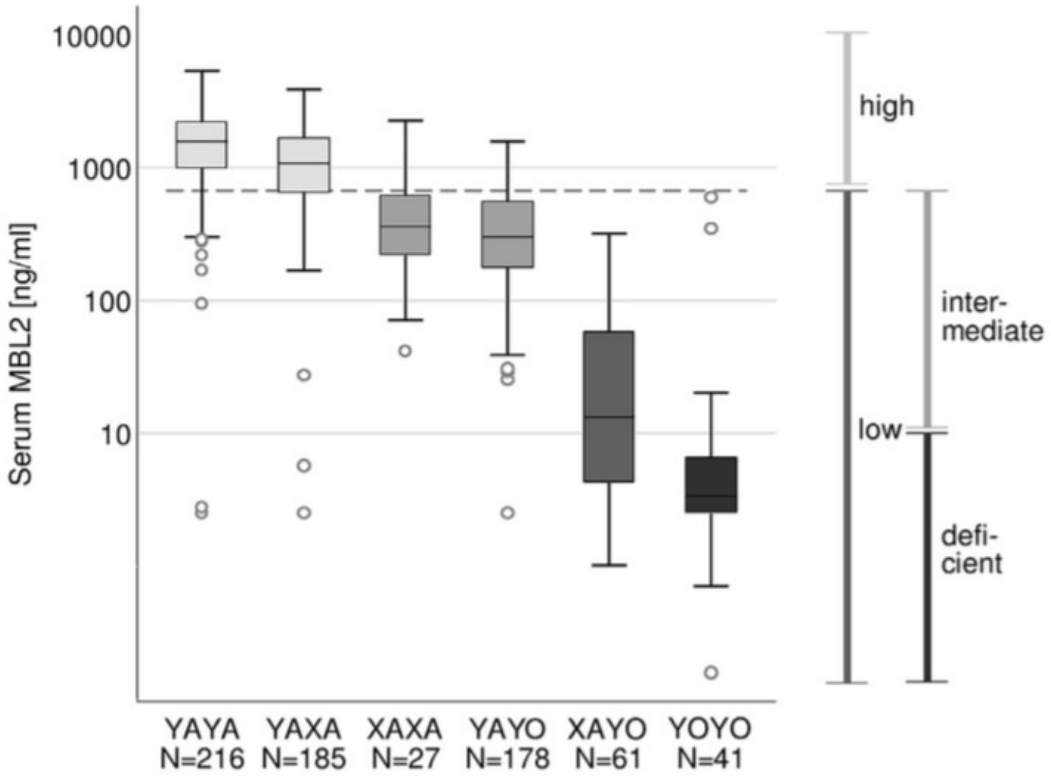
Mannose-Binding Lectin: Role in the Susceptibility to Infections and Ischemia-Reperfusion Related Injury



A model illustrates the activation of the lectin pathway by natural IgM in I/R injury or infective agents

Auriti C et al J Immunol Res 2017

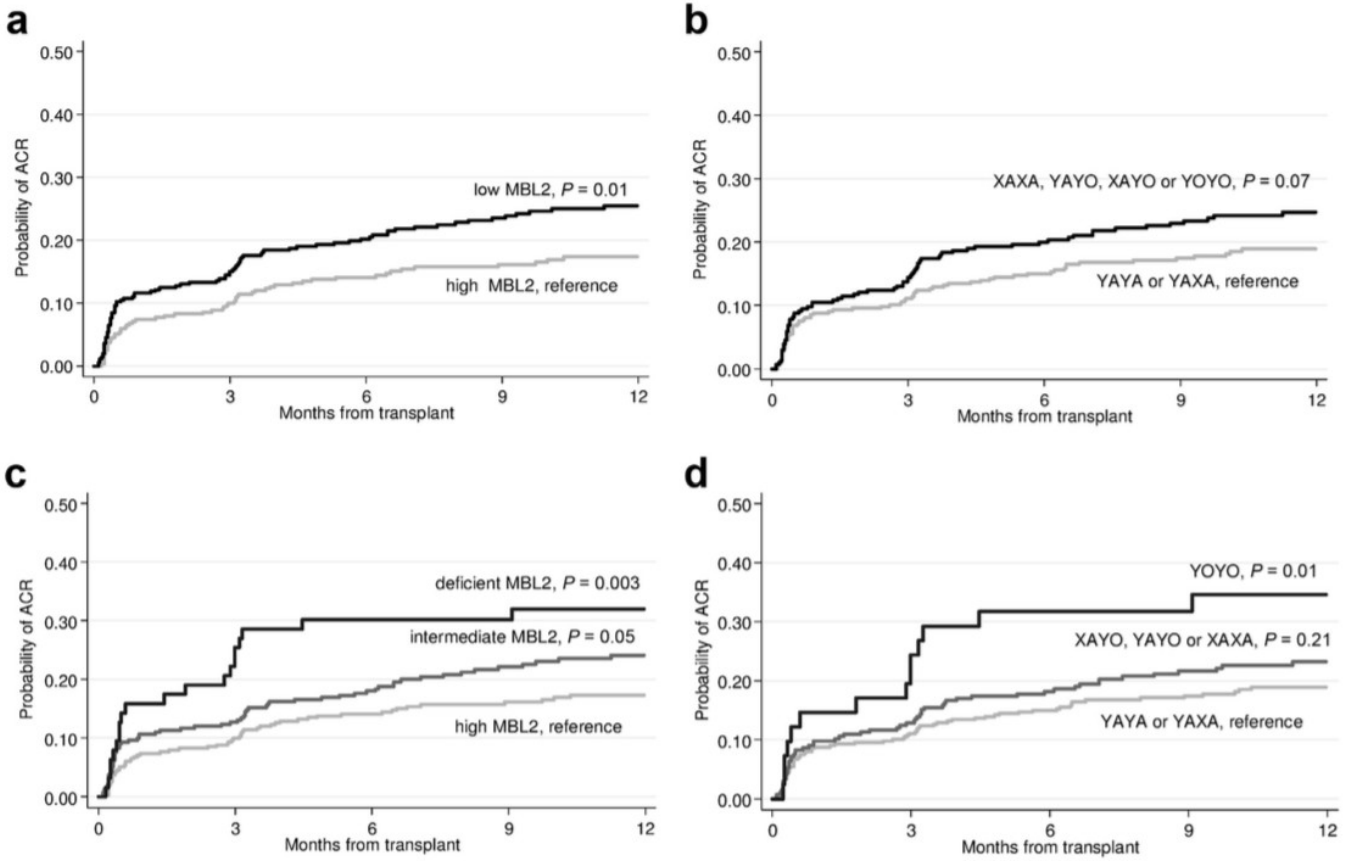
Serum MBL levels in kidney transplant recipients correlated with genotypes



710 consecutive Caucasian kidney transplant recipients included in the Swiss Transplant Cohort Study (STCS) together with all biopsy-proven rejection episodes and 1-year graft and patient survival

Golshayan D et al. Transplantation Direct 2016;2: e90

Polymorphisms in MBL2 resulting in low MBL serum levels are associated with an increased risk of acute cellular rejection in the first year after transplantation



710 consecutive Caucasian kidney transplant recipients included in the Swiss Transplant Cohort Study (STCS) together with all biopsy-proven rejection episodes and 1-year graft and patient survival

Golshayan D et al. Transplantation Direct 2016;2: e90

Influence of Mannose-Binding Lectin Gene Polymorphisms on The Invasiveness of Cytomegalovirus Disease After Solid Organ Transplantation

Table 1. Analysis of Risk Factors Associated With the Development of Invasive CMV Disease After Solid Organ Transplantation

	Univariate Analysis			Multivariate Analysis
	Invasive CMV Disease (n = 10)	Viral CMV Syndrome (n = 35)	P	Adjusted OR (95% CI) for Invasive CMV Disease
MBL2 exon 1				
AA	8 (80%)	14 (40%)		
A/O + O/O	2 (20%)	21 (60%)	.035	6.0 (1.1–32.5)
MBL2 promoter −550				
HH	2 (20%)	6 (17%)		
HL + LL	8 (80%)	29 (83%)	1.000	—
MBL2 promoter −221				
YY+YX	10 (100%)	34 (97%)		
XX	0	1 (3%)	1.000	—
MBL2 5′-UTR + 4				
QQ	0	3 (9%)		
QP + PP	10 (100%)	32 (91%)	1.000	—
Previous acute rejection	5 (50%)	21 (60%)	.720	—
Induction with ALG	2 (20%)	3 (9%)	.306	—
Use of mTOR inhibitors	1 (10%)	5 (14%)	1.000	—
CMV D+/R−	3 (30%)	11 (21%)	1.000	—

UTR, untranslated region; ALG, antilymphocyte globulins.

Exon 1 wild-type genotypes are associated with a higher risk of invasive CMV disease after solid organ transplantation

Cervera C et al. Transplant Proce 2009, 41: 2259–2261

Relative weight of in vitro, in vivo, and clinical evidence for effects of immunosuppressants against viruses

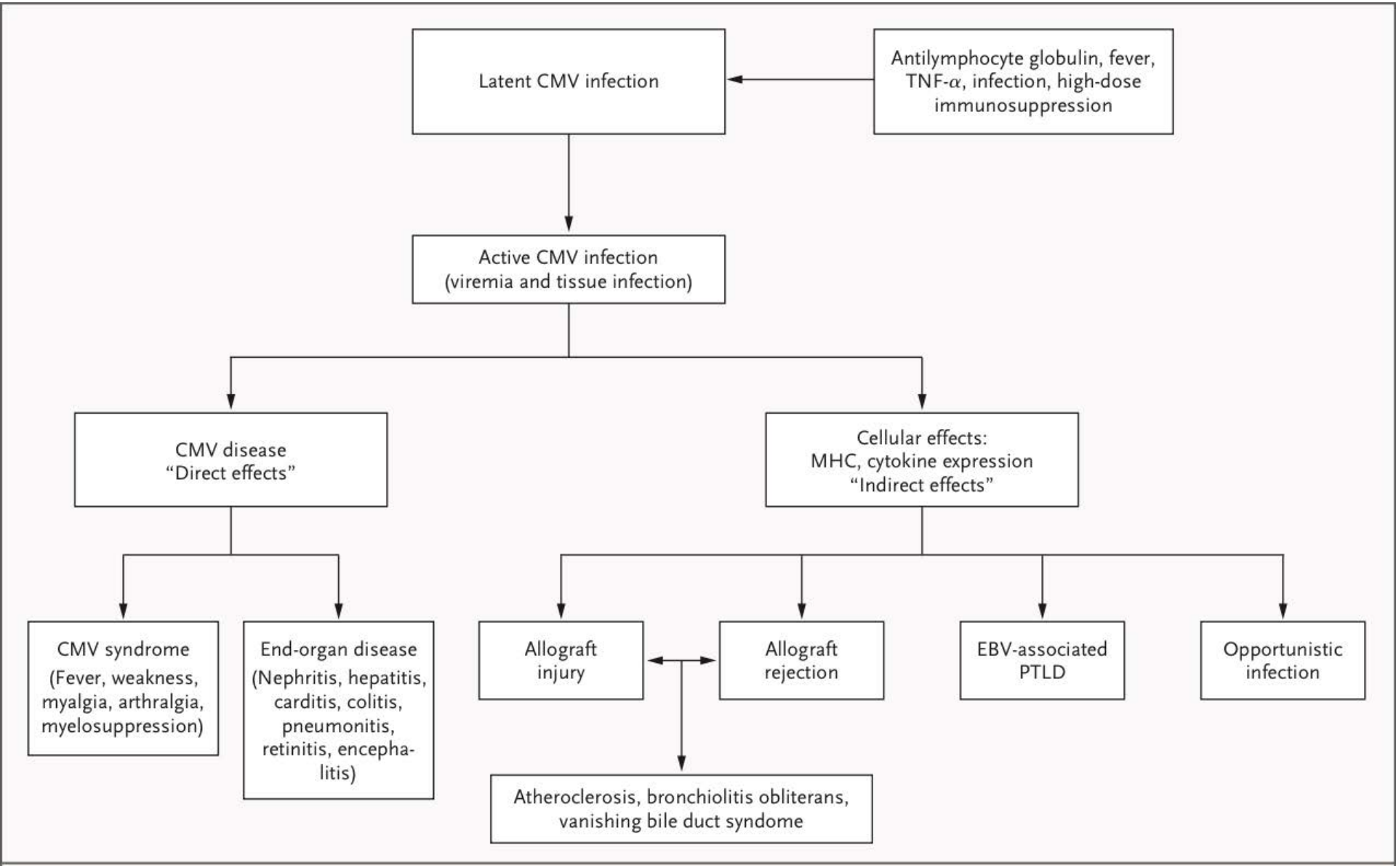
	HHV1	HHV2	VZV	EBV	CMV	HHV6	HHV7	HHV8	HCV	HBV	BKV	HIV	HPV	Parvovirus
CsA	↑	NA	NA	↑↑↑	↑↑↑	NA	NA	—[a]	↓↓↓	↓↓	—[b]	↓↓↓	↓	NA
Tacrolimus	NA	NA	NA	—[c]	↑↑↑	NA	NA	↓	↑	—	↑↑↑	—	NA	NA
Azathioprine	NA	NA	—	↑	↓↓	NA	NA	↓	—[d]	↑↑	↓	NA	NA	↑
MPA	↓↓↓[e]	↓↓↓[e]	—[f]	↓	↓↓[g]	NA	NA	NA	↓↓[h]	↓↓	↑	↓↓	—	NA
mTORi	NA	NA	NA	↓↓	↓↓	NA	NA	↓	↓[c]	↓	↓[i]	↓↓	↓	NA
Leflunomide	↓	NA	NA	NA	↓↓↓	NA	NA	NA	NA	NA	↓↓↓	↓	NA	NA
FK778	NA	NA	NA	NA	↓↓	NA	NA	NA	NA	NA	—[j]	NA	—	NA

MPA alone appears to be associated with increased incidence of CMV, albeit with better outcomes. However, MPA has consistently been demonstrated to act synergistically with antiherpesvirus treatment

Brennan DC et al, Rev. Med. Virol. 2013; 23: 97–125

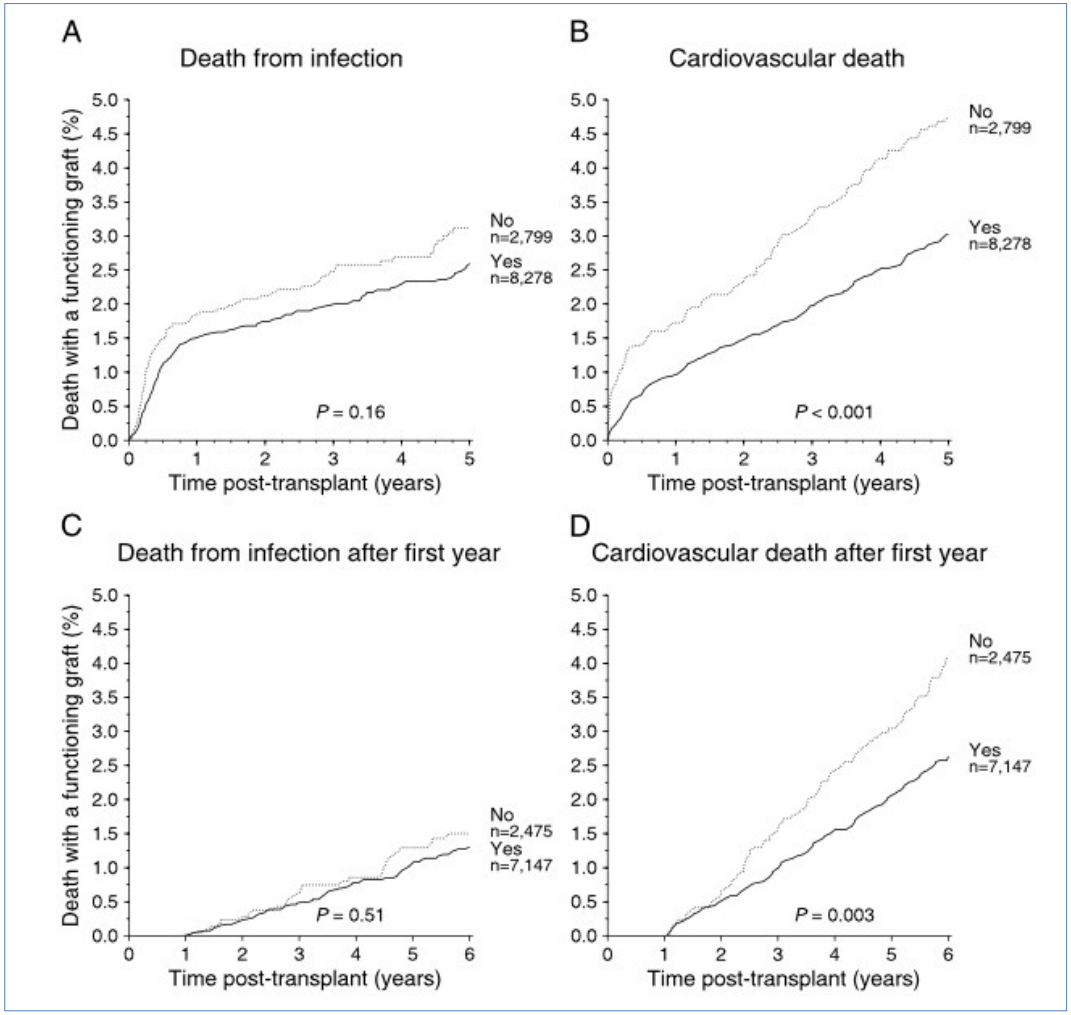
CMV infection

Cytomegalovirus causes both invasive disease ("direct effects") and immunologic phenomena ("indirect effects")



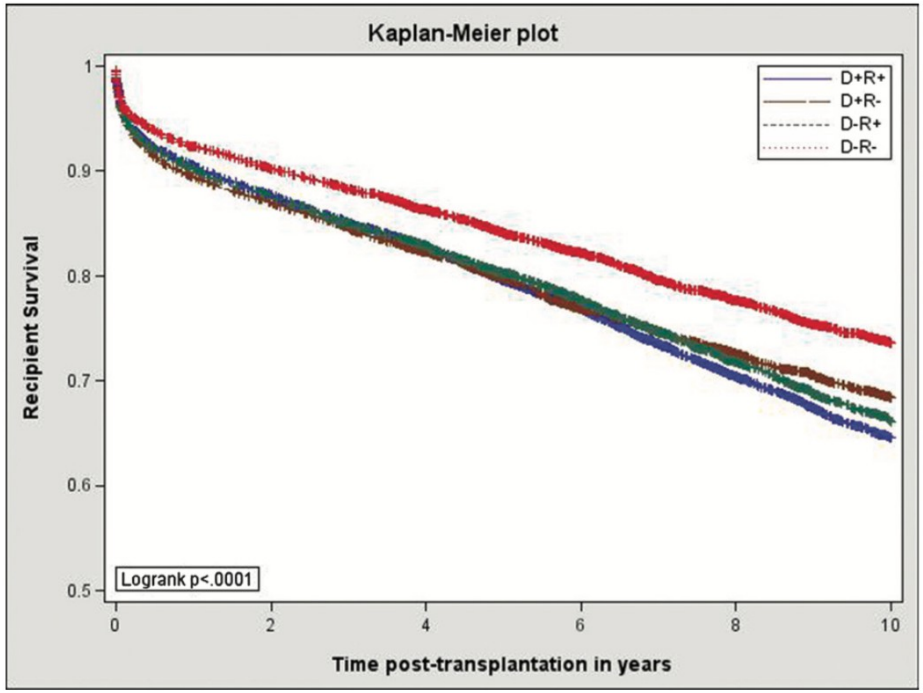
Fishman JA, N Engl J Med 2007;357:2601-14

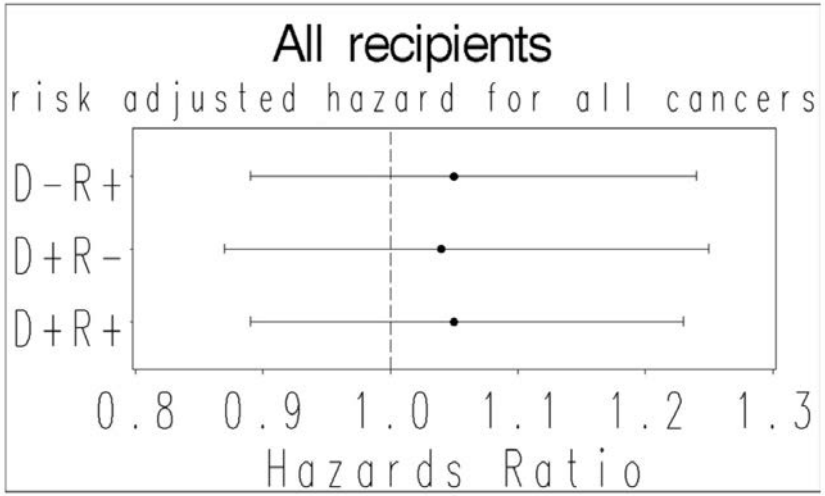
Reduced Rate of Cardiovascular Death After Cytomegalovirus Prophylaxis in Renal Transplant Recipients



Opelz G Döhler B, Transplantation 2015

CMV is associated with a significantly increased long-term mortality in kidney and cardiothoracic transplant recipients and an increased risk of cardiovascular death but not of post-transplant cancer

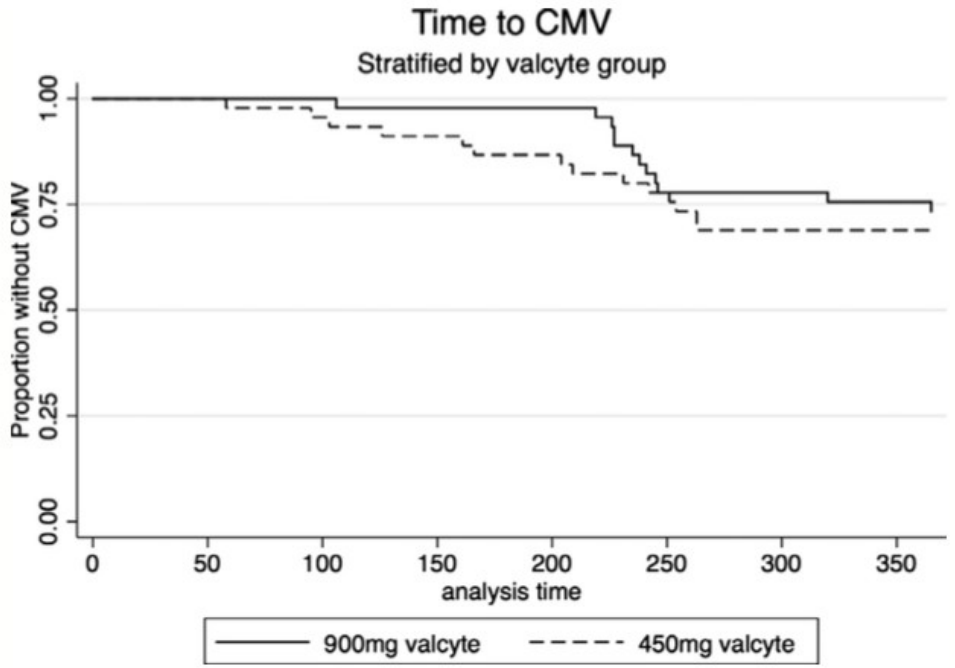




22461 U.K. Transplant Registry recipients of first solid organ (kidney, liver heart, and lung) transplantation between January 01, 1987, and December 31, 2007

Desai R. et al, Transplantation 2015, 99 (9):1989–94

Increased risk of breakthrough infection among cytomegalovirus donor-positive/recipient-negative kidney transplant recipients receiving lower-dose valganciclovir prophylaxis



Valganciclovir dosing regimens for cytomegalovirus donor (+)/recipient (−) kidney transplant recipients

Estimated CrCl (Cockcroft-Gault), mL/min	SD prophylaxis	LD prophylaxis
≥60	900 mg daily	450 mg daily
40–59	450 mg daily	450 mg daily
<40	450 mg every 48 h	450 mg every 48 h
Dialysis	450 mg every 48 h*	450 mg every 48 h*

*At the time of the study, the product information recommended using oral ganciclovir (GCV) in this population; however, oral GCV was on national drug shortage. As we did not want to subject these patients to home intravenous GCV therapy, we instead made a programmatic decision to administer oral valganciclovir at a dose of 450 mg orally every 48 hr and monitor patients closely for efficacy and adverse events.

CrCl, creatinine clearance; SD, standard dose; LD, lower dose.

1 patient in SD group (non-adherence) vs. 6 patient in LD group developed CMV infection during prophylaxis

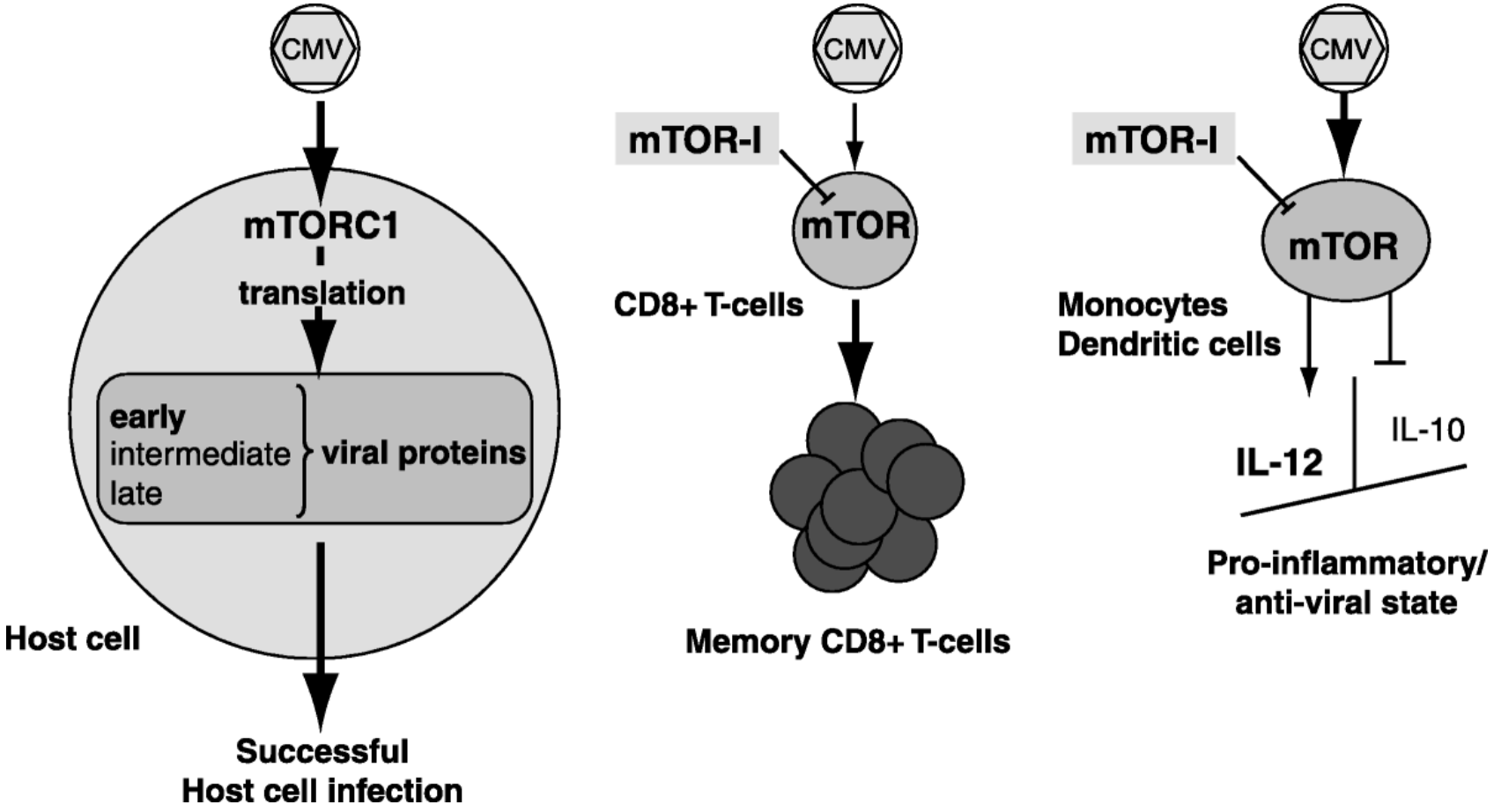
Stevens DR et al, Transpl Infect Dis 2015: 17: 163–173

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

- 14 days of pretransplant donor treatment with valganciclovir versus placebo
- 17 D+ / R- kidney transplant recipìennts: 7 Valganciclovir
  10 placebo
- All recipients received routine posttransplant viral prophylaxis with valganciclovir
- No disease in the valG group but one CMV disease and EBV-related PTLD in the placebo group (donor and recipient with similar EBV strain)

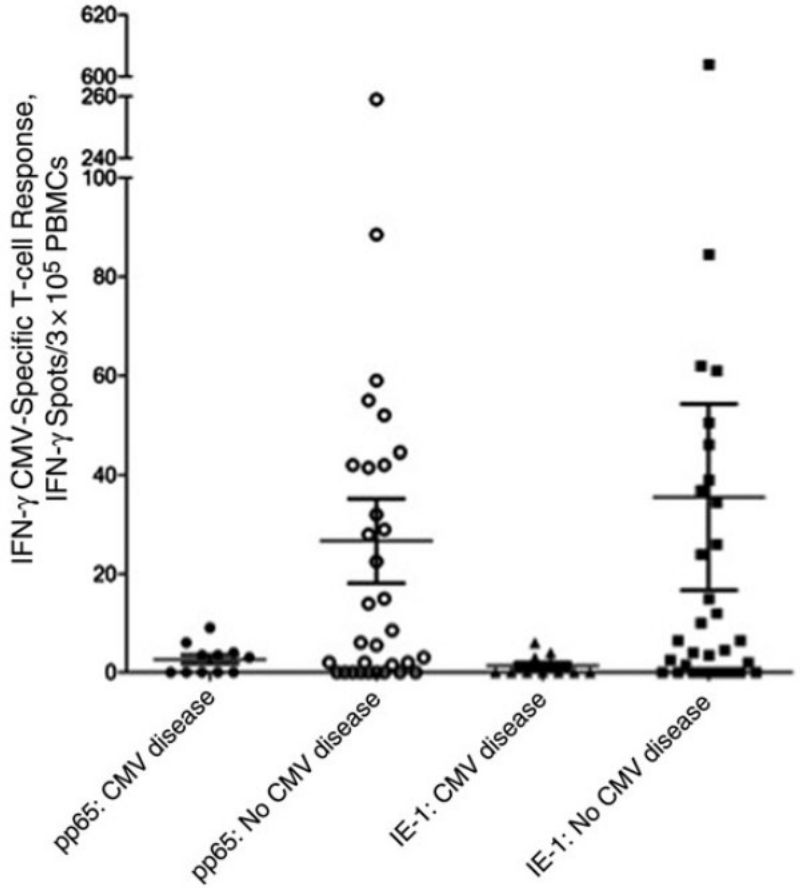
Verghese PS et al, Transplantation 2014

Several potential molecular mechanisms may account for the anti-CMV potency of mTOR inhibitors at the cellular level



Nashan B et al, Transplantation 2012 vol. 93 (11) pp. 1075-1085

Preformed Frequencies of CMV-Specific Memory T and B Cells Identify Protected CMV-Sensitized Individuals Among Seronegative Kidney Transplant Recipients



Lucia M et al, Clin Infect Dis 2014, 59:1537-45

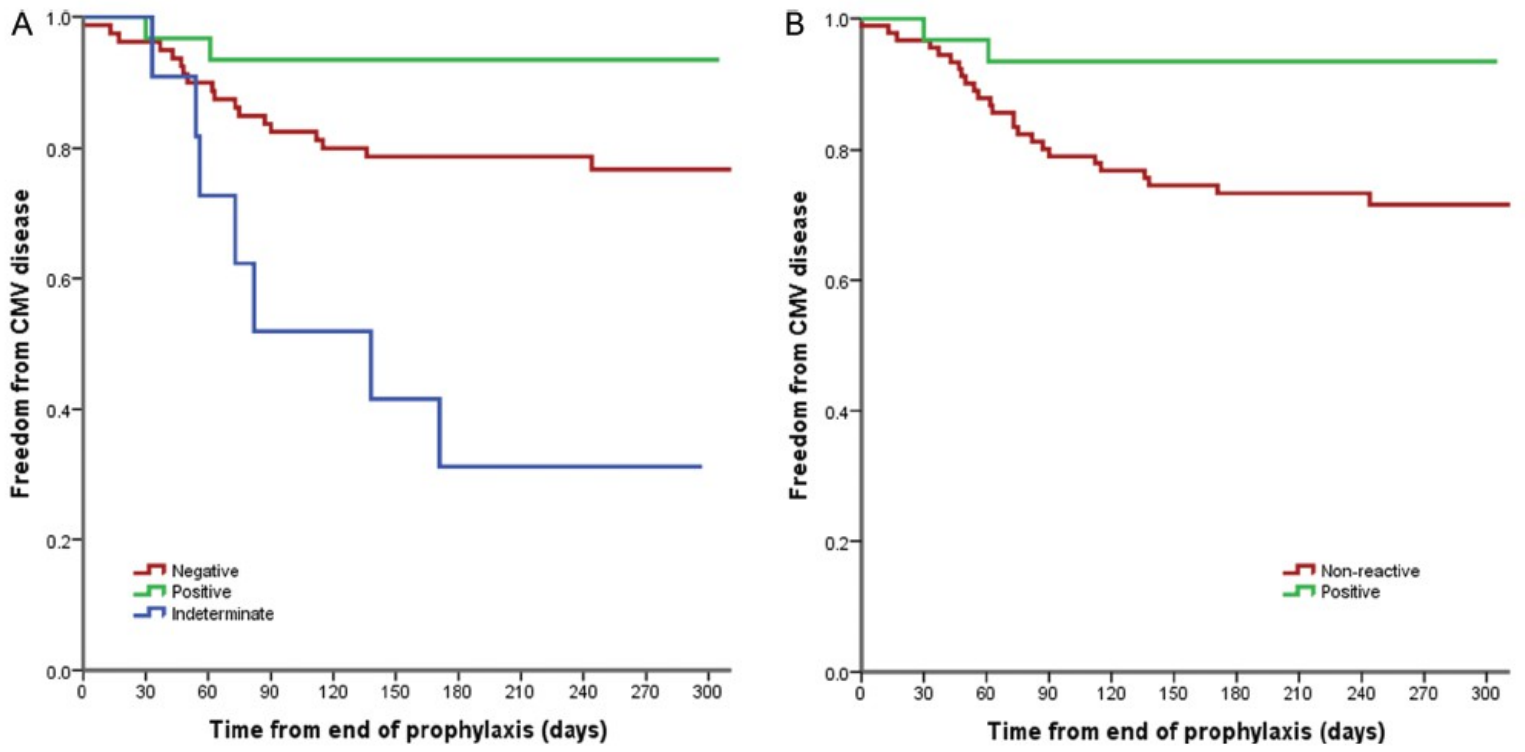
Resultado del análisis Quantiferon-CMV en pacientes D+/R- al terminar la profilaxis y 1 y 2 dos meses después

	First Sample (n = 124)	Second Sample (n = 107)	Third Sample (n = 73)
Positive	15 (12.1%)	21 (19.6%)	19 (26.0%)
Negative	80 (64.5%)	64 (59.8%)	43 (58.9%)
Indeterminate	29 (23.3%)	22 (20.6%)	11 (15.1%)

Samples collected after the development of CMV disease were excluded.

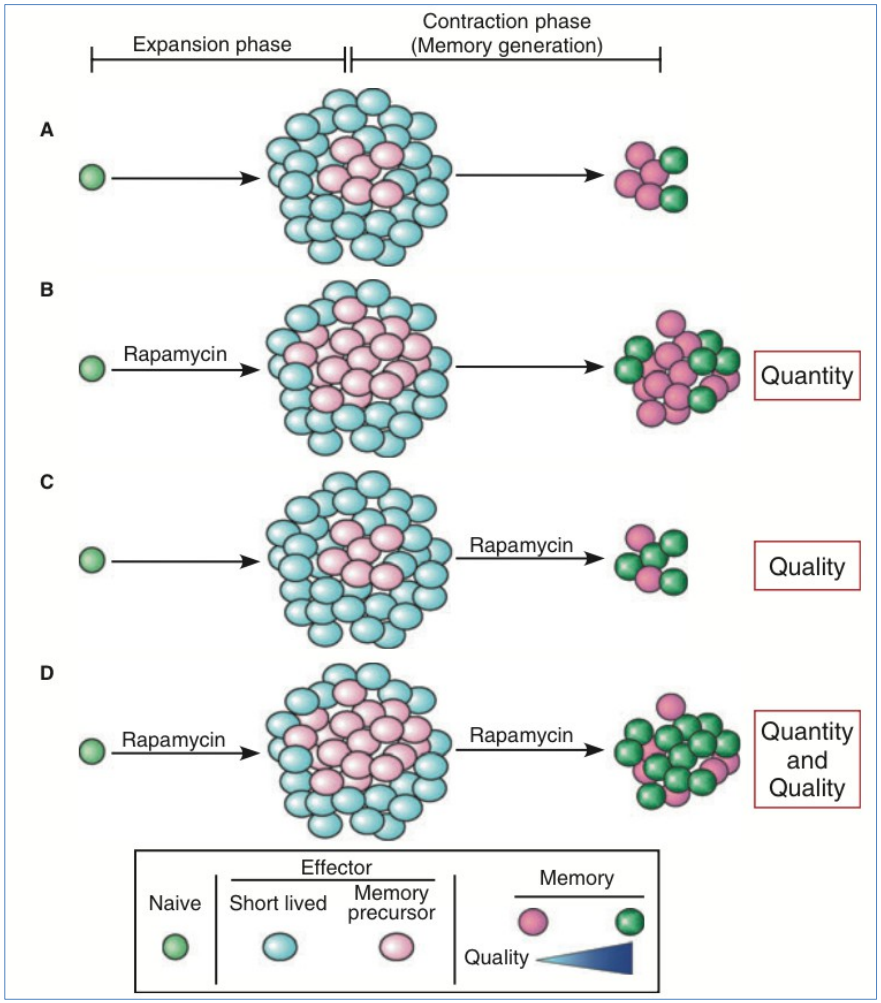
Manuel O et al,Clin Infect Dis. 2013 Mar;56(6):817-24

Kaplan-Meier curves of the incidence of cytomegalovirus (CMV) disease according to the result of the Quantiferon-CMV assay



Manuel O et al,Clin Infect Dis. 2013 Mar;56(6):817-24

Rapamycin improves the quantity and quality of memory CD8+ T cells



Araki K et al, Immunological Reviews 2010, 235: 234–243

Impact of Current Transplantation Management on the Development of Cytomegalovirus Disease after Renal Transplantation - **RESITRA Transplant Network**

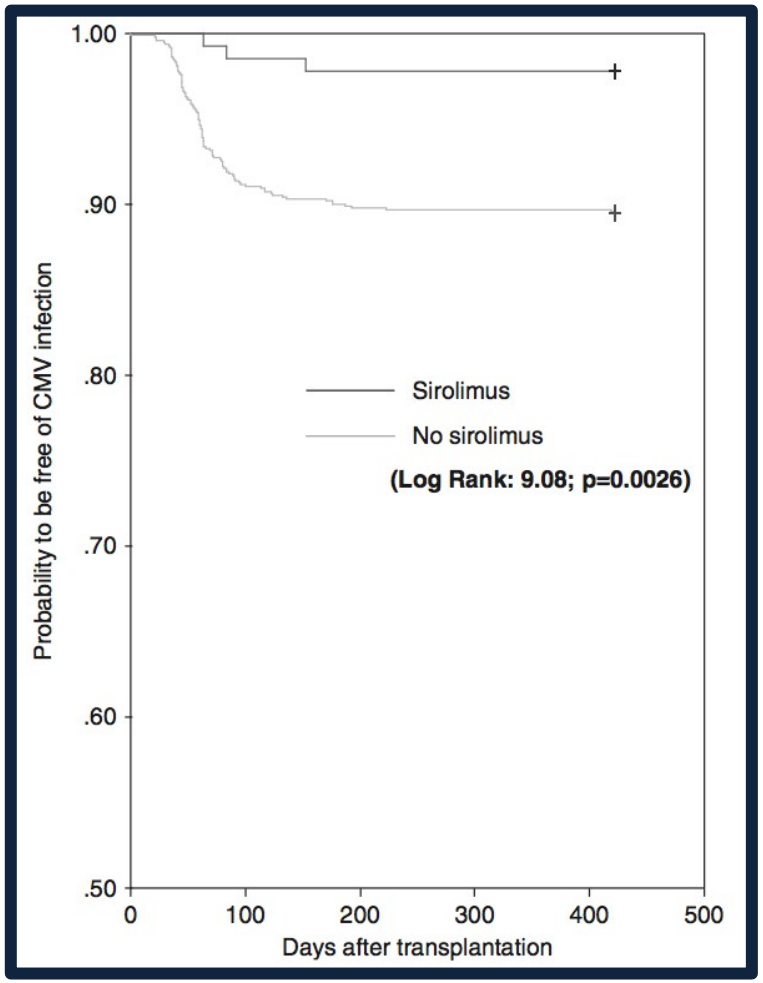
Table 3. Global risk factors for cytomegalovirus (CMV) disease in kidney allograft recipients.

	Univariate analysis		Multivariate analysis	
Variable	OR (CI 95%)	*P*	OR (CI 95%)	*P*
Donor age >60 years	1.93 (1.27–2.92)	.002	2.3 (1.5–3.7)	<.001
Cyclosporine use	1.9 (1.22–3.06)	.04	1.7 (1.1–2.9)	.03
Prophylaxis against CMV	2.2 (1.2–4)	.007	…	…
Sirolimus use	0.32 (0.12–0.9)	.03	0.27 (0.1–0.78)	.016
Kidney-pancreas transplantation	2.33 (1.1–5)	.03	3.7 (1.5–9.1)	.005
CMV D^+/R^-	5.9 (3.7–9.4)	<.001	7.3 (4.4–12)	<.001
Epstein-Barr virus D^+/R^-	4.87 (1.7–13.8)	.003	…	…
Use of OKT3 or antithymocite globulin for induction	2.1 (1.14–3.8)	.002	2.14 (1.1–4.4)	.04
Viral infection other than CMV[a]	1.97 (1.3–3)	.002	…	…
Acute rejection episode	2.63 (1.66–4.1)	<.001	2.7 (1.6–4.4)	<.001
Chronic graft malfunction	2.1 (1.4–3.2)	<.001	1.8 (1.1–2.9)	.01

San Juan R et al, Clinical Infectious Diseases 2008;47:875–82

The use of sirolimus as maintenance therapy in kidney recipients is associated with a low rate of CMV infection

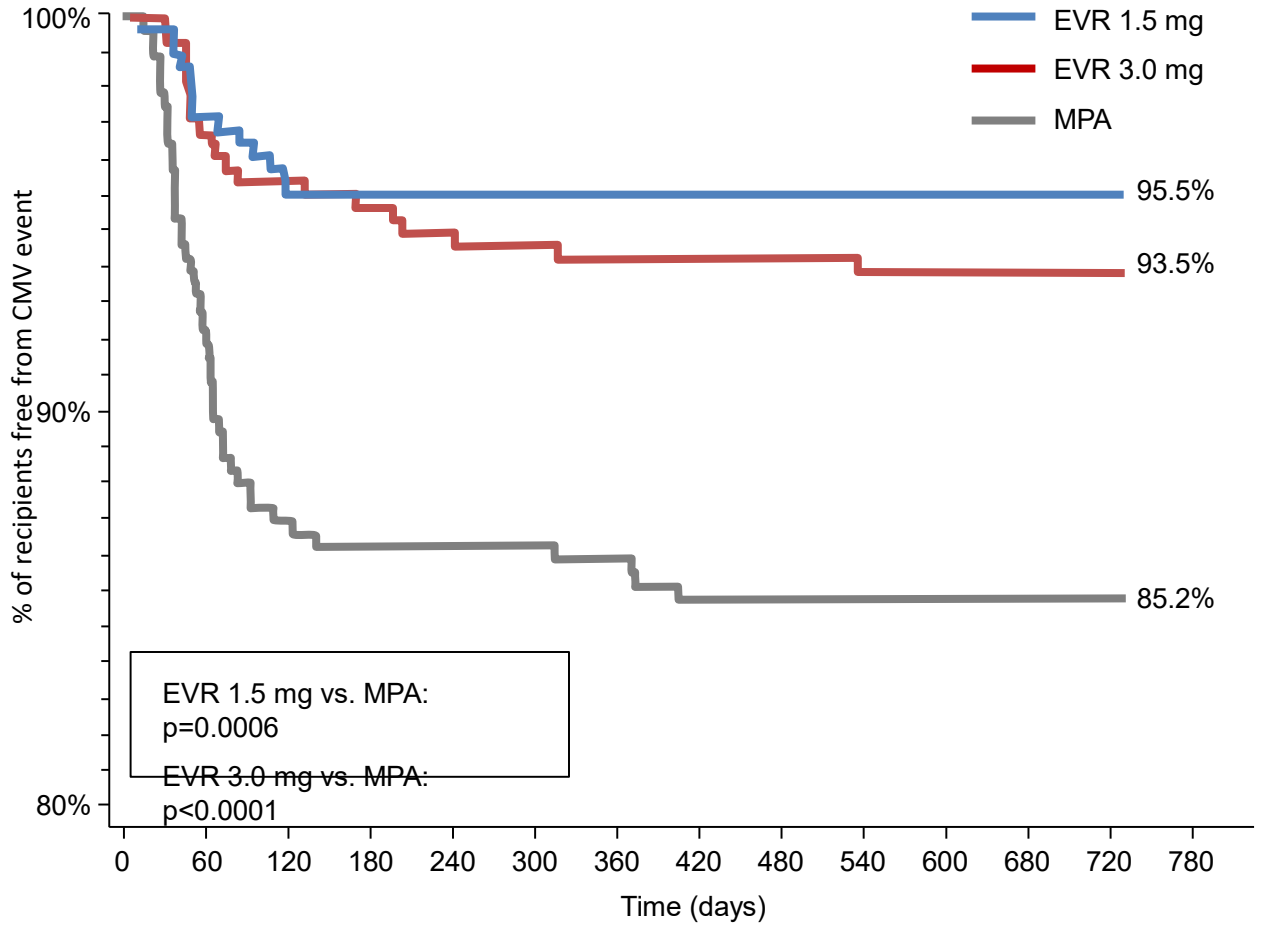
RESITRA Transplant Network



Fortun J et al, Transpl Infect Dis 2010: 12: 397-405

Fewer CMV infections with EVR than with MPA

Pooled analysis of RCTs



- A2309 (N = 833)
- B201 (N = 588)
- B251 (N = 583)

Brennan DC et al. *Am J Transplant* 2011;11;2453–62

Retrospective analysis of the incidence of CMV infection in patients treated with mTORi

de novo mTORi

Author, Year	Therapy	Induction	N	CMV INCIDENCE (%)	p
Ekberg, 2010 SYMPHONY	Stand-CsA Low-CsA Low-Tac Low-SRL	No Daclizumab Daclizumab Daclizumab	384 408 403 380	15.5 11.5 10.2 6.3	0.003
Büchler, 2007 SPIESSER	SRL CsA	Timo Timo	71 74	6.0 23	0.004
Flechner, 2002	SRL CsA	Basiliximab Basiliximab	31 30	10 7	NS
Larson, 2006	SRL Tac	Timo Timo	81 84	3 12	0.02
Glotz, 2010	SRL Tac	Timo Timo (DGF)	71 70	1.4 20	0.001
Durrbach, 2008	SRL CsA	Timo Timo	33 36	0 11	0.01

Andrassy J et al, Transplantation 2012;94: 1208-1217

Retrospective analysis of the incidence of CMV infection in patients treated with mTORi

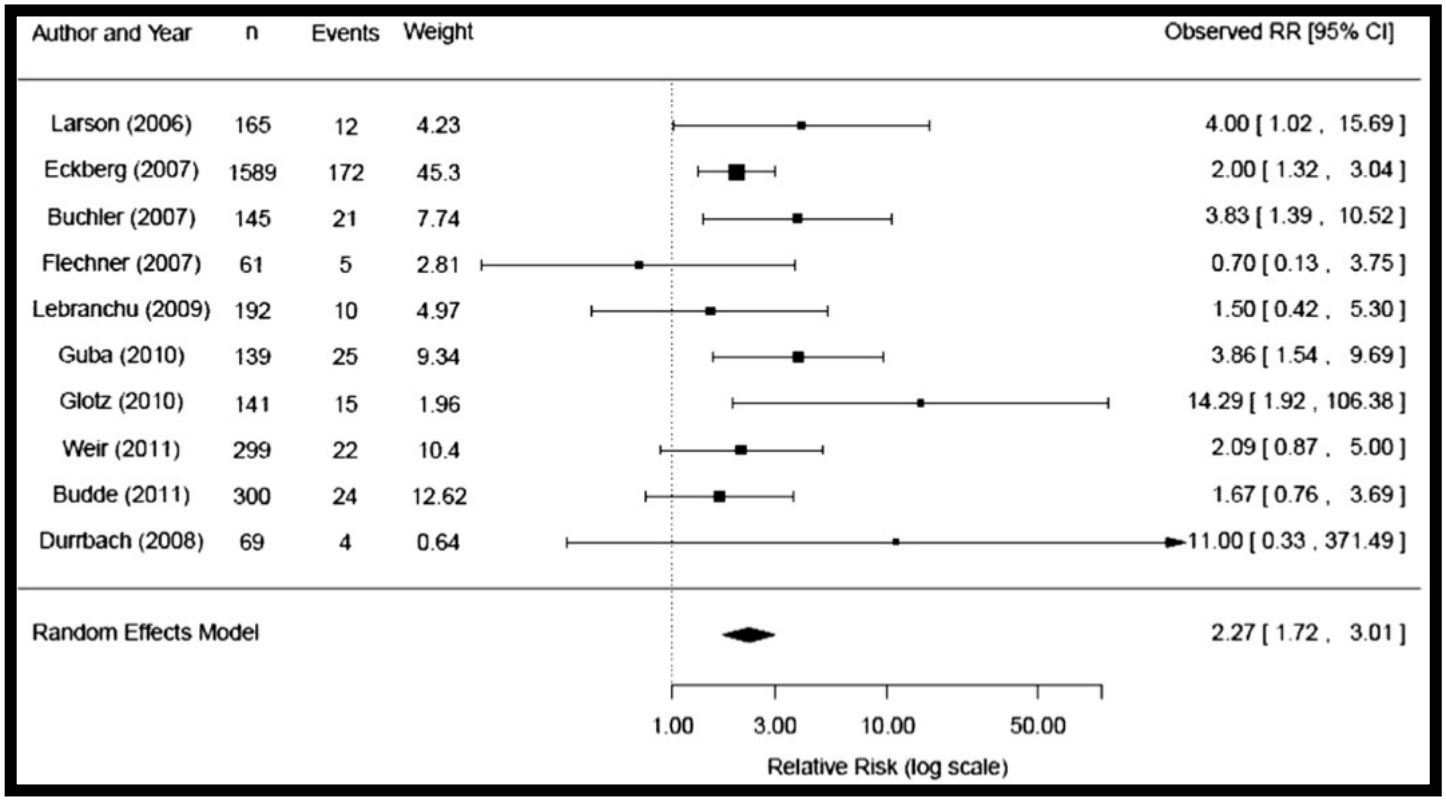
mTORi use in early conversion

Author, Year	mTORi initiation	Therpy	Induction	N	CMV Incidence (%)	p
Weir, 2011 SPARE-THE-NEPHRON	1- 6 m	SRL CsA/Tac	Timo, CD25 Timo, CD25, OKT3(1p)	148 151	4.7 9.8	0.09
Lebranchu, 2009 withVERT	3 m	SRL	Daclizumab Daclizumab	95 97	5 6	NS
Guba, 2010 SMART	14-21 d	SRL CsA	ATG-F ATG-F	69 70	7.3 28.2	0.001
Budde, 2011 ZEUS	4.5 m	Everol CsA	Basiliximab Basiliximab	155 145	6 10	NS

Andrassy J et al, Transplantation 2012;94: 1208-1217

Is cytomegalovirus prophylaxis dispensable in patients receiving an mTOR inhibitor-based immunosuppression? A systematic review and meta-analysis.

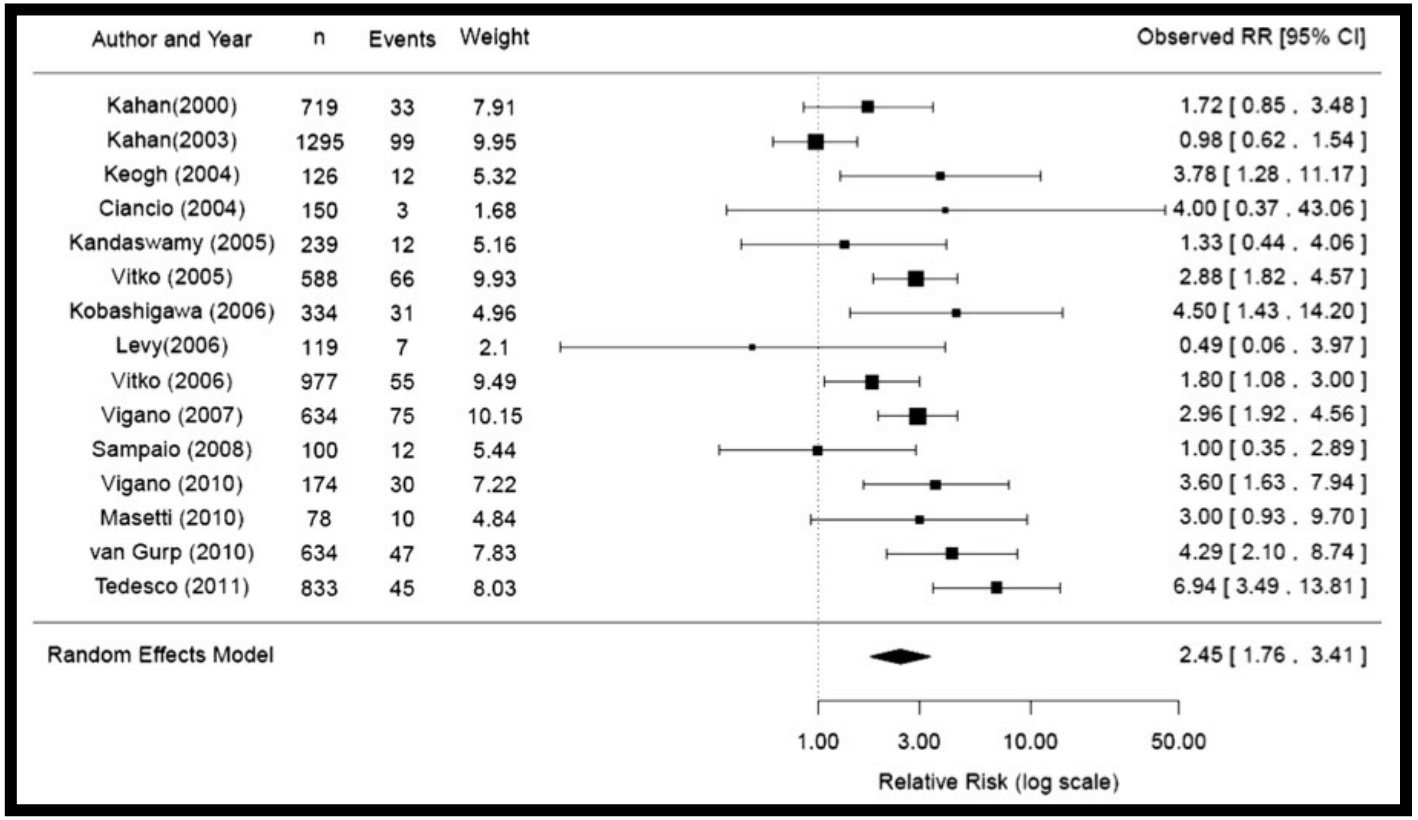
Forest plot indicating the odds ratio of the occurrence of CMV on mTOR-Is versus CNIs



Andrassy J et al, Transplantation 2012;94: 1208Y1217

Is cytomegalovirus prophylaxis dispensable in patients receiving an mTOR inhibitor-based immunosuppression? A systematic review and meta-analysis.

Forest plot indicating the odds ratio of the occurrence of CMV on a combination of mTOR-Is and CNIs versus CNIs

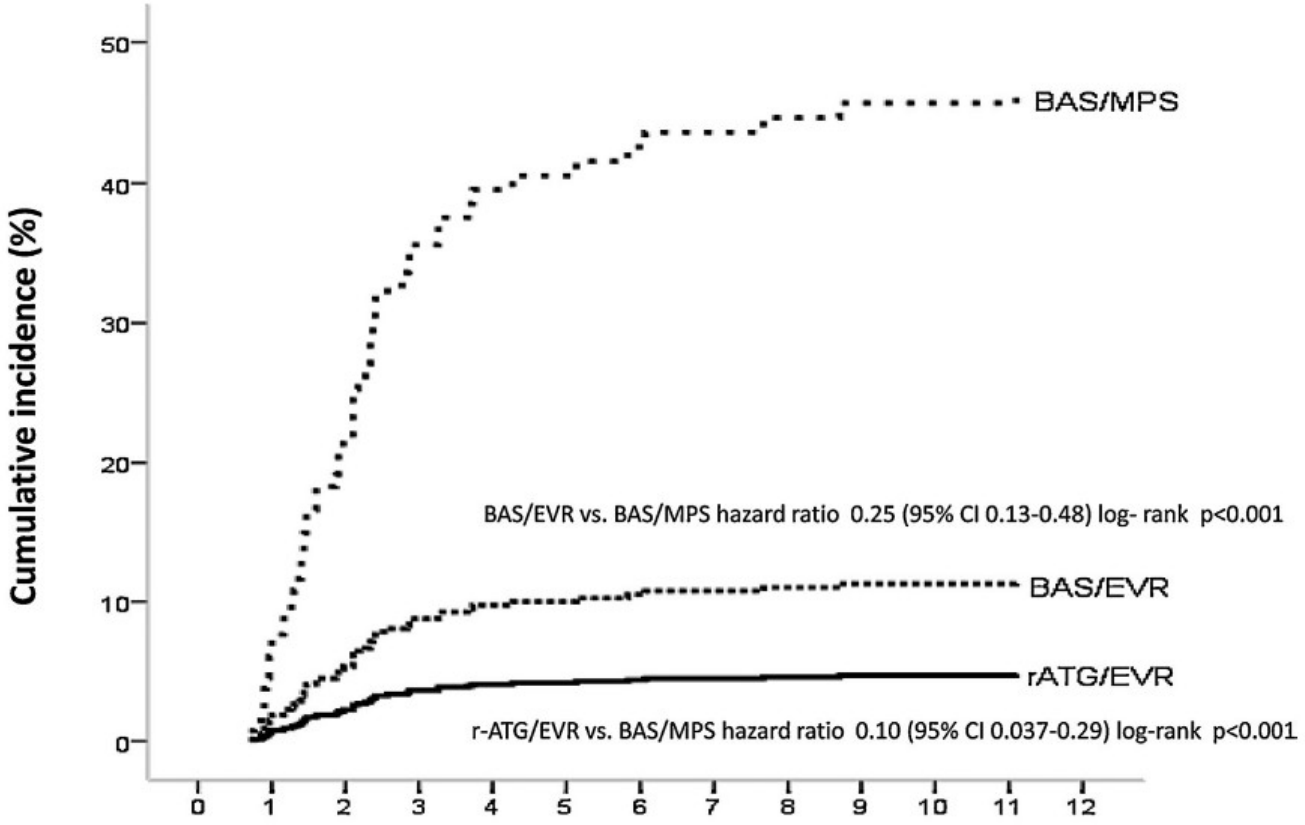


Andrassy J et al, Transplantation 2012;94: 1208Y1217

Reduced Incidence of Cytomegalovirus Infection in Kidney Transplant Recipients Receiving Everolimus and Reduced Tacrolimus Doses

H. Tedesco-Silva[1,*], C. Felipe[1], A. Ferreira[1], M. Cristelli[1], N. Oliveira[1], T. Sandes-Freitas[1], W. Aguiar[2], E. Campos[3], M. Gerbase-DeLima[3], M. Franco[4] and J. Medina-Pestana[1]

Tedesco-Silva H et al, Am J Transplant 2015; 15: 2655–2664



Number at Risk													
r-ATG/EVR	85	85	84	81	81	81	81	81	81	81	81	81	81
BAS/EVR	102	100	94	94	93	93	93	92	91	91	91	91	91
BAS/MPS	101	95	83	71	68	67	65	65	65	64	64	64	63

Figure 3: Cumulative incidence of CMV infection/disease during the 12 months of follow up.

Tedesco-Silva H et al, Am J Transplant 2015; 15: 2655–2664

Transplant International

ORIGINAL ARTICLE

Effect of mammalian target of rapamycin inhibitors on cytomegalovirus infection in kidney transplant recipients receiving polyclonal antilymphocyte globulins: a propensity score-matching analysis

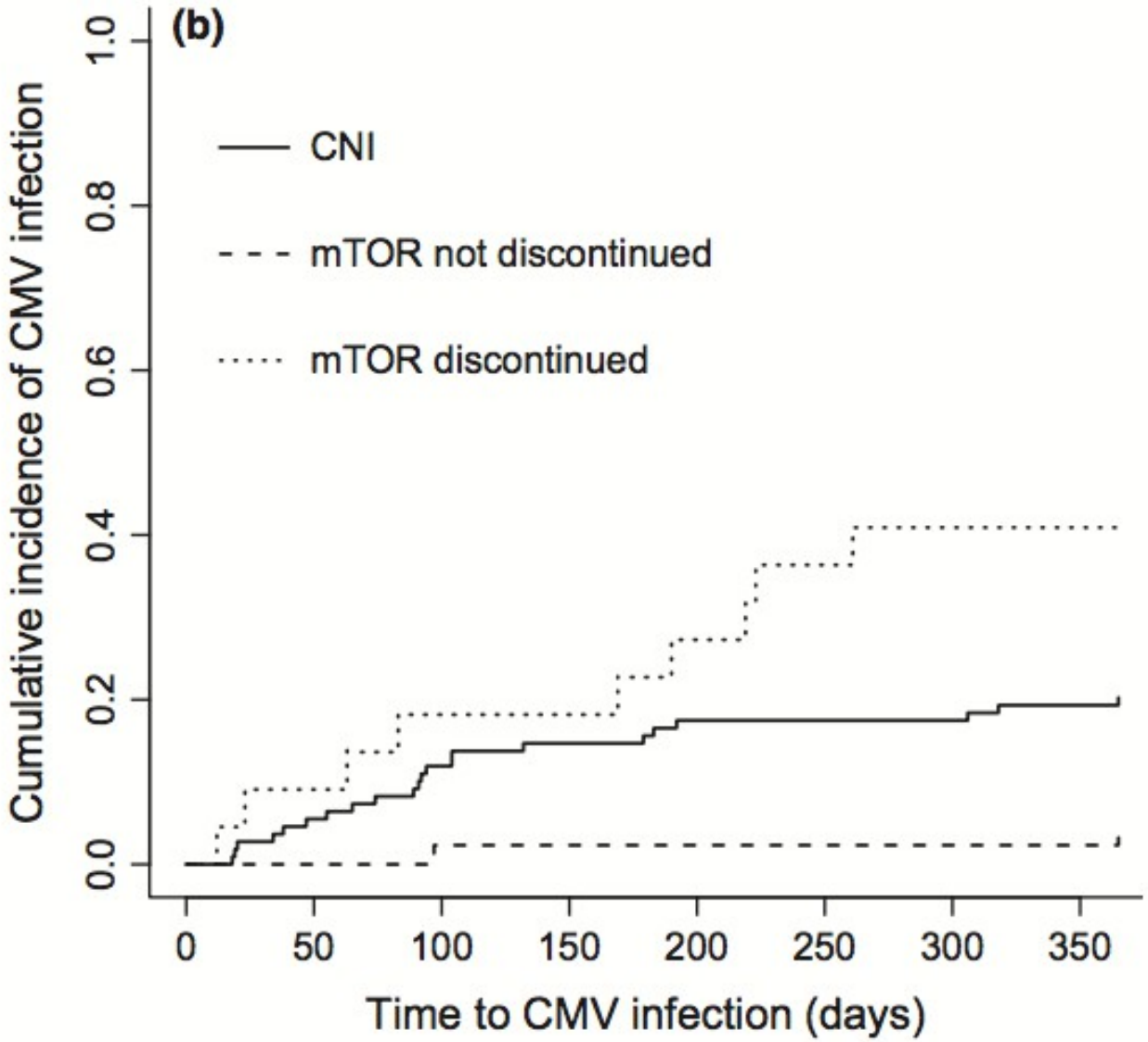
Carlos Cervera[1,2,*], Frederic Cofan[3,*], Cristina Hernandez[1], Dolors Soy[4], Maria Angeles Marcos[5], Gemma Sanclemente[1], Marta Bodro[1], Asunción Moreno[1], Fritz Diekmann[3], Josep Maria Campistol[3] & Frederic Oppenheimer[3]

Transplant International 2016; 29: 1216–1225

Table 2. Cox-regression analysis of the risk factors associated with cytomegalovirus (CMV) infection or disease.

				Univariate analysis		Multivariate analysis	
	Category	*N*	CMV infection/ disease *N* (%)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age more than 50	Yes	208	43 (21%)	1.9 (1.1–3.4)	0.032	1.8 (1.0–3.3)	0.045
	No	129	15 (12%)				
High-intensity immunosuppression	Yes	232	43 (19%)	2.0 (1.0–4.1)	0.053	2.6 (1.2–5.3)	0.011
	No	105	15 (14%)				
CMV donor +/recipient –	Yes	43	16 (37%)	2.7 (1.5–4.8)	0.001	4.4 (2.3–8.4)	<0.001
	No	294	42 (14%)				
Use of anti-CMV prophylaxis	Yes	218	38 (17%)	1.0 (0.6–1.8)	0.948	0.4 (0.2–0.7)	0.006
	No	119	20 (17%)				
Previous acute rejection	Yes	55	11 (20%)	0.9 (0.7–1.3)	0.561	–	–
	No	282	47 (17%)				
mTORi treatment	Time-dependent variable					0.4 (0.2–0.8)	0.008

Transplant Int 2016; 29: 1216–1225



Transplant Int 2016; 29: 1216–1225

EBV infection

Levels of evidence of analysed risk factors for PTLD

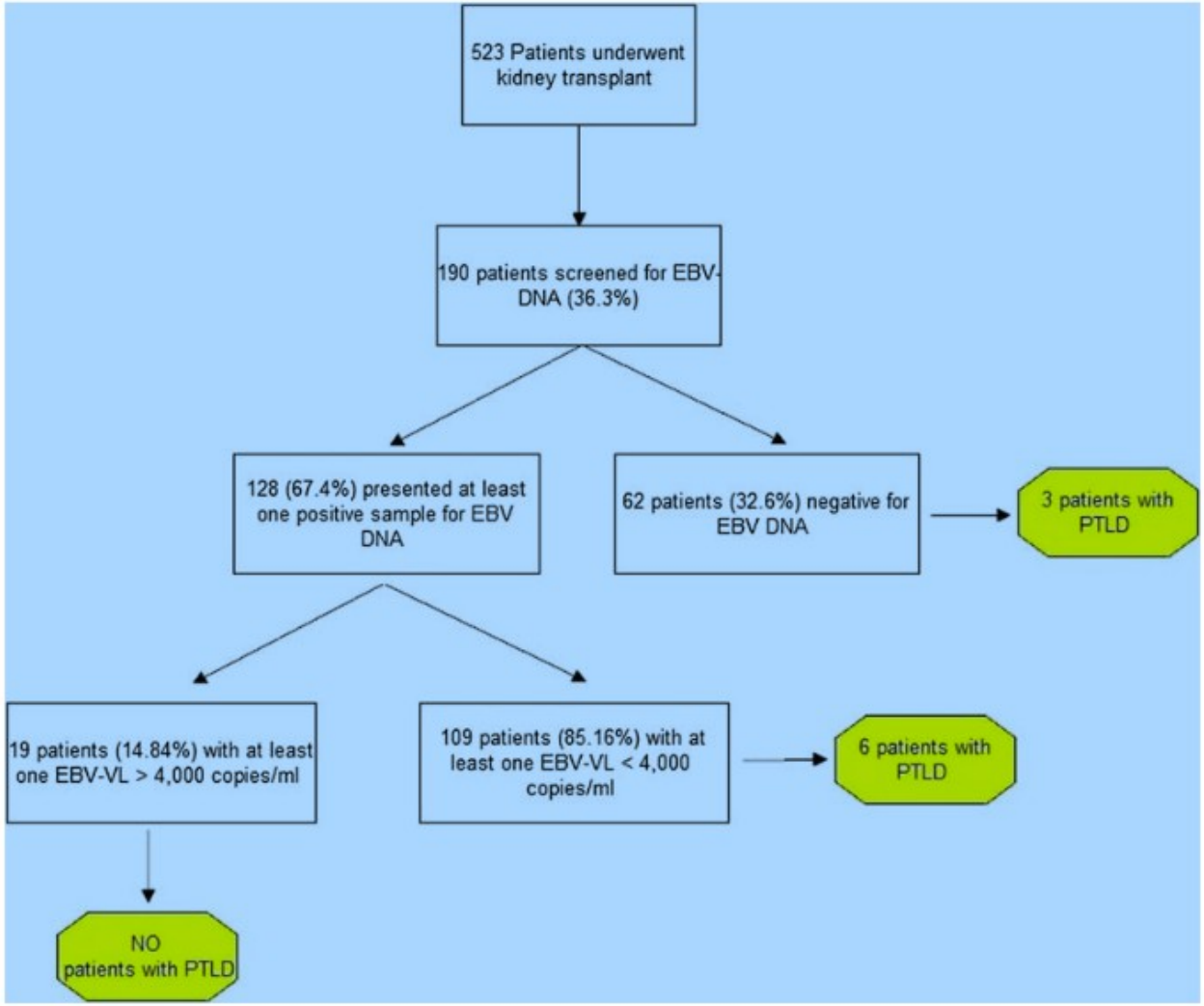
Type of PTLD	Potential risk factor for PTLD	Level of evidence	References
Early PTLD	EBV recipient seronegativity, D+/R- serostatus	A-II	[16,21–23]
	Use of anti-lymphocyte antibodies	B-II	[16,17,20,22,25,26,30]
	Maintenance IS with tacrolimus	C-II	[17,19,20,29,30,32]
	Maintenance IS with mycophenolate	D-II	[16,27,29,33–36]
Late PTLD	Older age (>60 years)	C-III	[16,22]
	Long-term IS	C-III	[16,22]

IS, immunosuppression.

San-Juan R et al. Clin Microbiol Infect 2014; 20 (Suppl. 7): 109–118

The keystone of PTLD diagnosis is the clinical suspicion

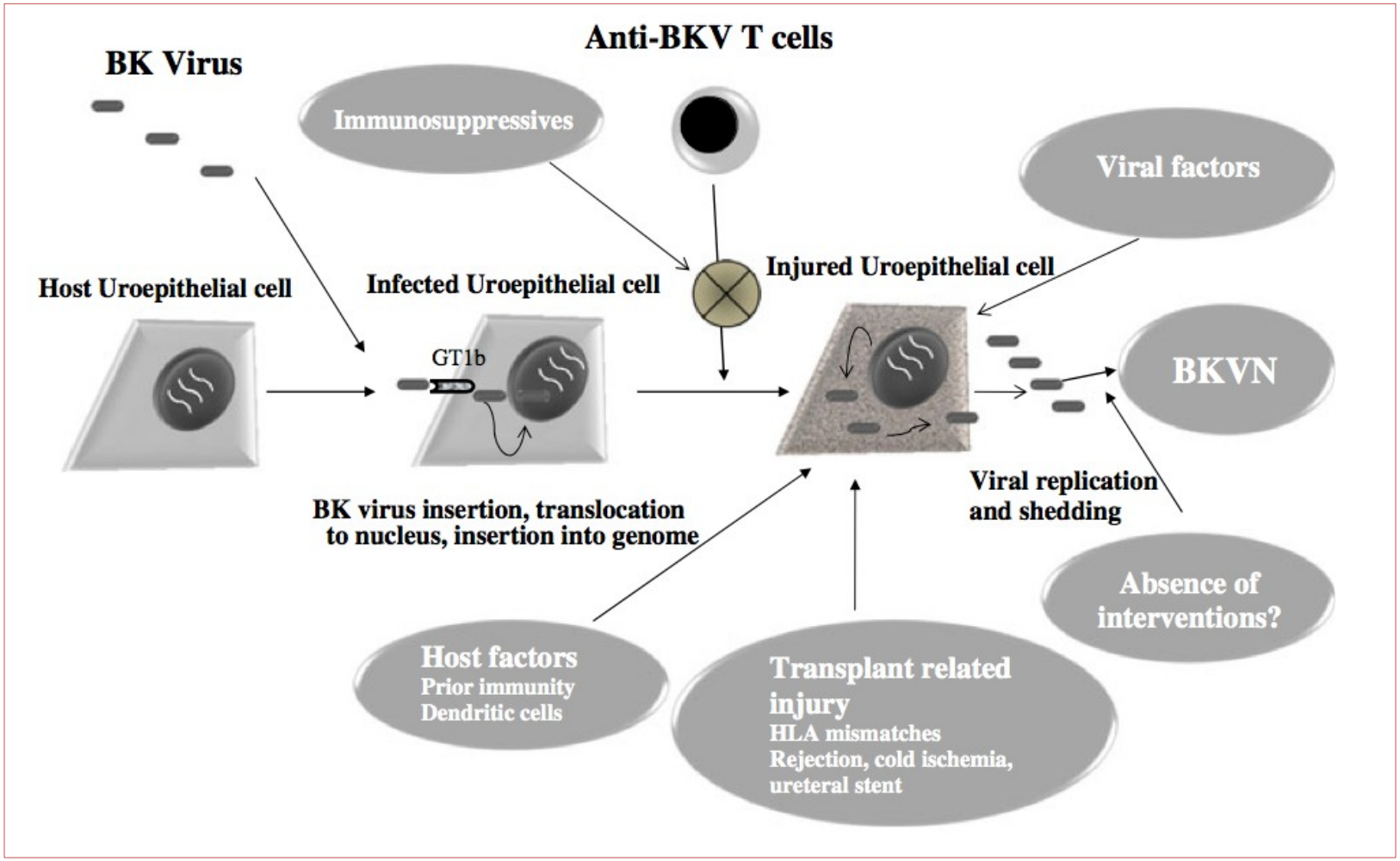
In line with guide- lines, EBV-VL assays may be avoided in low-risk patients in the absence of a strong clinical PTLD suspicion



Franceschini E et al, Transplantation Direct 2017;3:e182; doi: 10.1097/TXD.0000000000000070

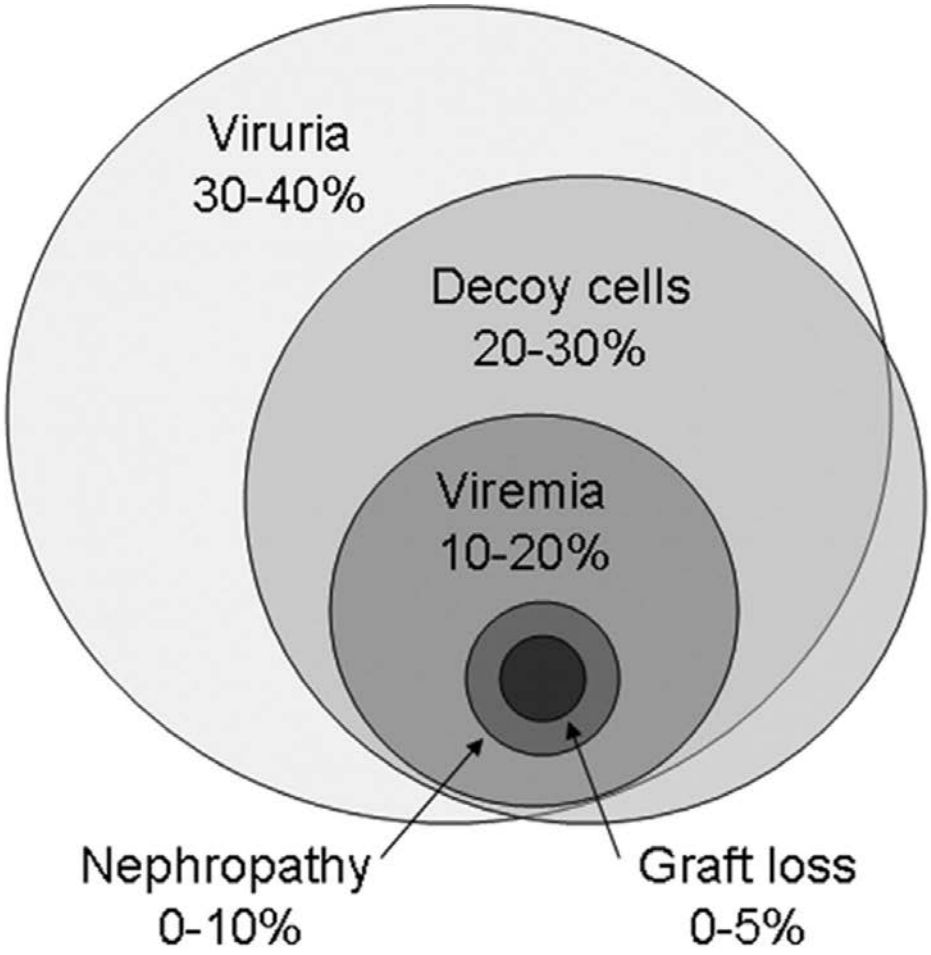
BKV infection

Pathogenesis of BK virus nephropathy



Dharnidharka VR et al, Pediatr Nephrol (2011) 26:1763–1774

Type and prevalence of BK virus (BKV) infections in kidney transplant recipients.

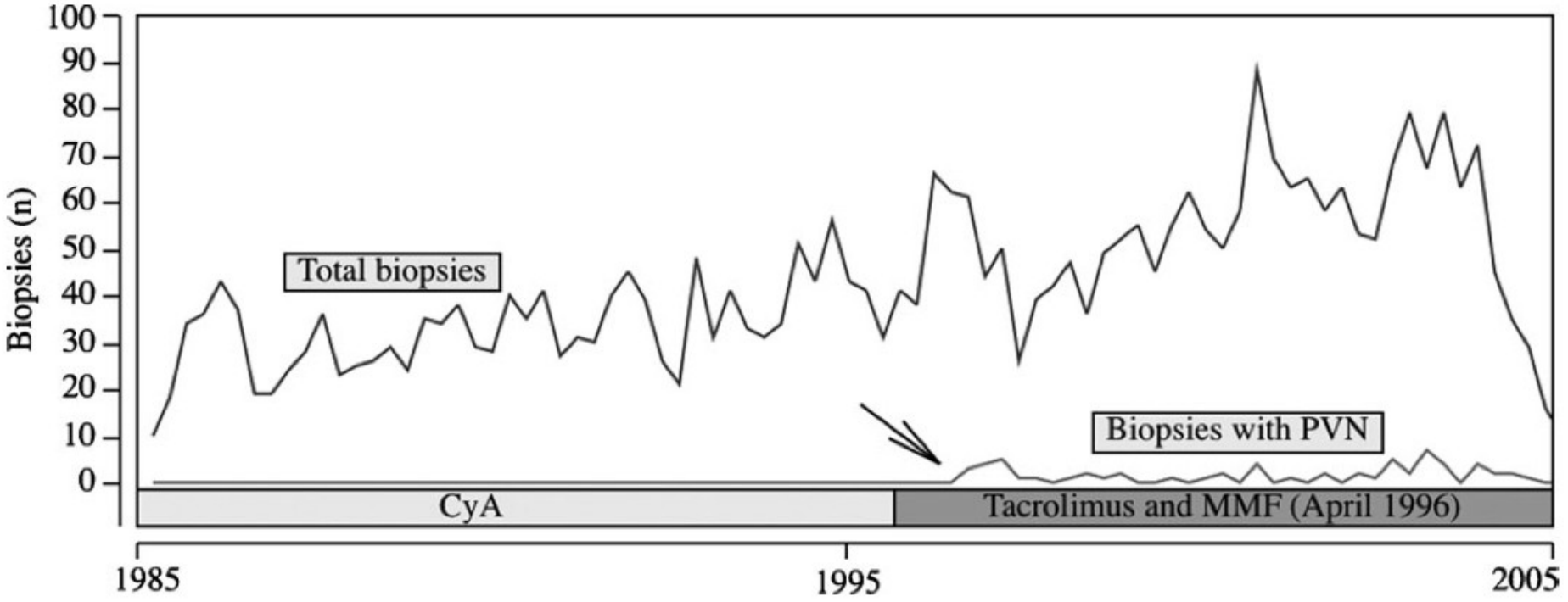


*Rare cases of nephropathy without viremia or viremia without viruria may occur

Bohl D L , and Brennan D C CJASN 2007;2:S36-S46

CJASN

Tacrolimus and MMF carry an increased risk for PVN.



Factors associated to PVN development

MMF and/or Tacrolimus

ATGAM

Male gender of the recipient

Rejections episodes

Prince O A et al, Nephrol Dial Transplant (2009) 24: 1024–1033

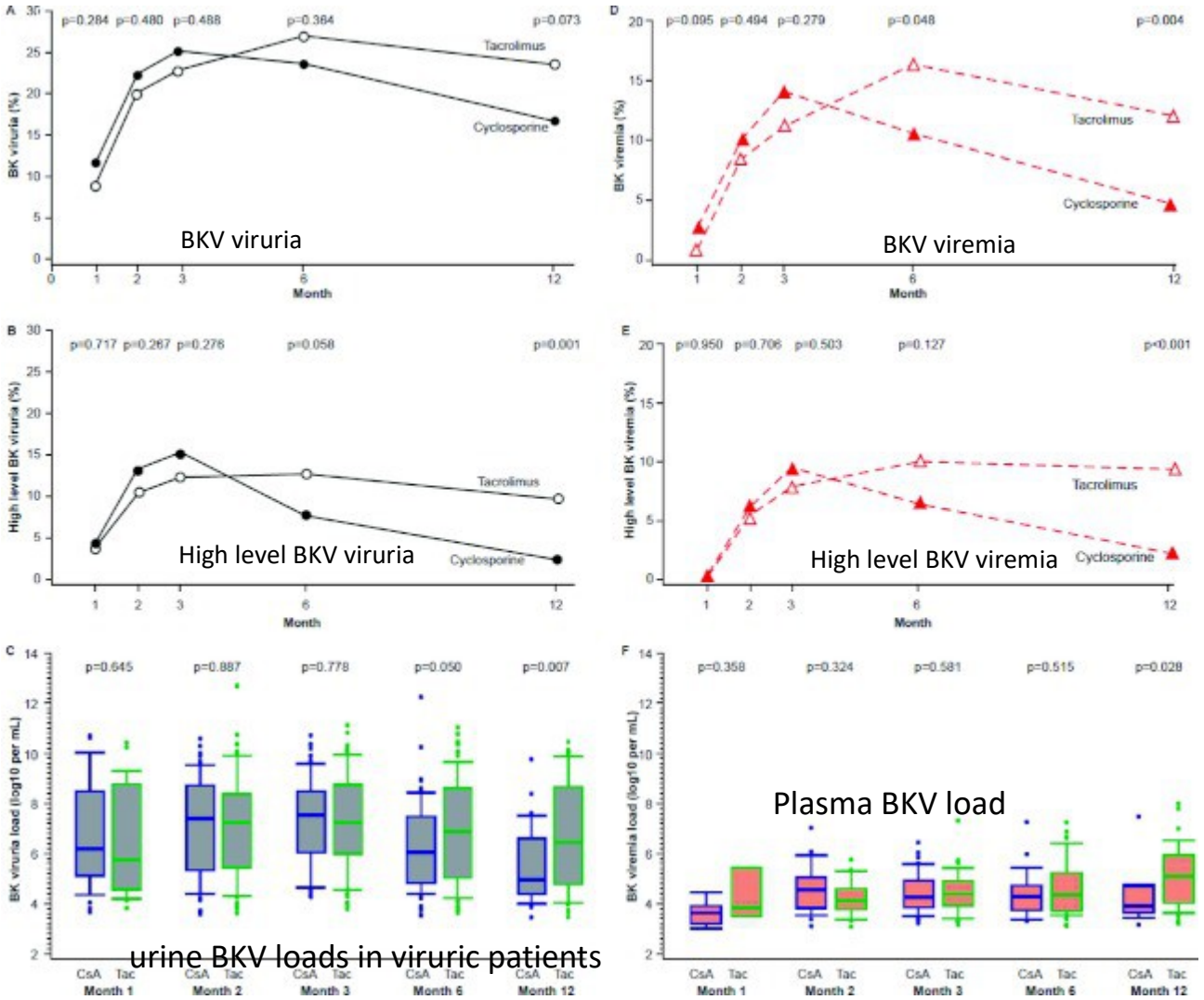
Polyomavirus BK Replication in *De Novo* Kidney Transplant Patients Receiving Tacrolimus or Cyclosporine: A Prospective, Randomized, Multicenter Study

H. H. Hirsch[a,b,*,†], F. Vincenti[c], S. Friman[d], M. Tuncer[e], F. Citterio[f], A. Wiecek[g], E. H. Scheuermann[h], M. Klinger[i], G. Russ[j], M. D. Pescovitz[k] and H. Prestele[l]

682 KTx randomized 1:1 CsA vs Tacrolimus
Basiliximab, MMF, PDN
Follow-up 12 months
BK viremia and viruria

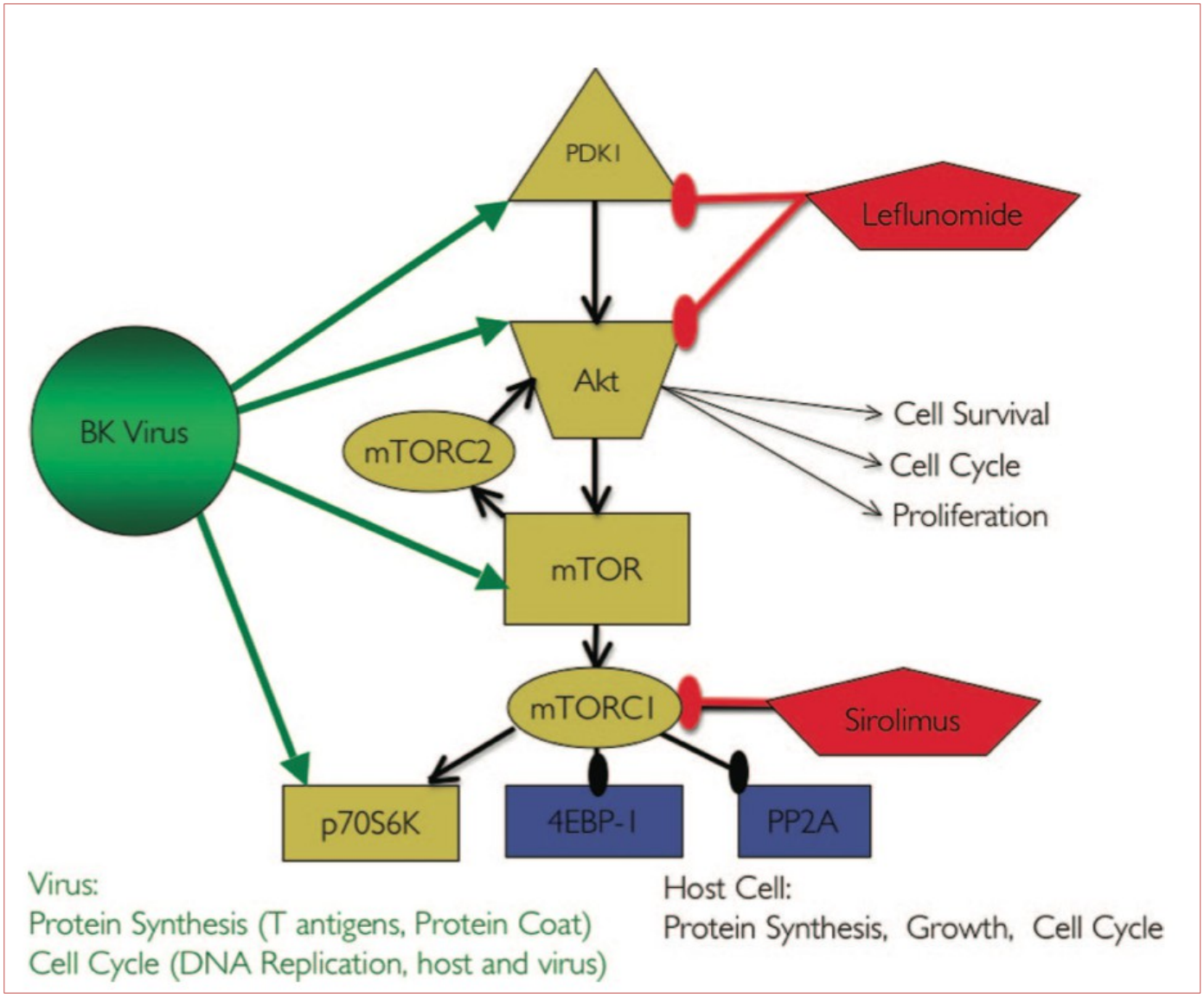
Hirsh HH et alAm J Transplant. 2013 January; 13(1): 136–145

Polyomavirus BK Replication in De Novo Kidney Transplant Patients Receiving Tacrolimus or Cyclosporine: A Prospective, Randomized, Multicenter Study



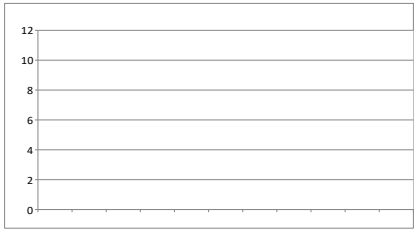
Hirsh HH et al, Am J Transplant. 2013 January; 13(1): 136–145

Inhibition of protein kinase pathways with a combination of sirolimus and leflunomide may be an effective therapy for BK virus reactivation.



Liacini A et al, Transplantation 2010;90: 1450–1457)

Kaplan-Meier estimated incidence of TBKV based on use of maintenance immunosuppressive agents at initial discharge posttransplant



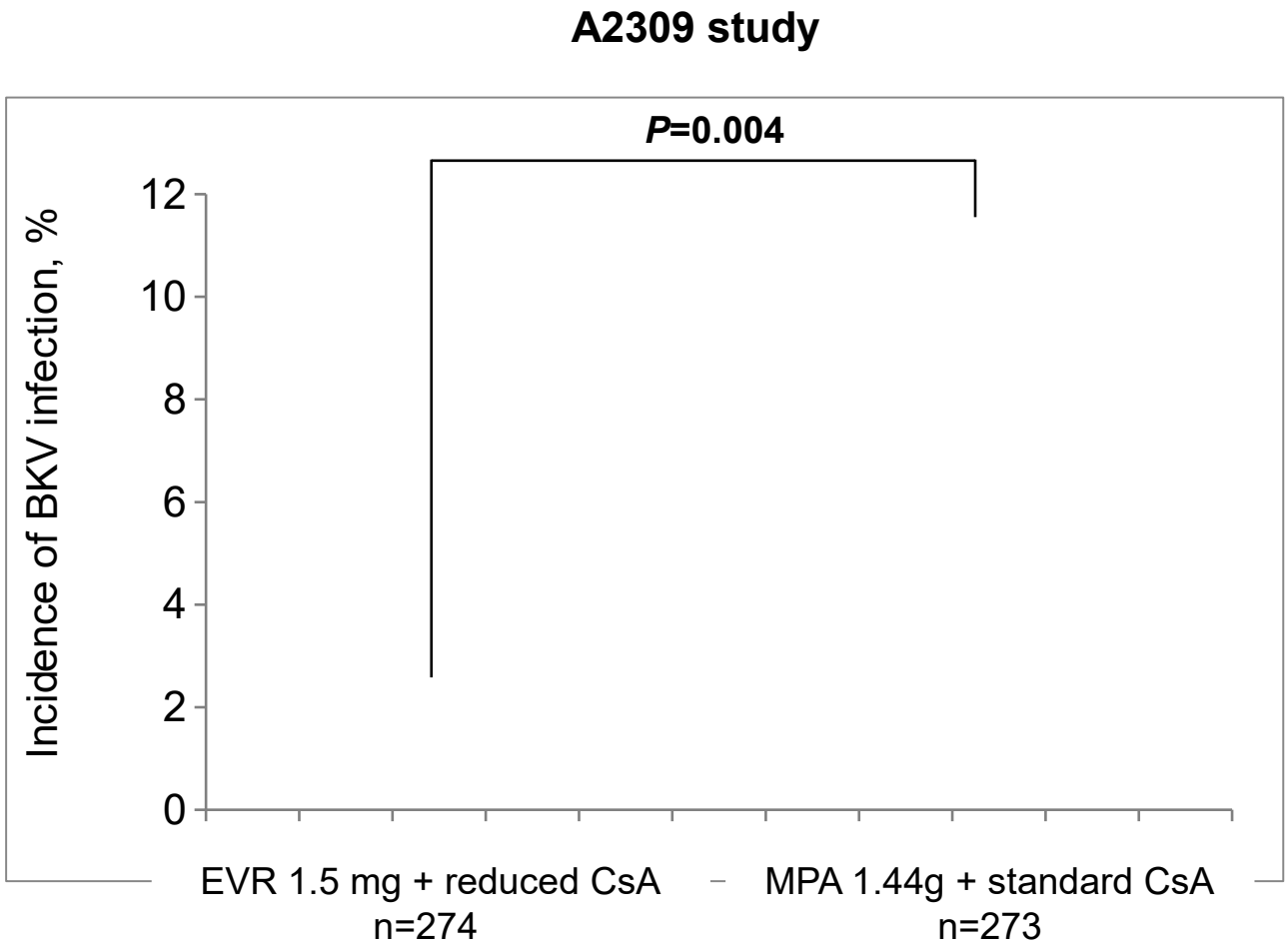
Dharnidharka VR et al, Transplantation 2009;87: 1019–1026)

Immunosuppressant-specific risk factors for treated BKV analyzed in a recent Organ Procurement and Transplantation Network registry analysis

Variable	Adjusted hazard ratio for treated BKV (95% CI)	*p* value
Induction therapy		
IL-2 versus no induction	1.03 (0.89, 1.20)	0.6894
Alemtuzumab versus none	1.22 (0.97, 1.53)	0.0884
Thymoglobulin versus none	1.42 (1.24, 1.63)	<0.0001
ATG versus none	1.19 (0.73, 1.95)	0.4792
CNIs		
CsA based versus tacrolimus based	0.53 (0.45, 0.63)	<0.0001
No CNI versus tacrolimus based	0.78 (0.58, 1.05)	0.1045
Antimetabolites		
Azathioprine based versus MMF based	0.42 (0.17, 1.01)	0.0517
No antimetabolites versus MMF based	0.73 (0.61, 0.87)	0.0006
mTORis		
mTORi: yes versus no	0.69 (0.54, 0.89)	0.0048
Steroids		
Steroid discharge maintenance: yes versus no	1.16 (1.02, 1.31)	0.0237

Brennan DC et al, Rev. Med. Virol. 2013; 23: 97–125

Reported incidence of BKV infection was lower with EVR plus reduced CNI at 24 months



- BKV, BK virus; CsA, cyclosporine; EVR, everolimus; MPA, mycophenolic acid

NOVARTIS PHARMACEUTICALS

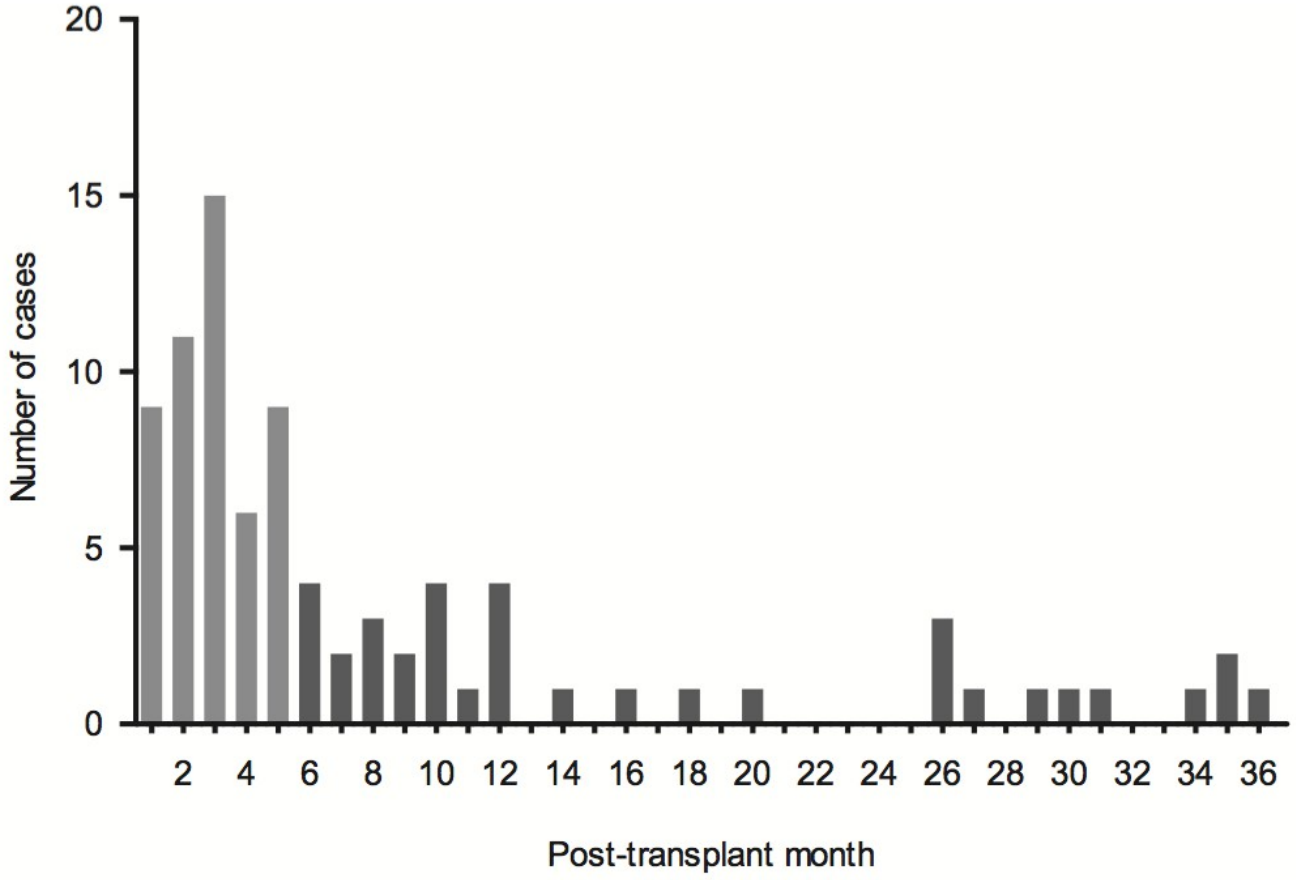
Aspergilosis pulmonar invasiva

Aspergilosis pulmonar invasiva

- Estudio multinacional retrospectivo (2000 – 2013)
- 112 pacientes diagnosticados (probable 75%; probado 25%)
- A. Fumigatus fue la especie más frecuente (78.8%)
- Positividad para galactomanano: suero 61.3%; BAL 57.1%
- Supervivencia: 6 semanas 68.8%; 12 semanas: 60.7%
- Factores relacionados con mortalidad:
    - Formas tempranas (< 6 meses post-trasplante)
    - Afectación bilateral
- Administración de voriconazol desde el inicio reduce el riesgo de mortalidad

F. López-Medrano et al. Am J Transplant 2016; 16: 3220–3234

Aspergilosis pulmonar invasiva



F. López-Medrano et al. Am J Transplant 2016; 16: 3220–3234

Muchas gracias

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