
بسم الله الرحمن الرحيم

Indirect Effects of CMV Infection in Renal Transplantation: An Overview

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Disclosure Information

- I have no financial relationship to disclose
- I will not discuss off label use and/or investigational use of drugs in my presentation

Cytomegalovirus: A major problem following transplantation

- Most common opportunistic infection after transplantation
- Incidence of clinically apparent CMV disease between 20 and 60%
- High mortality if untreated (up to 90%)

Gane et al. *Lancet* 1997; 350:1729-33.
Kanj et al. *Clin Infect Dis* 1996; 22:537-49.

. 2012;3(2):74-8.

Cytomegalovirus Infection following Kidney Transplantation: a Multicenter Study of 3065 Cases

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ABSTRACT

Background: Cytomegalovirus (CMV) infection is a common complication following kidney transplantation.

Objective: To assess the incidence and risk factors of CMV infection among renal transplant recipients.

Methods: In a retrospective multicenter study, 3065 renal transplant recipients from 17 transplant centers of Iran were studied between April 2008 and January 2011. Kidney transplant patients were routinely monitored by sequential blood samples drawn for use in the CMV-pp65 antigenemia assay, and for hematological and biochemistry tests.

Results: 63% of studied patients were males; the mean±SD age of participants was 38±15 years. The majority of cases (81%) received a kidney from a living unrelated donor (LURD), 9% from living related

The incidence of CMV infection was 21.9% (95% CI: 20.4%–23.4%).

transplantation (p<0.001) and renal allograft failure (p<0.001) were the only risk factors associated with CMV infection.

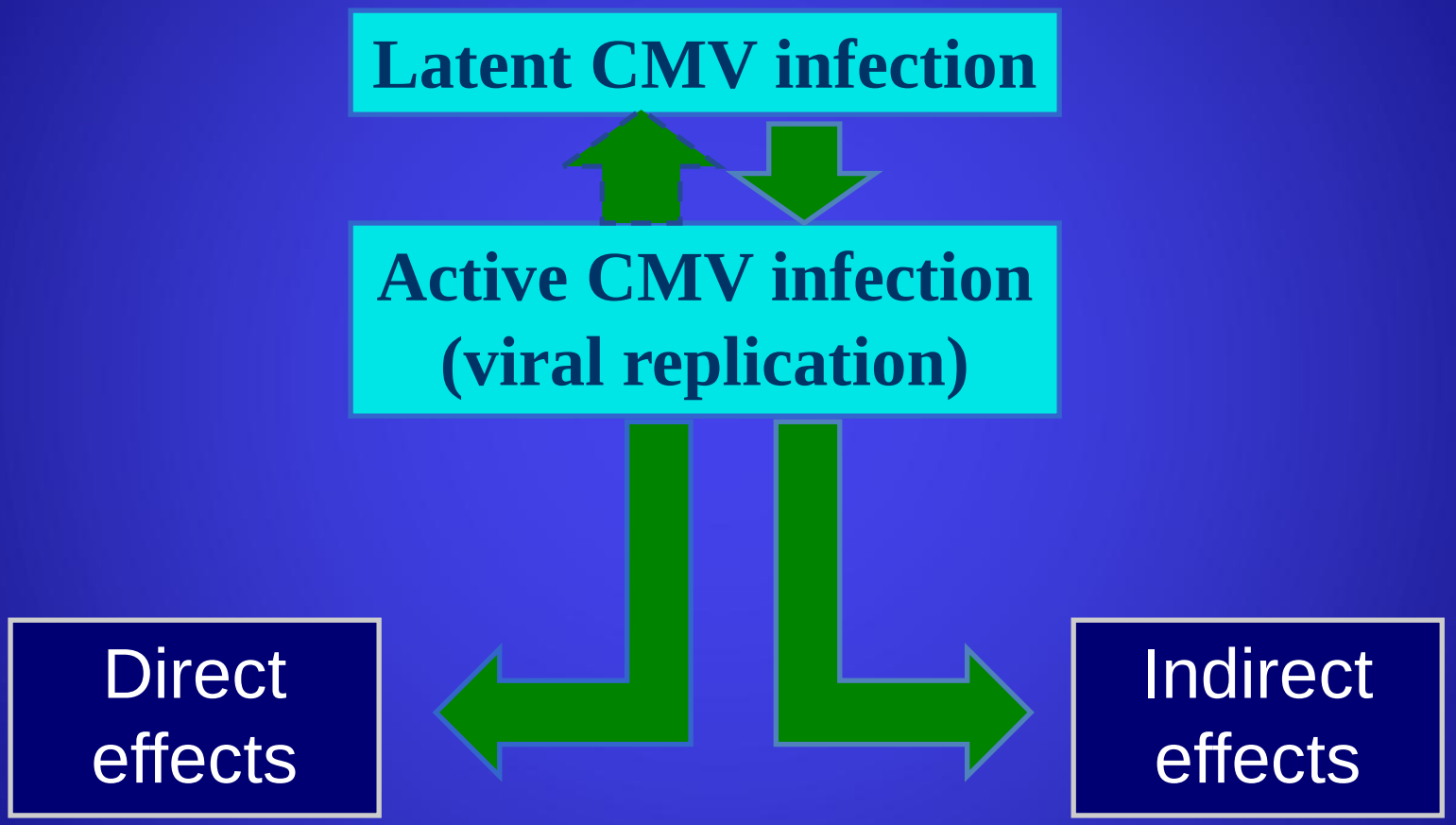
Conclusions: CMV infection was a common complication in the first 6 months of kidney transplantation, particularly among patients with kidney graft impairment.

J Organ Transplant Med. 2012;3(2):74-8.

Risk Factors for Post Transplant CMV

- Donor/Recipient Serology
- Immunosuppression
  - Depleting antibody> anti-IL-2R
  - Mycophenolic Acid
  - Steroids
- CMV prophylaxis and duration
- Viral load
- Renal Function
- Genetics
  - Mannose binding ligands
  - Cytokine gene polymorphisms
  - ABO type A
  - Female

CMV Infection



Direct Effects of CMV Infection

Direct Effects

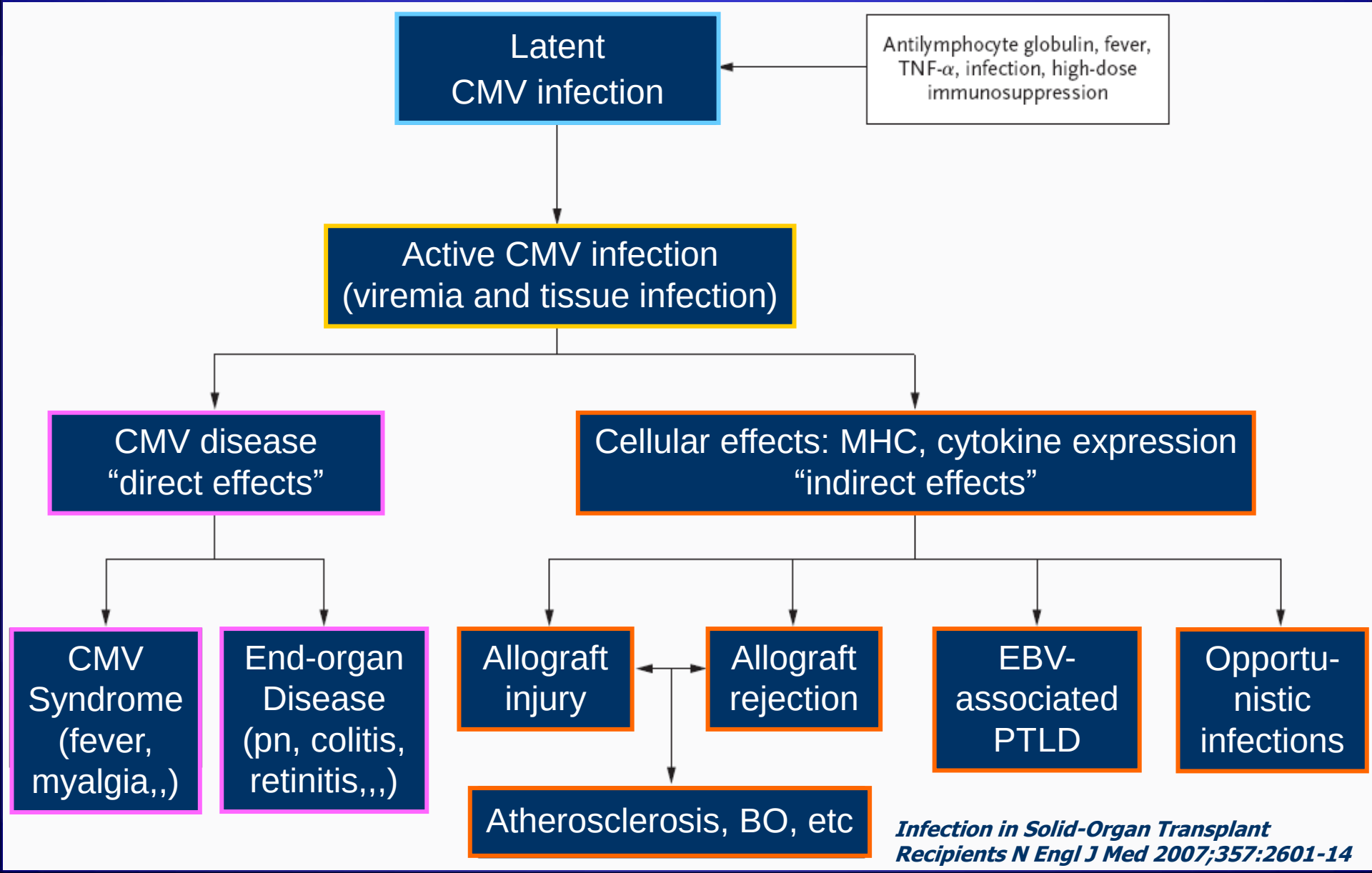
CMV Viral Syndrome

- Fever, malaise, myalgias
- Leukopenia, thrombocytopenia, and other laboratory abnormalities

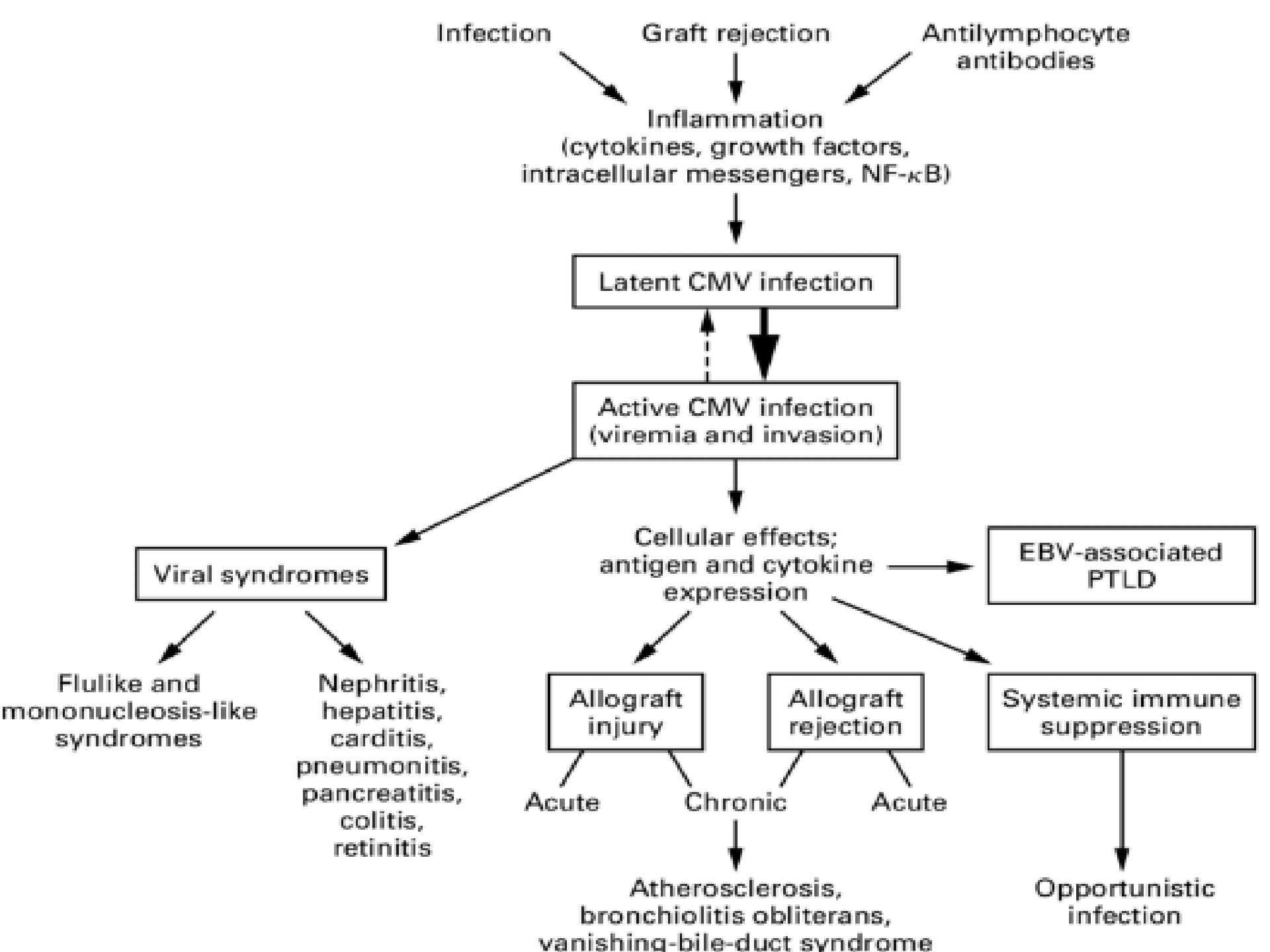
Tissue Invasive Disease

- Hepatitis
- Pneumonitis
- Colitis
- Carditis
- Nephritis
- Pancreatitis
- Retinitis

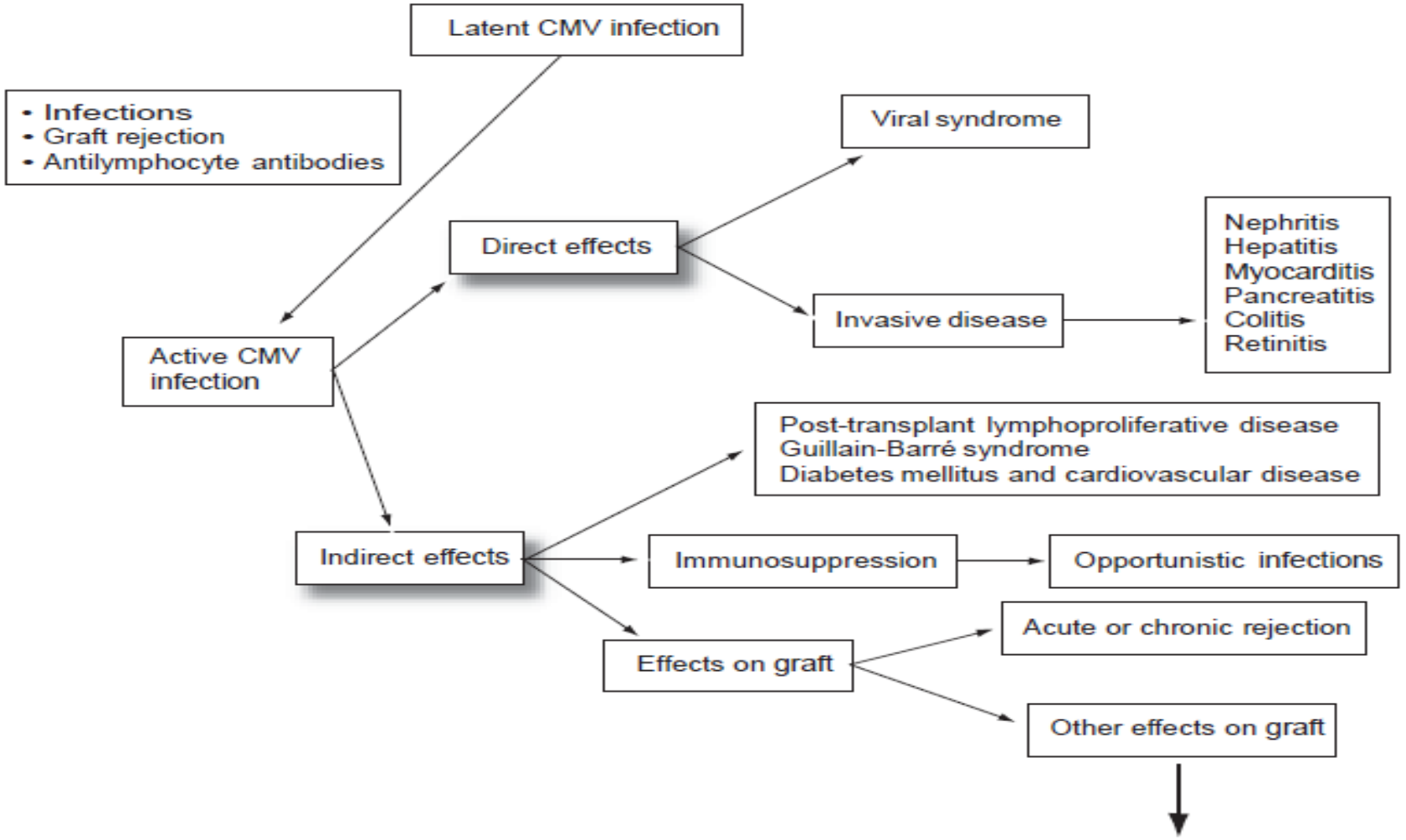
Clinical features



Infection in Solid-Organ Transplant Recipients N Engl J Med 2007;357:2601-14


Infection
Graft rejection
Antilymphocyte antibodies
Inflammation (cytokines, growth factors, intracellular messengers, NF-κB)
Latent CMV infection
Active CMV infection (viremia and invasion)
Viral syndromes
Cellular effects; antigen and cytokine expression
EBV-associated PTLD
Flulike and mononucleosis-like syndromes
Nephritis, hepatitis, carditis, pneumonitis, pancreatitis, colitis, retinitis
Allograft injury
Allograft rejection
Systemic immune suppression
Acute
Chronic
Acute
Atherosclerosis, bronchiolitis obliterans, vanishing-bile-duct syndrome
Opportunistic infection

Direct and indirect effects of CMV



Lung	Kidney	Heart	Liver
Bronquiolitis obliterans syndrome	Chronic nephropathy	Accelerated coronary sclerosis, endothelial dysfunction, vascular remodeling	Post-transplant HCV recurrence, vanishing bile duct syndrome, hepatice artery thrombosis

Indirect Effects of CMV Infection

➢ CMV is immunosuppressive

- CMV may be a risk factor for acute rejection and chronic graft injury
- Decreased graft and patient survival
- Cardiovascular events
- Opportunistic infections: Bacterial, fungal and viral superinfections
- Immunosenescence
- Malignancies: PTLD
- New-onset diabetes mellitus (NODAT)
- Guillain-Barré syndrome
- Thrombosis
- TTP-HUS after renal transplantation
- Increased healthcare expenses
- Linked to heart allograft atherosclerosis

Immunosuppression

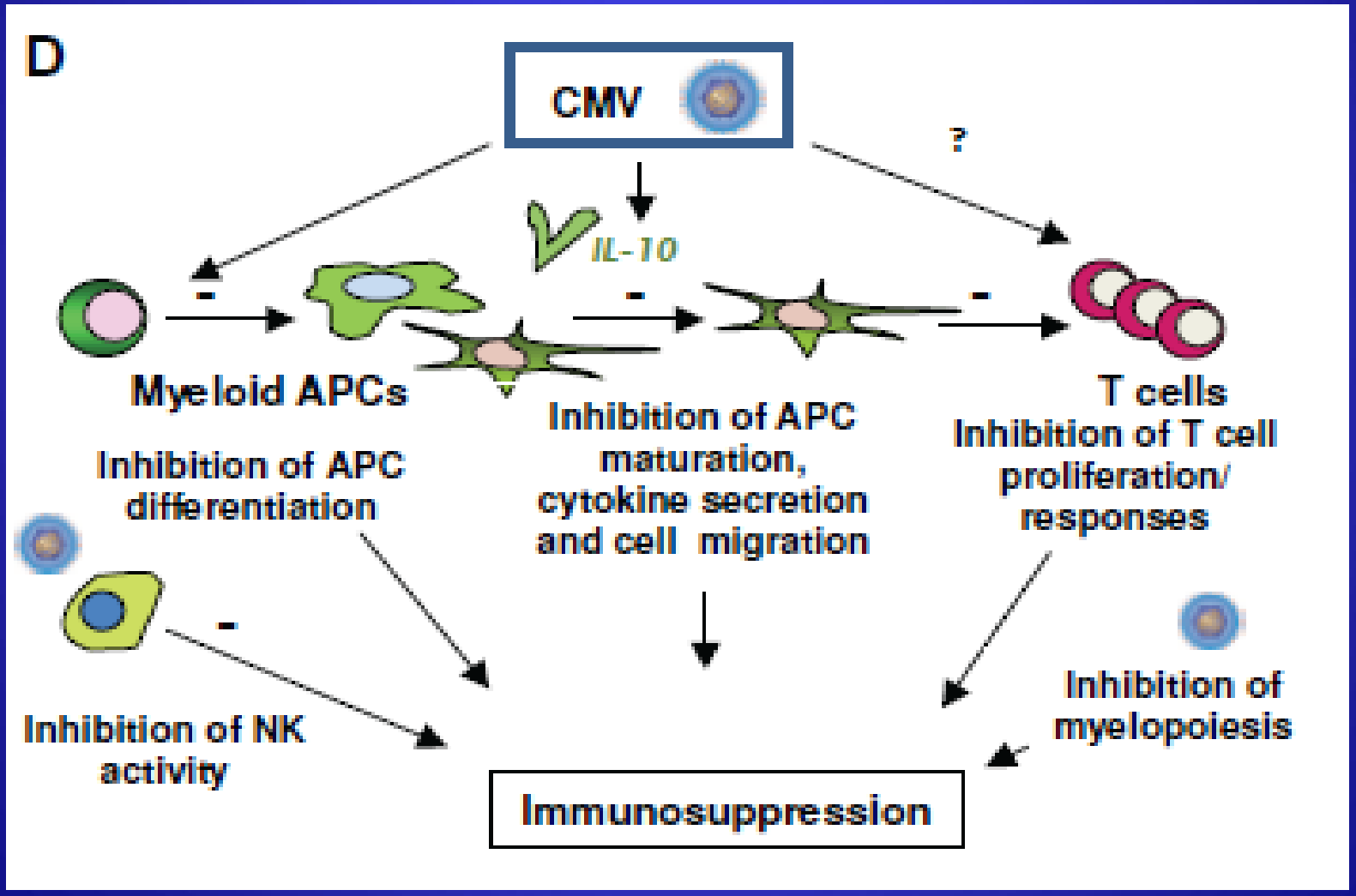
- CMV infection (mainly primary infection) causes transient but substantial immunosuppression.
- CMV effects immunosuppression in solid organ transplant recipients, potentiating superinfections with various pathogens.

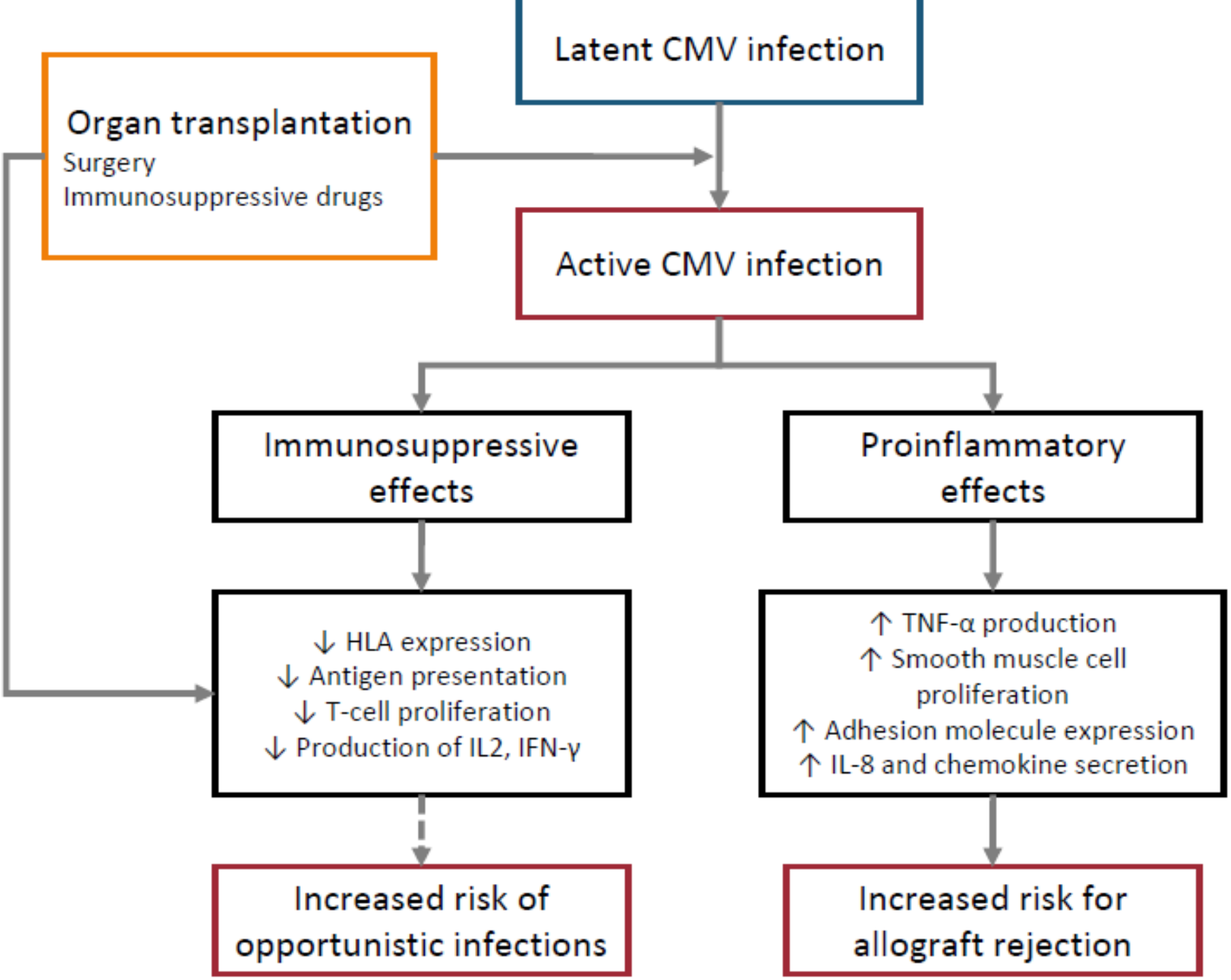
Varani and Landini Herpesviridae 2011, 2:6

Immunosuppressive mechanisms of CMV infection

- ↓ *HLA expression*
- ↓ *Antigen presentation*
- ↓ *T-cell proliferation*
- ↓ *Production of IL-2, INF-γ, PD-1*
- ↑ *Fc receptor expression*
- ↑ *Complement inhibitors*
- ↓ *Macrophage migration*

Mechanisms by which CMV can induce host immunopathology




Latent CMV infection
Organ transplantation
Surgery
Immunosuppressive drugs
Active CMV infection
Immunosuppressive effects
Proinflammatory effects
↓ HLA expression
↓ Antigen presentation
↓ T-cell proliferation
↓ Production of IL2, IFN-γ
↑ TNF-α production
↑ Smooth muscle cell proliferation
↑ Adhesion molecule expression
↑ IL-8 and chemokine secretion
Increased risk of opportunistic infections
Increased risk for allograft rejection

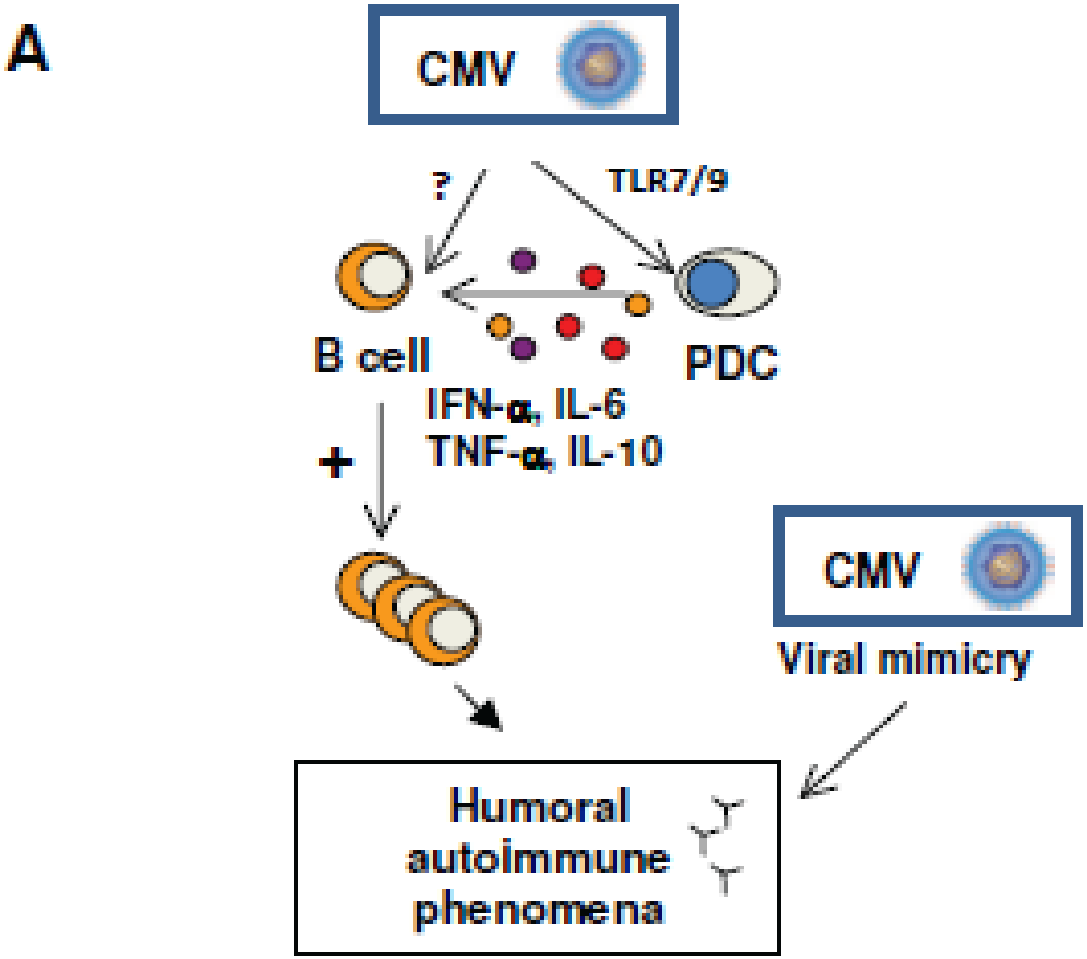
CMV "Indirect Effects": Possible Mechanisms

- Upregulation of MHC class II antigens and homolog of MHC class-I (HLA-DRβ, Fujinami RS, et al. *J Virol.* 1988;62:100-105. S. Beck, *Nature.* 1988;331:269-272)
- Blocks CD8+ (MHC class I) recognition
- Blocks CMV antigen processing and display (immediate early Ag modification, poor CTL response)
- Increased ICAM-1, VCAM, cellular *myc & fos*
- Inversion of CD4/CD8 ratio (Schooley 1983, Fishman 1984)
- Increased cytokines: IL-1β, TNFα, IFNγ, IL-10, IL-4, IL-8, IL-2/IL-2R, C-X-C chemokines and IL-8 (Kern et al, 1996; CY Tong, 2001)
- Increased cytotoxic IgM (Baldwin et al, 1983)
- Stimulation of alloimmune response by viral proteins (Fujinami et al, 1988, Beck et al, 1988)
- Increased PDGF, TGFβ
- Increased granzyme B CD8+ T-cells, γδ-T-cells

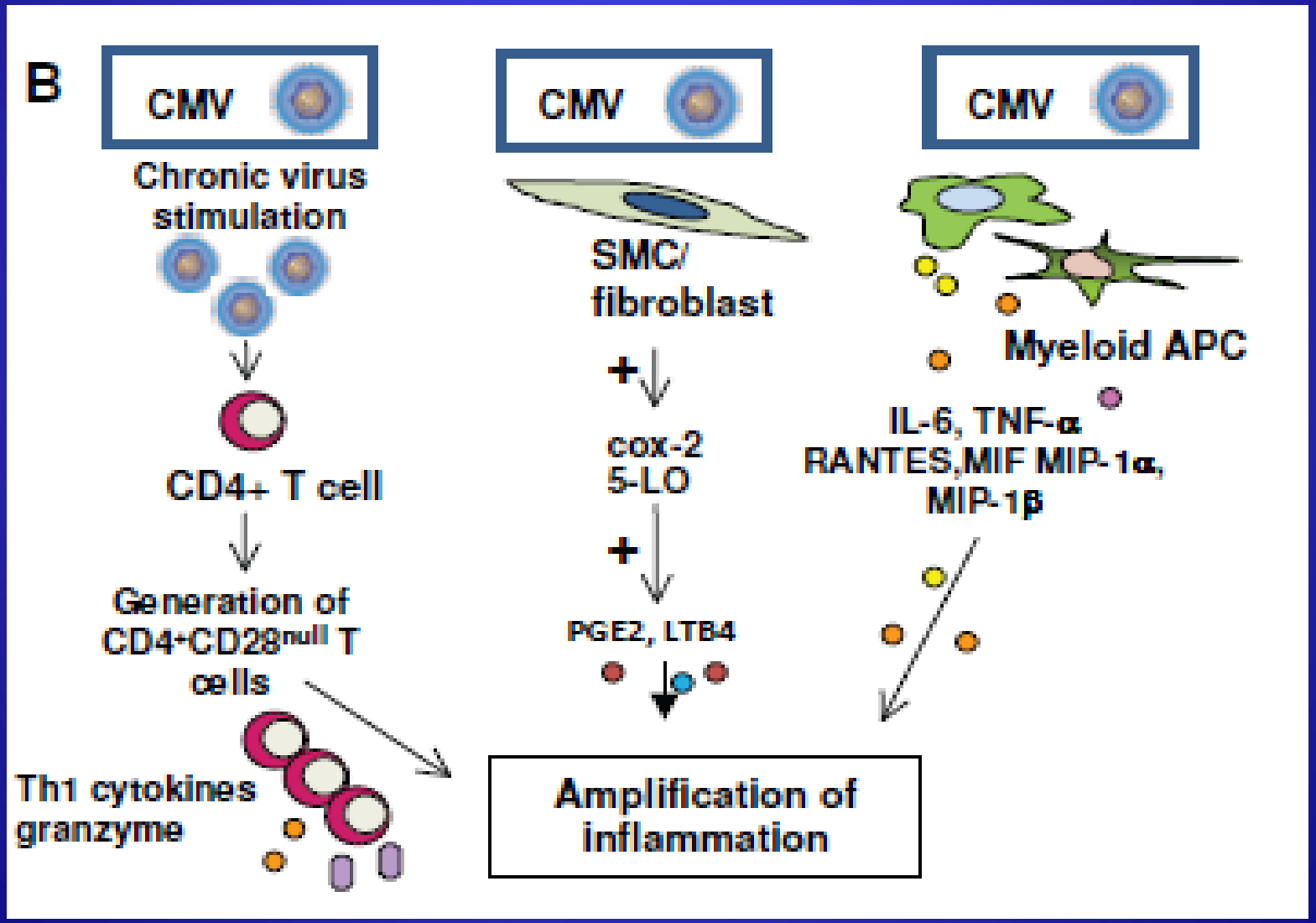
Mechanisms of CMV-induced immunopathology

- Humoral autoimmunity
- Inflammation
- Generation of CD4+ CD28null T cells

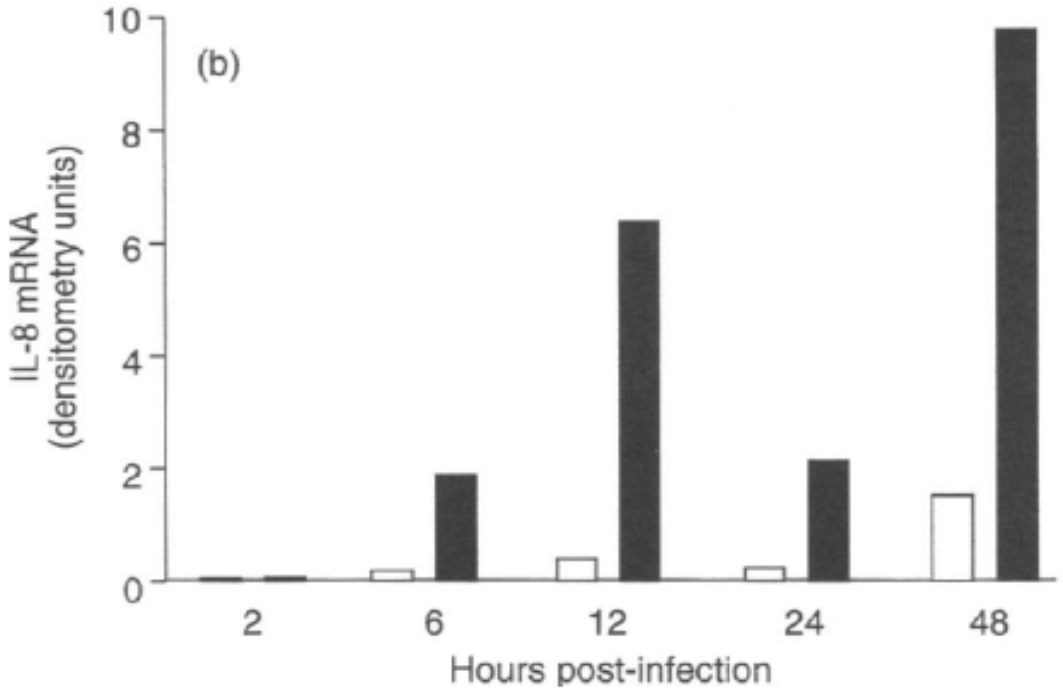
Mechanisms by which CMV can induce host immunopathology



Mechanisms by which CMV can induce host immunopathology



CMV infection up-regulates interleukin-8 gene expression in fibroblasts



Il-8

Major mediators of the inflammatory response

Induction of chemotaxis in neutrophils

Plays a role in the pathogenesis of bronchiolitis

Craigen JL et al. Immunology. 1997;92:138

The virus as an immunopathological agent: Autoimmunity

- Induction of autoantibodies
- Induction of vasculitides and scleroderma
- Induction of encephalitis associated with autoimmune phenomena
- Increased risk for post-transplant diabetes mellitus
- Active infection during autoimmune disorders
- Inflammatory bowel diseases and other enteropathies

Active infection during autoimmune disorders

- Current findings suggest that latent CMV can be reactivated by allogeneic stimulation in monocytes from seropositive donors.
- Involve T cell activation and inflammation may facilitate the reactivation of latent CMV in monocytes in vivo.

Varani and Landini Herpesviridae 2011, 2:6

Active infection during autoimmune disorders

- Thus, the chronic inflammation might provide the ideal microenvironment in which latent CMV can be reactivated in Macrophages
- This inflammation can induce DC maturation, which can also provoke viral reactivation from latency.

Varani and Landini Herpesviridae 2011, 2:6

Immune evasion strategies employed by CMV

Immune strategy	Mechanism of action	Effect produced
Interference with apoptosis	Delays apoptosis in CMV-infected astrocytes	Prolongs survival of target cells
Alteration of cytokines	Metabolic defect in lymphocytes and monocytes, modulating production of and response to cytokines	Impaired antigen-specific activity and cytotoxic T lymphocyte activity
Modulation of antigen presentation through downregulation of MHC class I molecules	Expression of glycoproteins US11 and US2, which modify MHC class I molecules causing their rapid degradation	Avoids lysis by cytotoxic T lymphocytes
Modulation of antigen processing	Expression of glycoprotein US3 with action similar to US11 and US2, and glycoprotein US6, which blocks transporter molecules associated with antigen processing	Avoids lysis by cytotoxic T lymphocytes. Inhibition of cytotoxic T lymphocyte-mediated lysis and T helper lymphocyte activity
Evasion of innate immunity	Expression of UL18, a MHC class I decoy protein, which binds β2-microglobulin and acts like a MHC class homologue to engage NK cell inhibitory receptors	Protection against attack by NK cells

Indirect Effects of CMV Infection

- CMV is immunosuppressive
- **CMV may be a risk factor for acute rejection and chronic graft injury**
- **Decreased graft and patient survival**
- Cardiovascular events
- Opportunistic infections: Bacterial, fungal and viral superinfections
- Immunosenescence
- Malignancies: PTLD
- New-onset diabetes mellitus (NODAT)
- Guillain-Barré syndrome
- Thrombosis
- TTP-HUS after renal transplantation
- Increased healthcare expenses
- Linked to heart allograft atherosclerosis

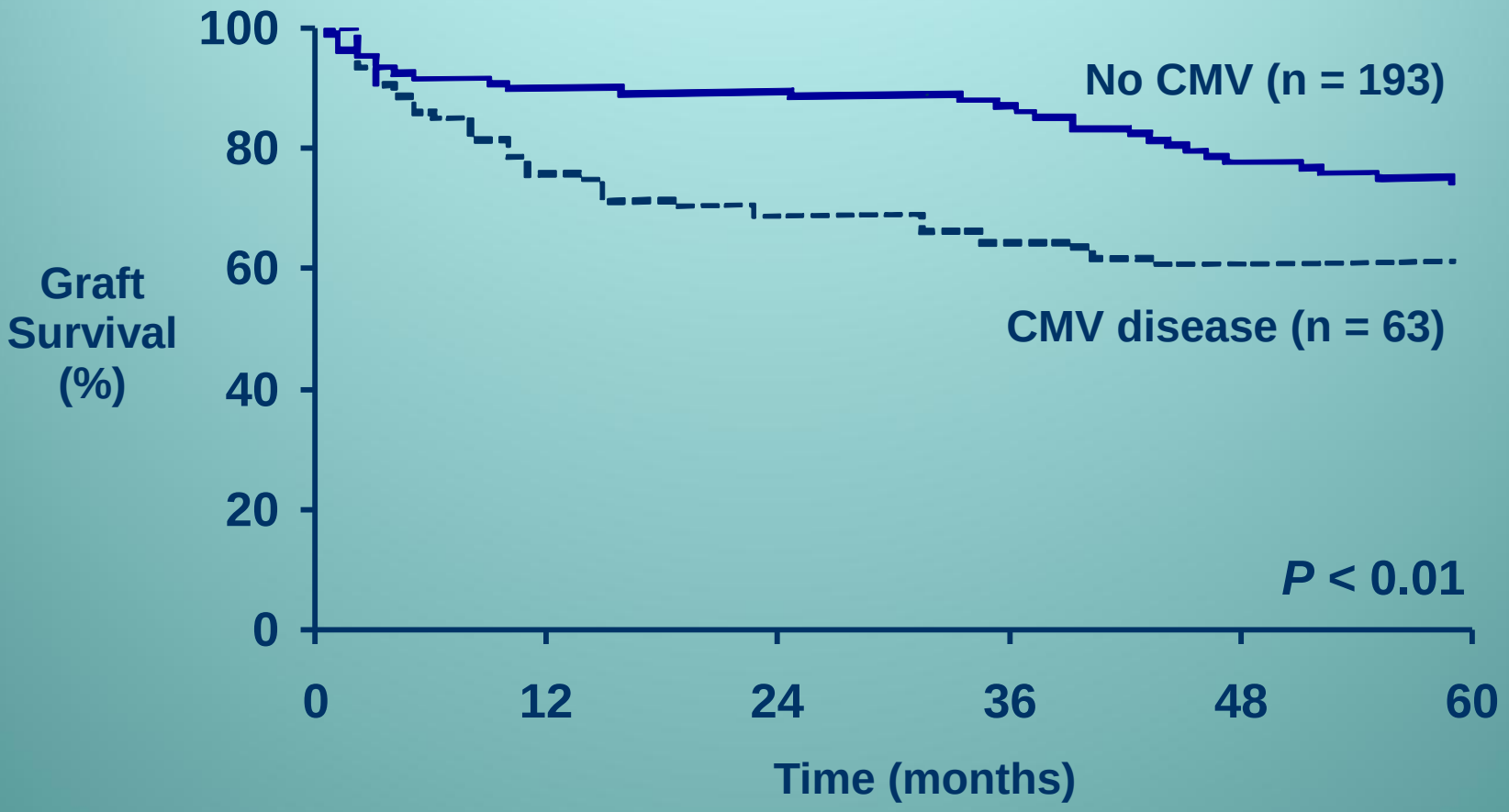
Graft rejection

- CMV promotes classical rejection and vasculopathy of an allograft, which impacts its longevity.
- Several cohort studies have shown that CMV infection is associated with an ***increased risk of graft rejection*** in renal, liver, and lung transplant patients.

Inflammatory properties associated with CMV

- *Translocation of NF-kB to nucleus*
- *↑ TNF-α production*
- *↑ Smooth muscle cell proliferation*
- *↑ Adhesion molecule expression*
- *↑ IL-8 and chemokine secretion*

Graft Survival in the Presence/Absence of CMV Disease



Giral M et al. *J Am Soc Nephrol.* 2001;12:1758-1763.

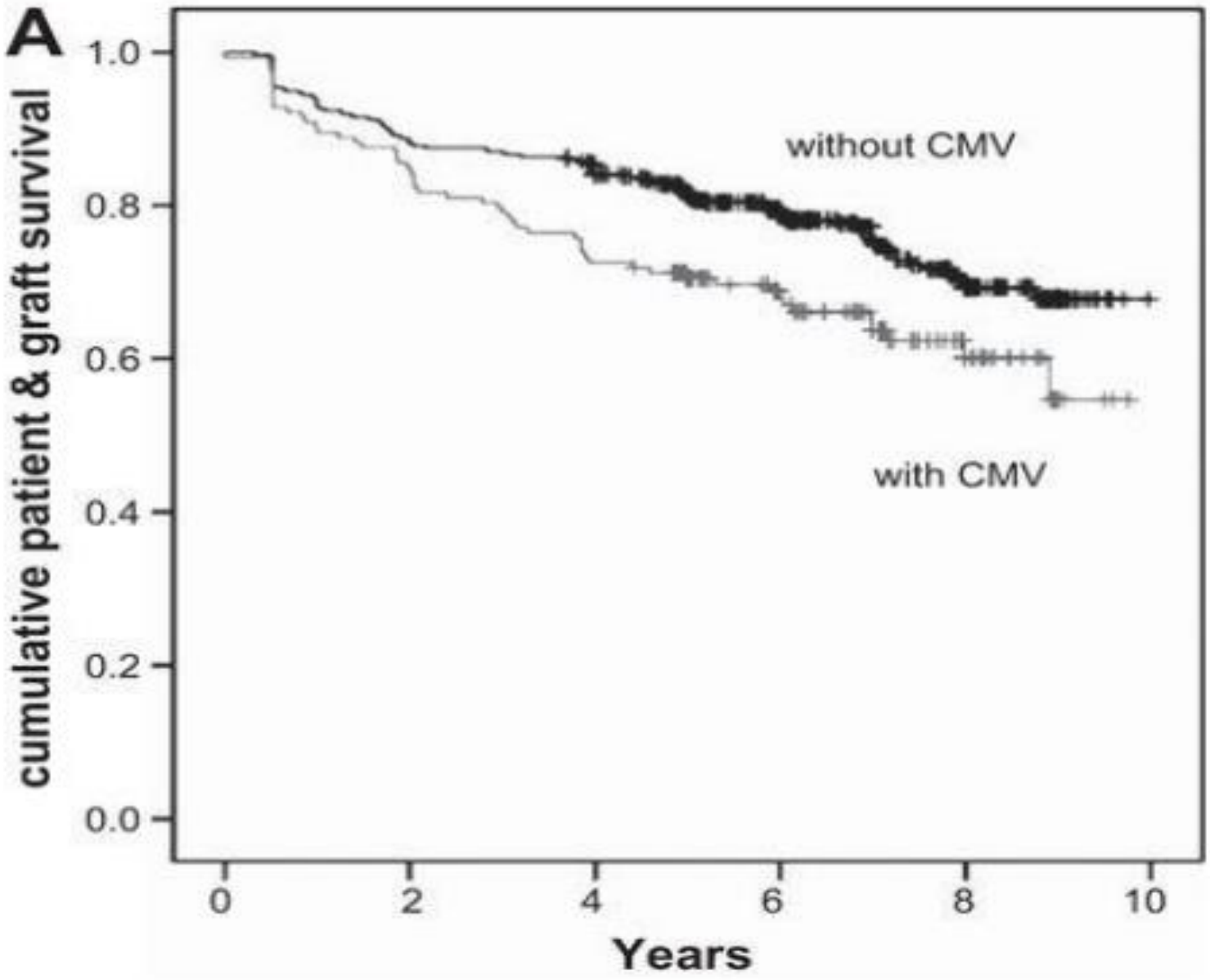
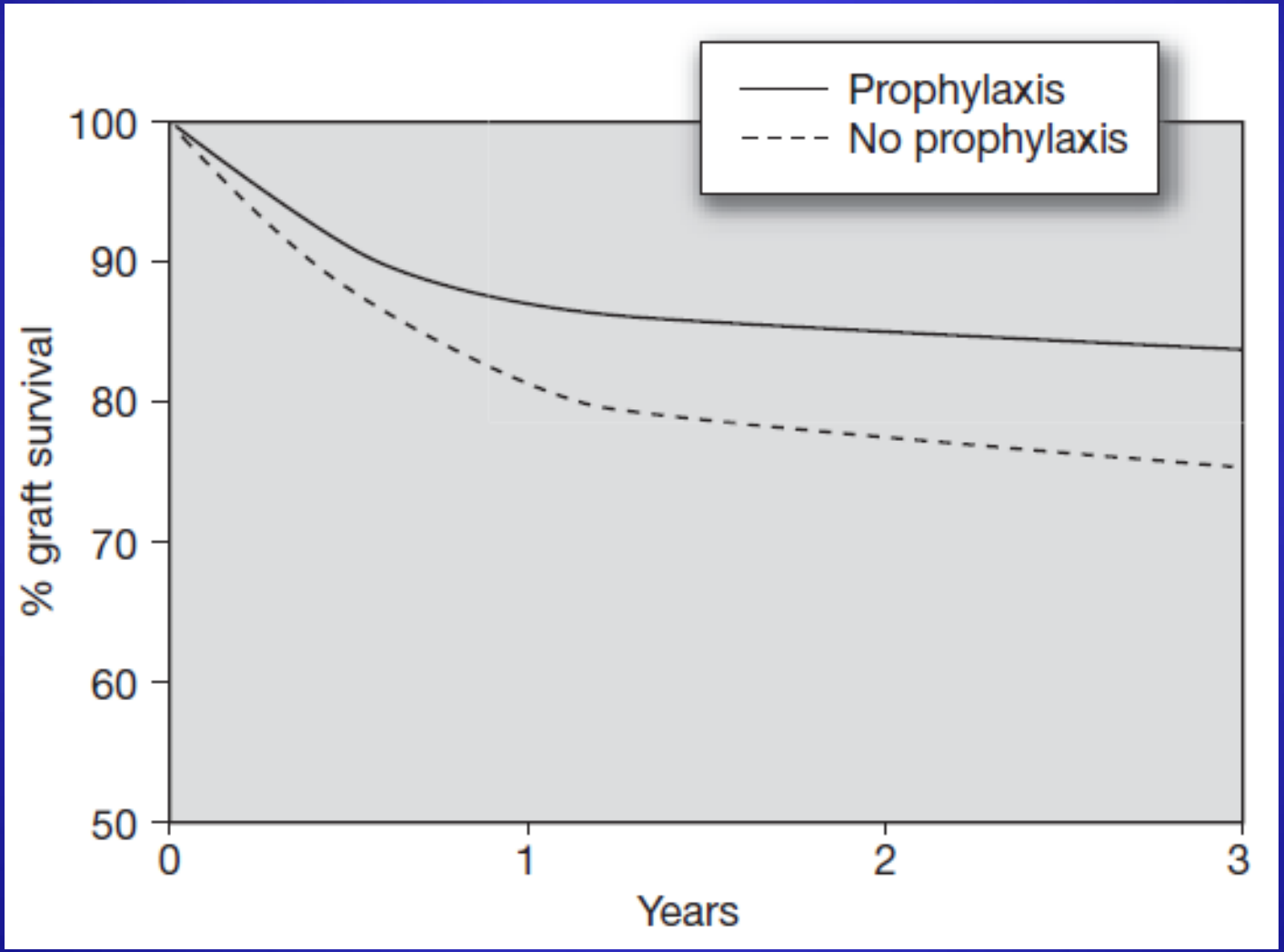


Figure 1.2: Patient and graft survival in patients with and without CMV

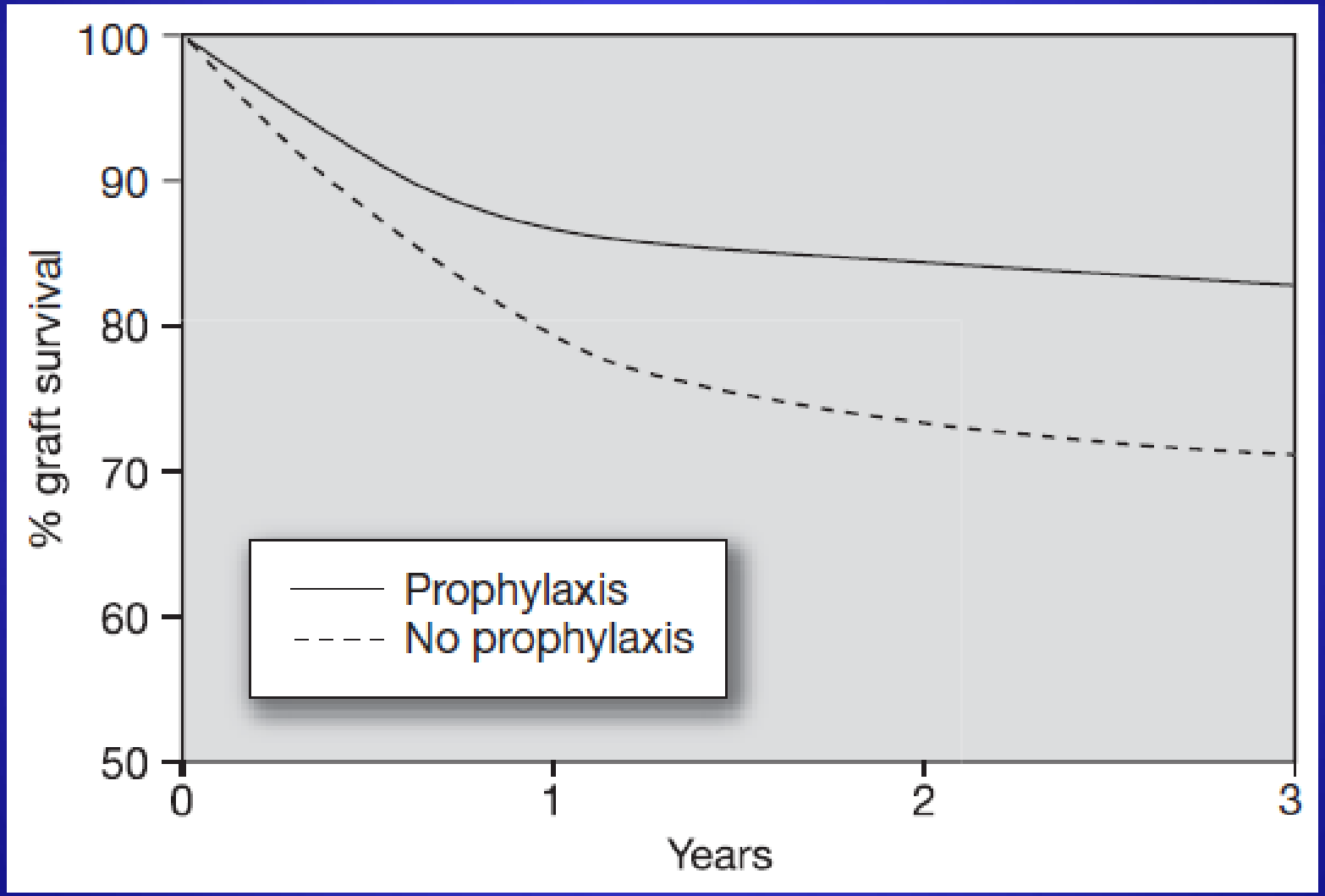
CMV infection following kidney transplantation significantly reduced long-term patient and graft survival ($p = 0.008$) [5].

Effect of CMV prophylaxis on kidney graft survival in D+/R– patients



Smith R. Diabetologia. 2004;47:1473-5.

Effect of CMV prophylaxis on heart graft survival in D+/R– patients



Smith R. Diabetologia. 2004;47:1473-5.

CMV is Associated with an Increased Risk of Acute Rejection

- Increased incidence of acute rejection is associated with CMV infection
- Amongst 477 kidney Tx patients, both CMV infection and disease were independent risk factors for acute clinical rejection
  - CMV infection RR 1.6, $p = 0.02$
  - CMV disease RR 2.5, $p = 0.01$

Pouteil-Noble C et al. *Transplantation* 1993; 55:851-7.
Sagedal S et al. *Am J Transplant* 2002; 2:850-6.

ANTIBODY MEDIATED ACUTE REJECTION IN KIDNEY TRANSPLANT RECIPIENTS WITH CMV INFECTION

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Einollahi B, Fukushima J Med Sci. 2012;58(1):88.

AMR in kidney transplant recipients with CMV infection

- The titers of ***anti-endothelial cell antibodies (AECAs)*** against endothelial cell lining the vasculature were significantly higher in recipients with vascular rejection, supporting a humorally mediated pathogenesis.
- The occurrence of ***high levels of AECAs*** in relation to CMV infection has been also demonstrated in 80% of renal and heart and in more than 40% of liver transplant patients.

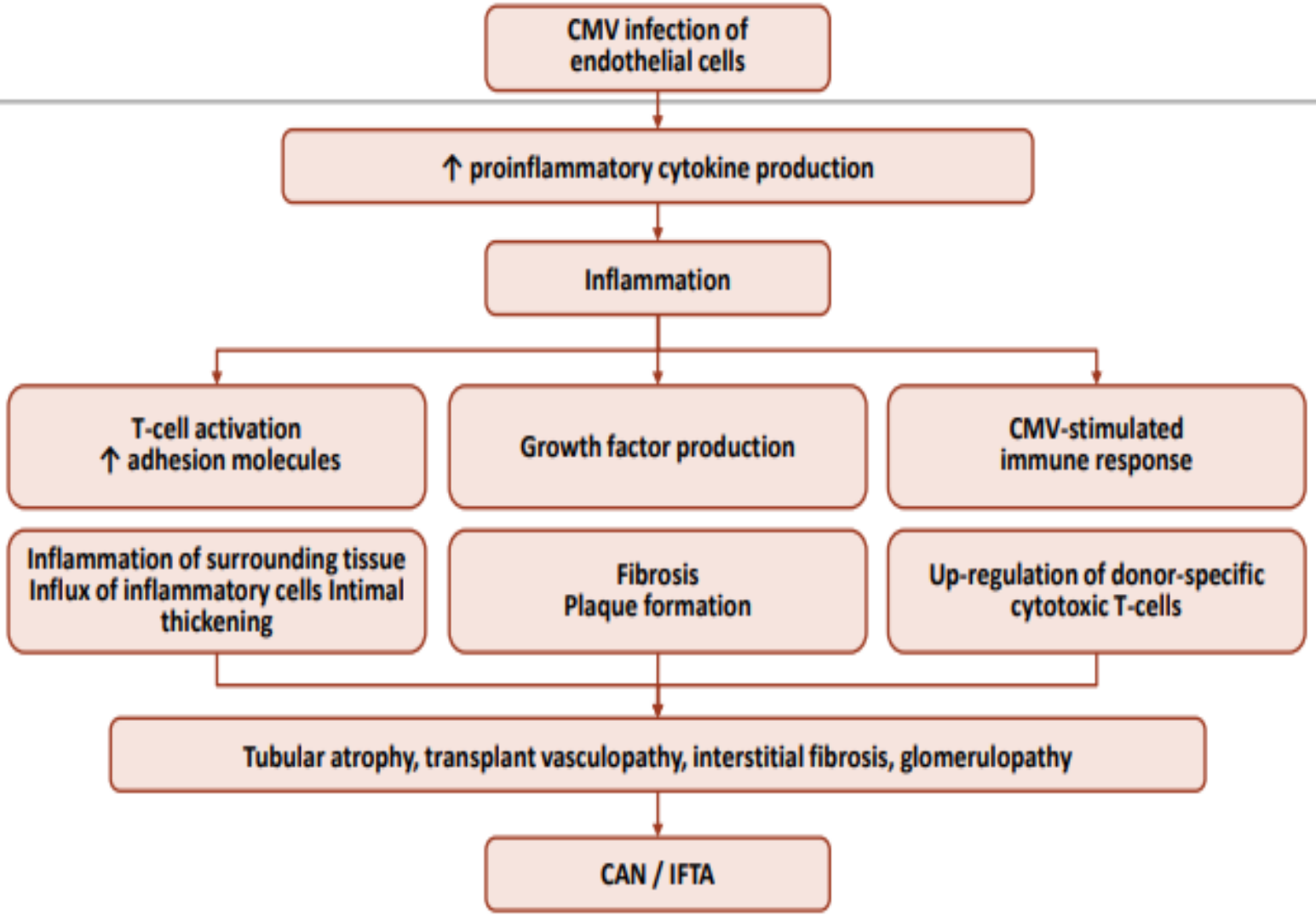
Einollahi B, Fukushima J Med Sci. 2012;58(1):88.

CMV Infection and Chronic Renal Rejection

	Chronic Rejection	Normal
Number	96	48
CMV	28%	13%
No CMV	72%	88%

***P* = 0.038**
Solez K et al. *Transplantation.* 1998;66:1736-1740.

CMV infection can lead to CAN / IFTA



CMV, cytomegalovirus; CAN, chronic allograft nephropathy; IFTA, interstitial fibrosis and tubular atrophy

Lautenschlager I *et al. Monogr Virol Basel, Karger* 2003;24:10–22

Long-term CMV monitoring and chronic rejection in renal transplant recipients.

Background

Cytomegalovirus (CMV) has been well known to an independent risk factor for graft loss and mortality after kidney transplantation. However, monitoring for CMV in chronic period is not defined in recent guideline [12]. The effects of CMV infection including asymptomatic CMV viremia in chronic period are unclear.

Objective

To examined how CMV viremia in chronic phase influenced in kidney transplant recipients.

Methods and Cohort

Retrospective cohort study

Kidney transplant recipients after >1 year post transplantation
n=205

Long-term CMV monitoring were continued

Chronic rejection and graft loss

Findings

80.6 m (13.1-172.1)	30.7 %	2.9 %
Median follow-up	Asymptomatic CMV viremia	CMV disease

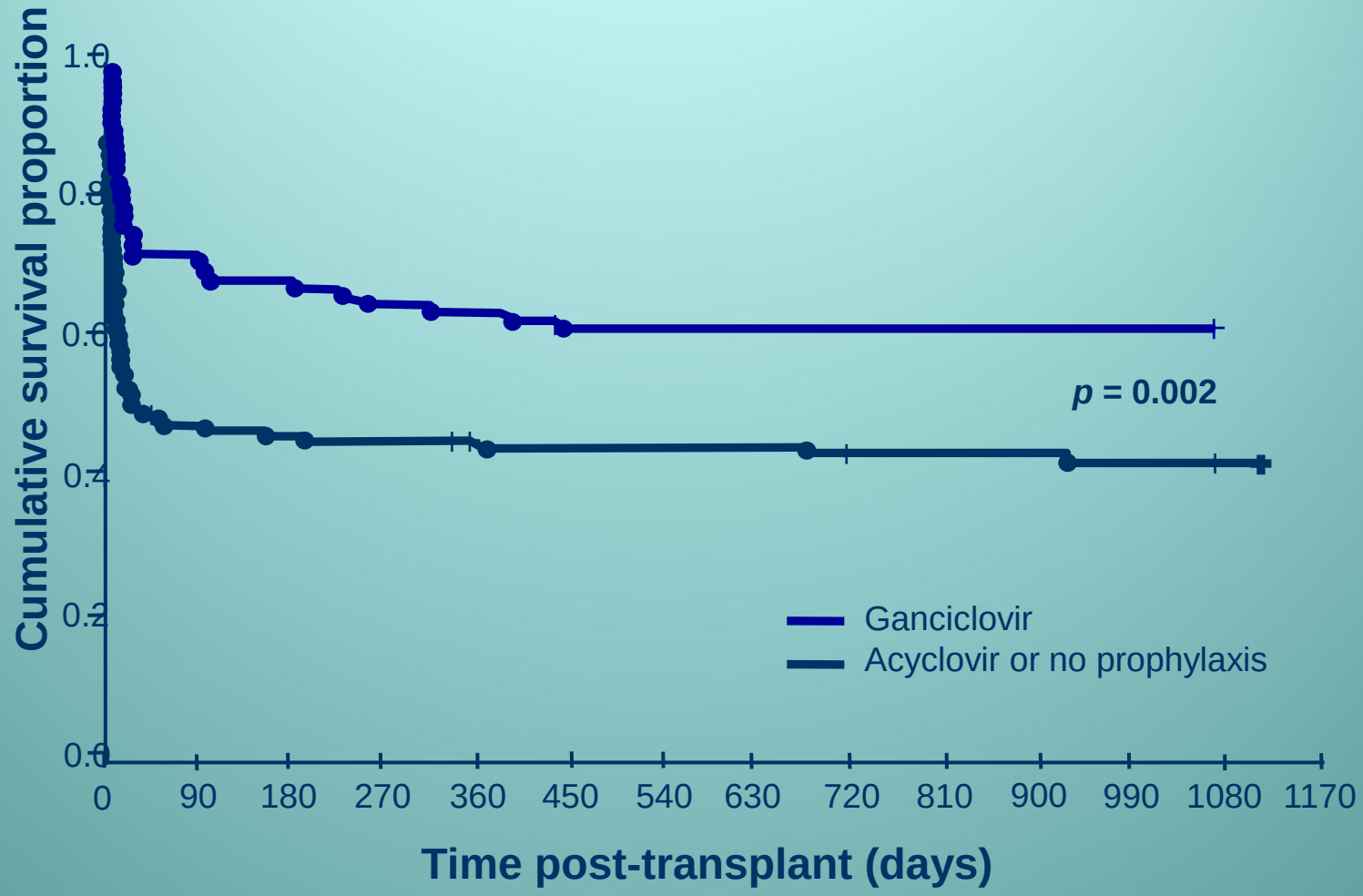
Hazard ratio (95% CI) in CMV viremia of chronic phase	Chronic rejection 2.77	Graft loss 9.24

Conclusions

CMV viremia were existed in 10-20% of chronic kidney transplant recipients under the long-term immunosuppression, which were significantly related to chronic rejection and graft loss. Preventing latent CMV infection may contribute to decreasing chronic rejection and graft loss.

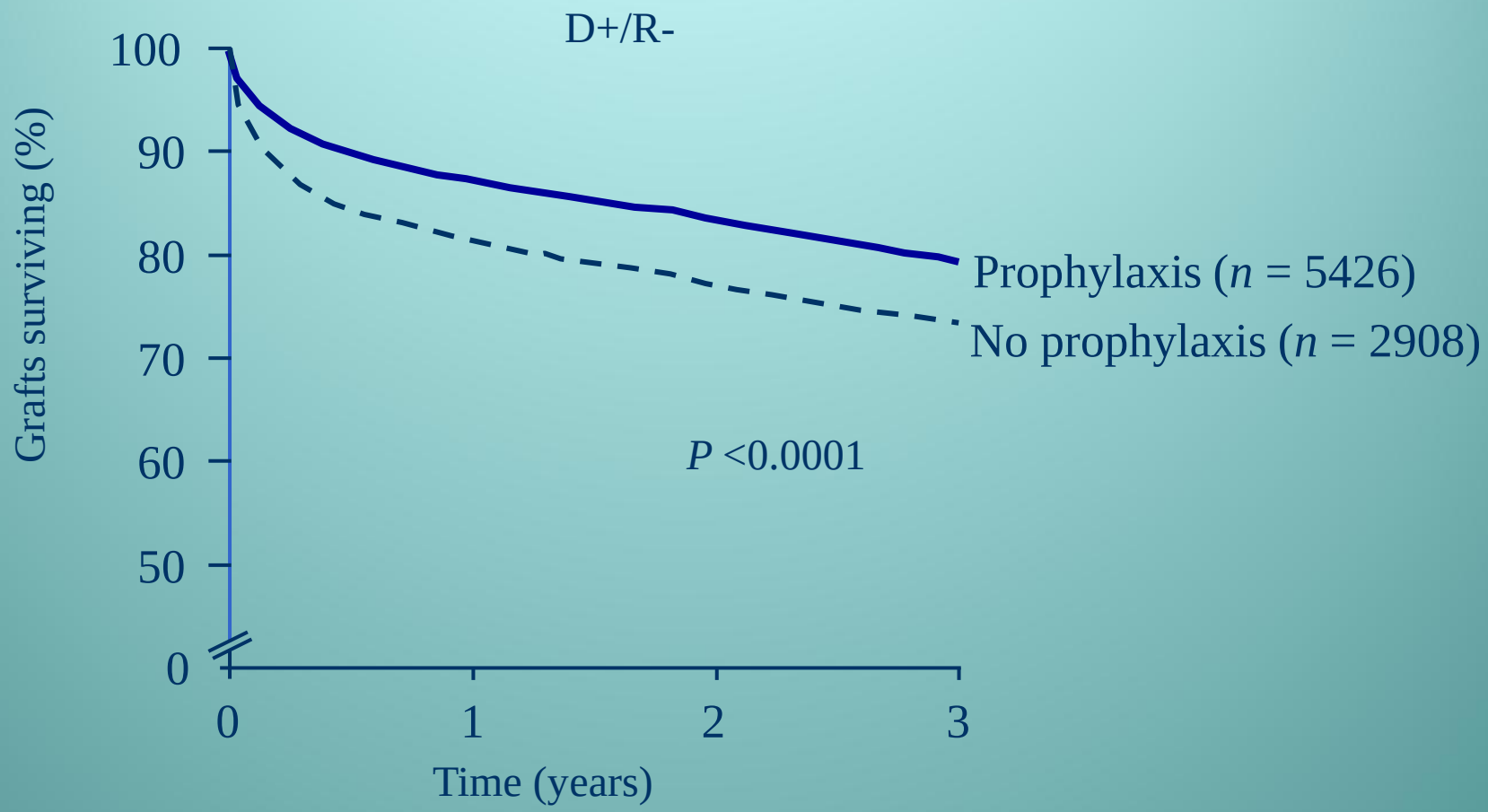
Ishikawa Shoko, et al. Frontiers in Cellular and Infection Microbiology
Manuscript ID: 1190794

Ganciclovir Prophylaxis Reduces the Incidence of Acute Rejection



Ricart MJ *et al*. *Nephrol Dial Transplant* 2005 20 (Suppl 2):ii25–ii32.

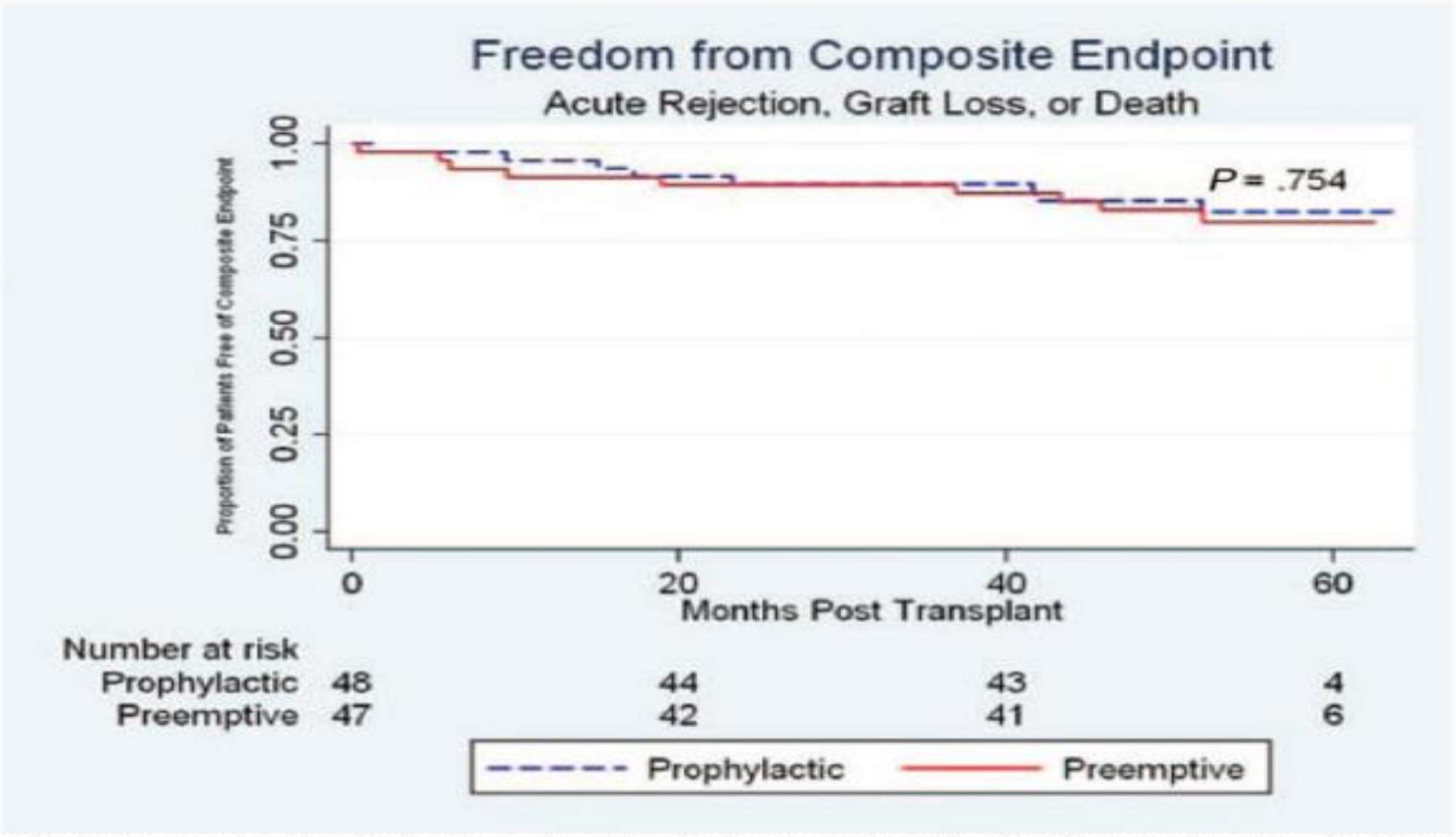
Improved Renal Allograft Survival with Anti-CMV Prophylaxis



Opelz G et al. *Am J Transplant* 2004; 4:928-36.

Impact of Prophylactic Versus Preemptive Valganciclovir on Long-Term Renal Allograft Outcomes

Michael L. Spinner,[1] Georges Saab,[1] Ed Casabar,[2] Lyndsey J. Bowman,[2] Gregory A. Storch,[1,3] and Daniel C. Brennan[1,4]



Spinner ML et al. Transplantation 2010; 90:412

Indirect Effects of CMV Infection

- CMV is immunosuppressive
- CMV may be a risk factor for acute rejection and chronic graft injury
- Decreased graft and patient survival

Cardiovascular events

- Opportunistic infections: Bacterial, fungal and viral superinfections
- Immunosenescence
- Malignancies: PTLD
- New-onset diabetes mellitus (NODAT)
- Guillain-Barré syndrome
- Thrombosis
- TTP-HUS after renal transplantation
- Increased healthcare expenses
- Linked to heart allograft atherosclerosis

Risk Factors for Post–Renal Transplant Cardiac Complications

Risk Factor	Group	Odds Ratio	*P*
Age	**>50 vs <50**	**2.5**	**0.0001**
Diabetes	**Y vs N**	**1.99**	**0.0001**
CMV Dx	Y vs N	1.5	0.01
Smoking	**Y vs N**	**1.37**	**0.01**
Cardiac Hx	**Y vs N**	**1.34**	**0.04**
Hypertension	**Y vs N**	**1.16**	**NS**

Humar A et al. *Transplantation.* 2000;70:310-313.

CMV and Cardiovascular Mortality after Renal Transplantation

- Independent risk factors for cardiovascular death after renal transplantation
  - Increasing age ($p < 0.004$)
  - Presence of diabetes ($p < 0.04$)
  - ***CMV seropositivity*** ($p < 0.01$)

Kalil RSN et al. *Am J Transplant* 2003; 3:79-81.

Published online 2018 June 23.

Review Article

Effect of Cytomegalovirus Exposure on the Atherosclerotic Events Among Kidney-Transplanted Patients, A Systematic Review and Meta-Analysis

Mohammad Saeid Rezaee-Zavareh,[1,2] Reza Ajudani,[1] Mohammad Hossein Khosravi,[1] Mahdi Ramezani-Binabaj,[3] Zohreh Rostami,[2] and Behzad Einollahi[2,*]

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[3]Resident of Urology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

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Received 2017 No

Abstract

Context: At
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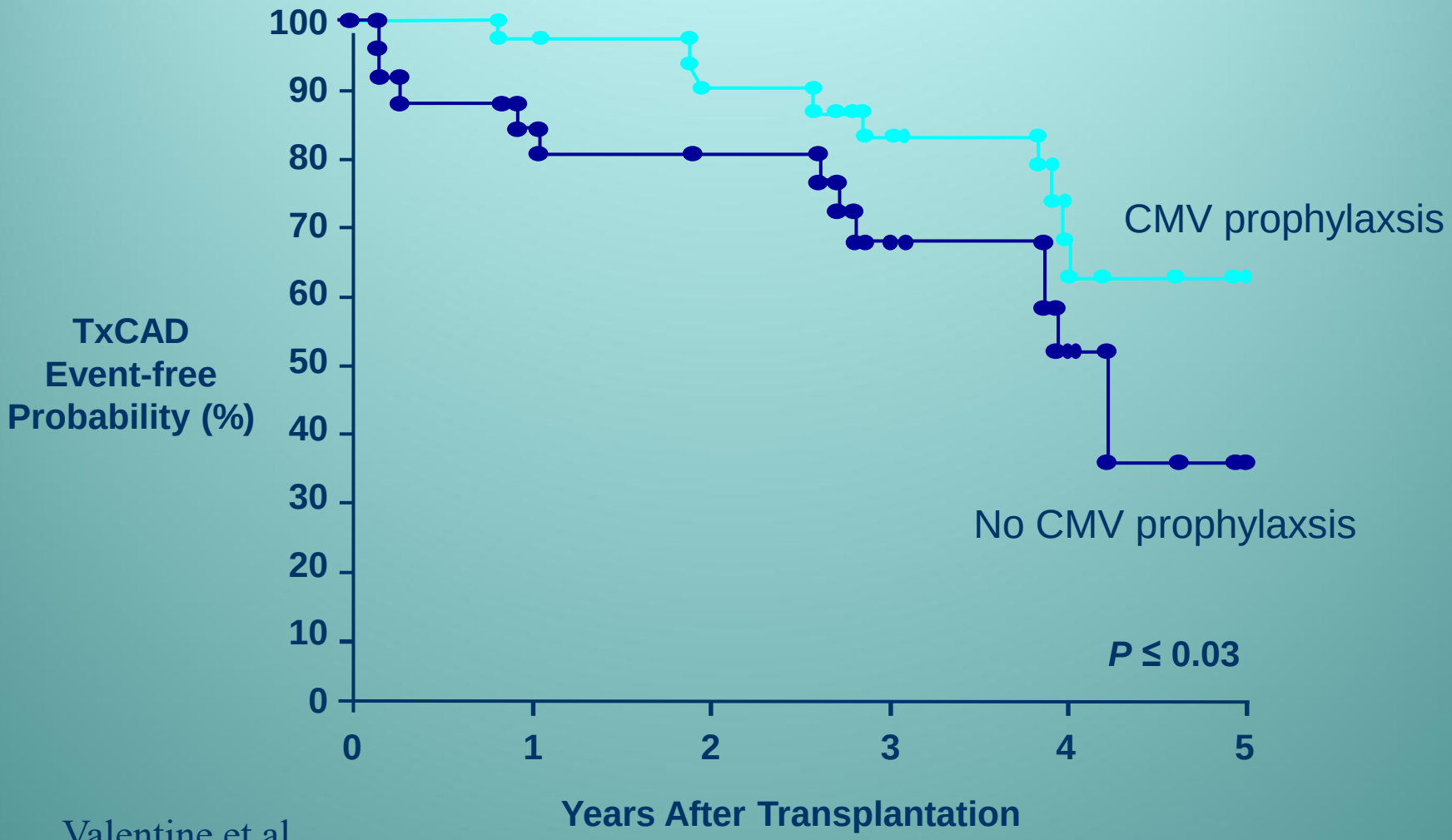
Results: Ten
kidney-trans
RR of 1.46 (95%
- 1.65).

According to available data for analysis, seven papers were included in our meta-analysis and showed ***RR of 1.46*** (95% CI: 1.15 - 1.85) for the mentioned effect and based on the trim and fill method ***the corrected RR was as 1.26*** (95% CI: 1.01 - 1.65).

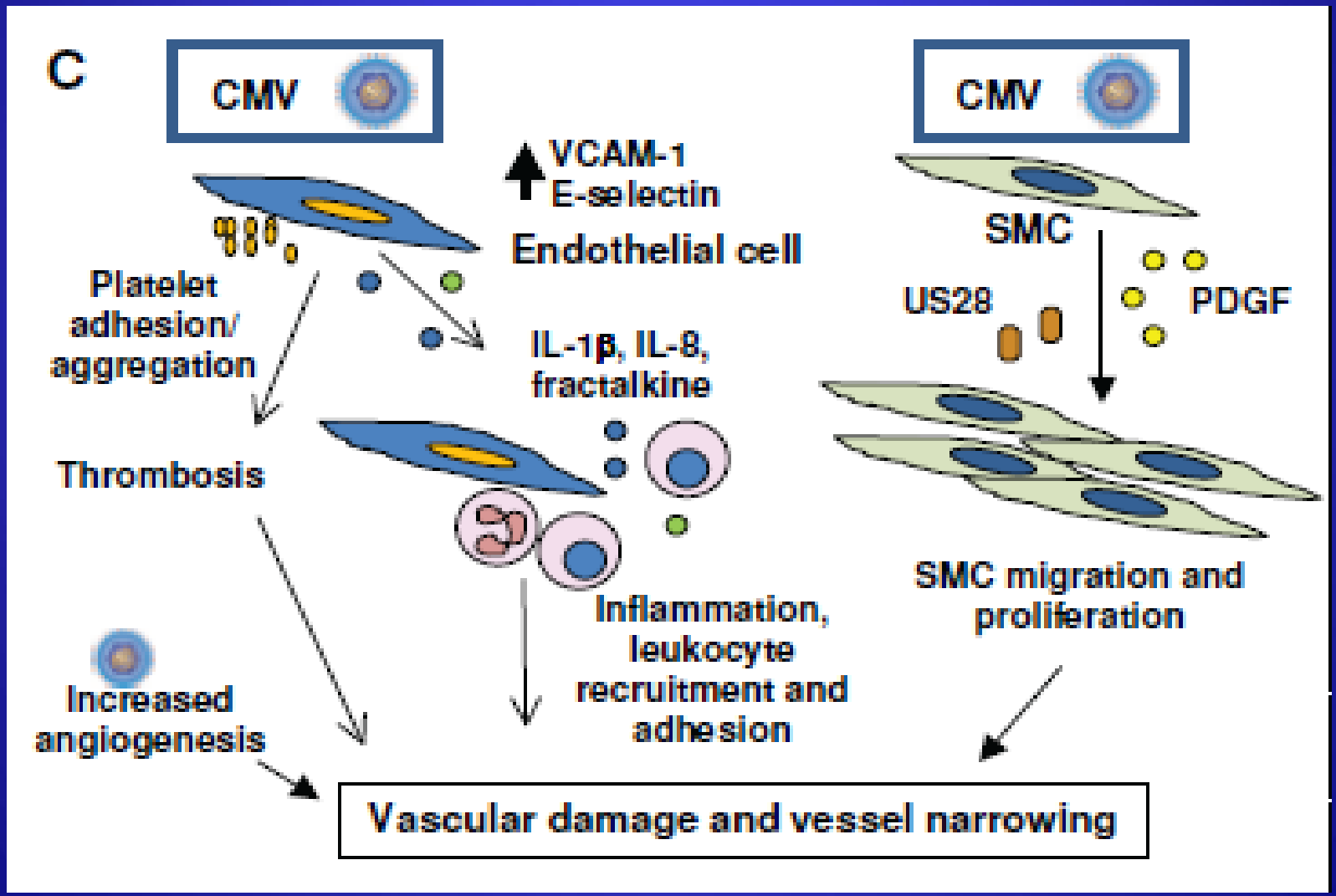
Conclusions: Our meta-analysis showed that exposure with CMV can lead to atherosclerosis events among kidney-transplanted patients.

Prevention of CMV Results in Reduced Transplant Atherosclerosis



Valentine et al.

Mechanisms by which CMV can induce vascular damage and vessel narrowing



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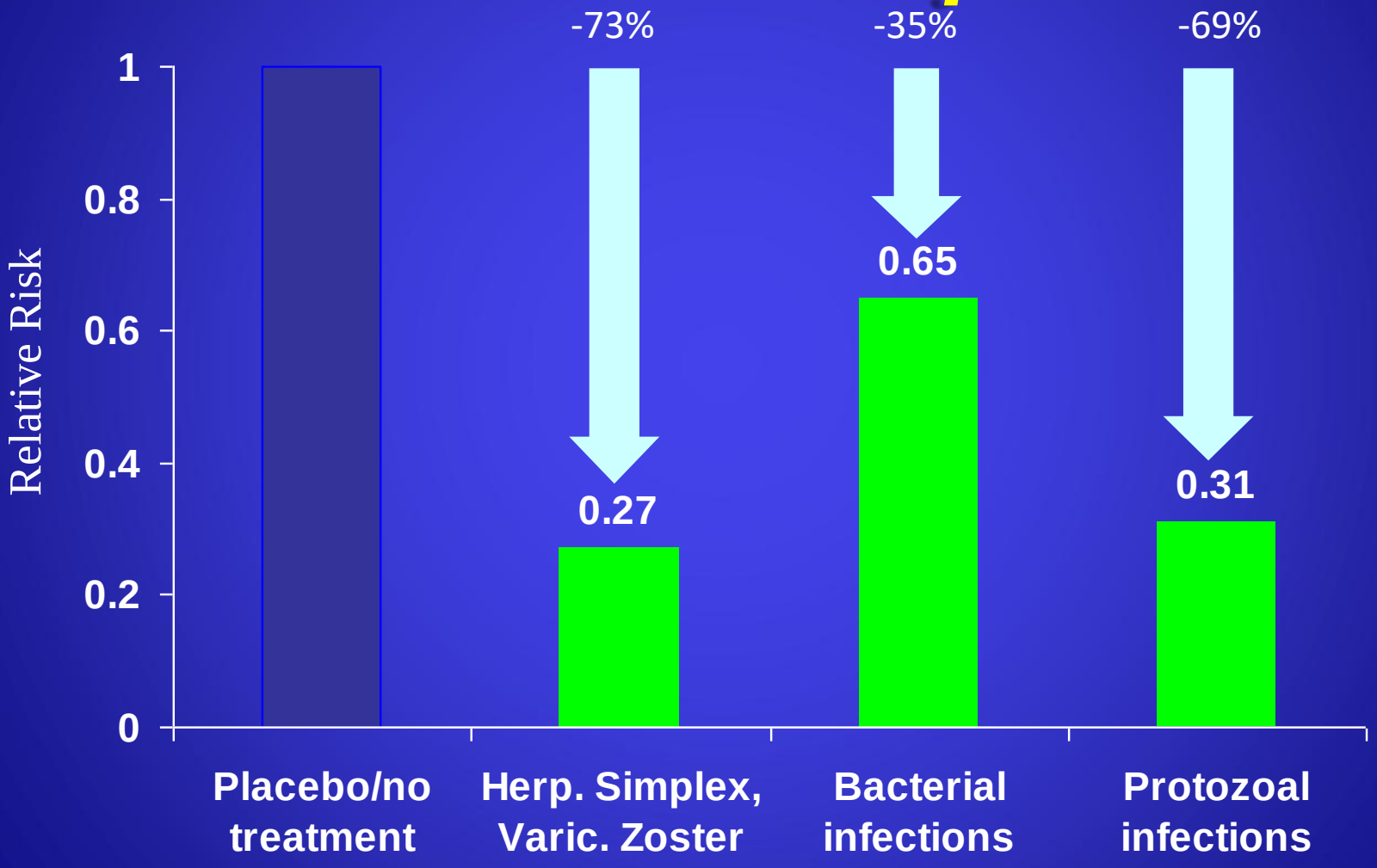
Effects of Anti-CMV Prophylaxis on Concomitant Infections



Hodson EM et al. *Lancet* 2005; 365:2105-15.

Opportunistic Infections Promoted by CMV Infection in Transplant Patients

- Fungal infections
  - →*Aspergillus spp*
  - →*Pneumocystis carinii (jirovecii)*
  - →*Candidemia* and intra-abdominal infection after liver and pancreas transplants
- Bacteremia: *Listeria monocytogenes*
- Epstein-Barr virus infection (RC Walker et al, CID, 1995, 20:1346-55), HHV6/7, HHV8/KSHV
- HCV: risk for cirrhosis, fulminant HCV hepatitis, retransplantation, mortality

© Ann Transplant, 2009; 14(1): 32-37

Original Paper

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Dose CMV infection increase the incidence of infective endocarditis following kidney transplantation?

Behzad Einollahi[1], Mahboob Lessan-Pezeshki[2], Vahid Pourfarziani[1], Eghlim Nemati[1], Mohsen Nafar[3], Fatemeh Pour-Reza-Gholi[3], Mohammad Hassan Ghadiani[1], Maryam Moshkani Farahani[4]

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[3] Department of Nephrology Labbafi-Nejad Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
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Summary

Background: Infective endocarditis (IE) is a rare but life threatening infection after renal transplantation. In addition, coinfection of CMV and IE has not been reported. Therefore, the current study was initiated to determine whether CMV infection is a risk factor for developing of IE after kidney transplantation.

Material/Methods: In a retrospectively study, we analyzed the medical records of 3700 kidney recipients at two transplant centers in Iran, between January 2000 and June 2008 for infective endocarditis.

Results: During th
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survival fr
tion (P=0
CMV coinfection was more likely to be early when compared to CMV negative

The presentation time of infective endocarditis in recipients with CMV coinfection was more likely to be early when compared to CMV negative coinfection patients (P=0.03).

Does CMV infection increase the incidence of infective endocarditis following kidney transplantation?

- In a retrospectively study, we analyzed the medical records of 3700 kidney recipients at two transplant centers in Iran, between January 2000 and June 2008 for infective endocarditis.
- During the study, **15 patients with IE** hospitalized in our centers were included, **8 patients with CMV co-infection**.
- The presentation time of infective endocarditis in recipients with CMV coinfection was more likely to be early when compared to CMV negative coinfection patients (P=0.03).
- The present study indicates that CMV infection may lead to predispose to infective endocarditis after kidney transplantation.

Einollahi B, et al. Ann Transplant. 2009 Jan-Mar;14(1):32-7.

Miliary Tuberculosis and CMV Infection in a Kidney Recipient

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F Nephro-Urology Monthly 2009; 1 (2) : 153-155; Language: EN

Abstract

Cytomegalovirus (CMV) is the leading cause of infectious complications after organ transplantation. Tuberculosis can occur in the early postoperative period and is potentially curable. We report here a 45-year-old renal transplant recipient with a rare coinfection of CMV infection and miliary tuberculosis, as early as 6 months after the transplant. In addition, HCV Ab was positive with normal liver function tests before kidney transplantation. The organism was isolated from sputum and broncoalveolar lavage (BAL) specimen cultures. The patient was given 12 months of quadruple anti-TB therapy. With antituberculous therapy, and reduction in the patient's conventional immunosuppression, intravenous ganciclovir was also used. The patient remained disease-free after a follow-up period of 6 years. To

Miliary Tuberculosis and CMV Infection in a Kidney Recipient

- We report a 45-year-old renal transplant recipient with a rare coinfection of CMV infection and miliary tuberculosis, as early as 6 months after the transplant.

Nafar et al. Nephro-Urol Mon. 1(2): 153-155.

Indirect Effects of CMV Infection

- CMV is immunosuppressive
- CMV may be a risk factor for acute rejection and chronic graft injury
- Decreased graft and patient survival
- Cardiovascular events
- Opportunistic infections: Bacterial, fungal and viral superinfections

➢ Immunosenescence

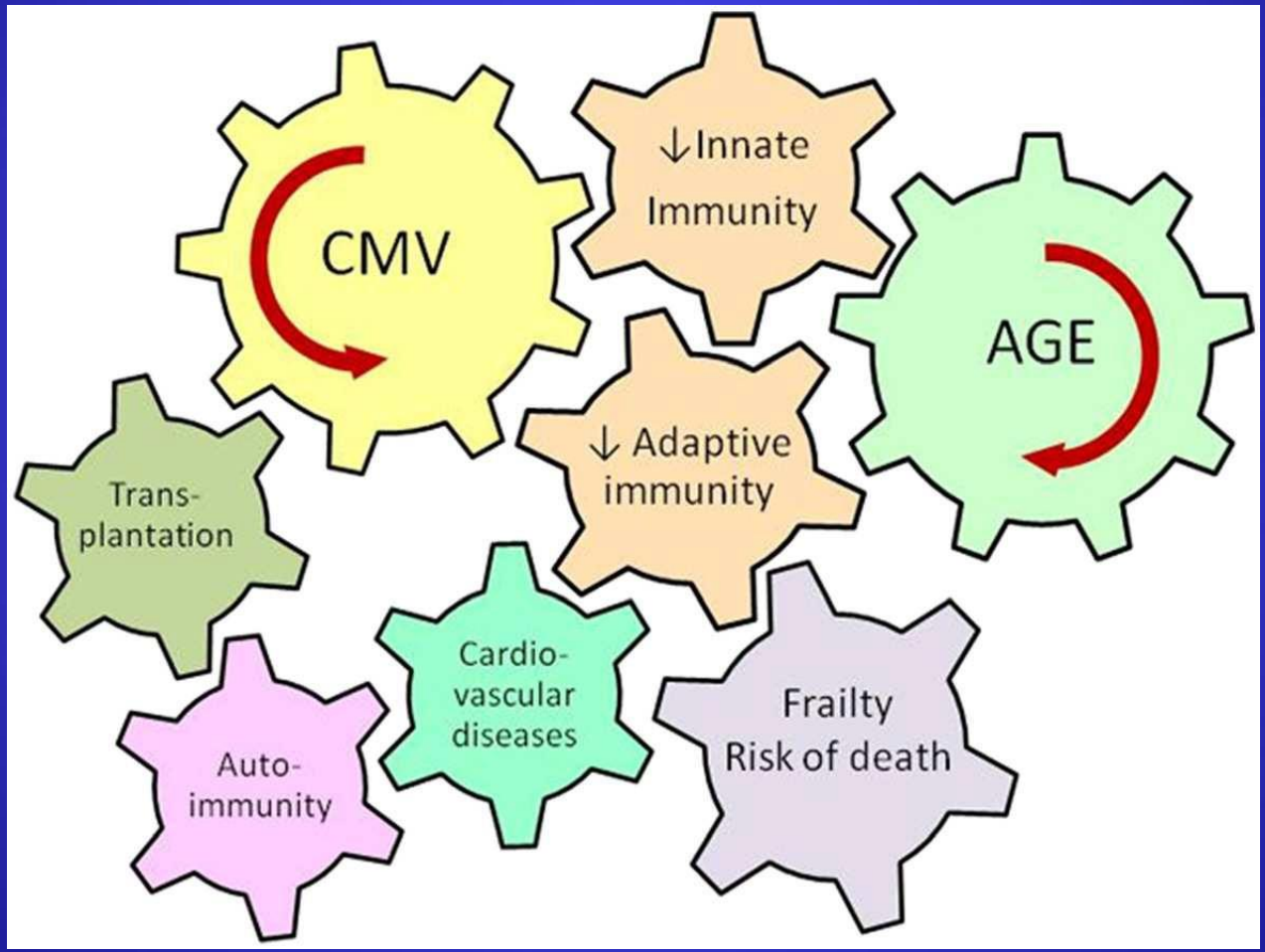
- Malignancies: PTLD
- New-onset diabetes mellitus (NODAT)
- Guillain-Barré syndrome
- Thrombosis
- TTP-HUS after renal transplantation
- Increased healthcare expenses
- Linked to heart allograft atherosclerosis

CMV and Immunosenescence

Immunosenescence defined as the deleterious age-associated changes to immunity

Solana et al. Immunity & Ageing 2012, 9:23

Age and CMV infection are major driving forces contributing to the deterioration of innate and adaptive immunity



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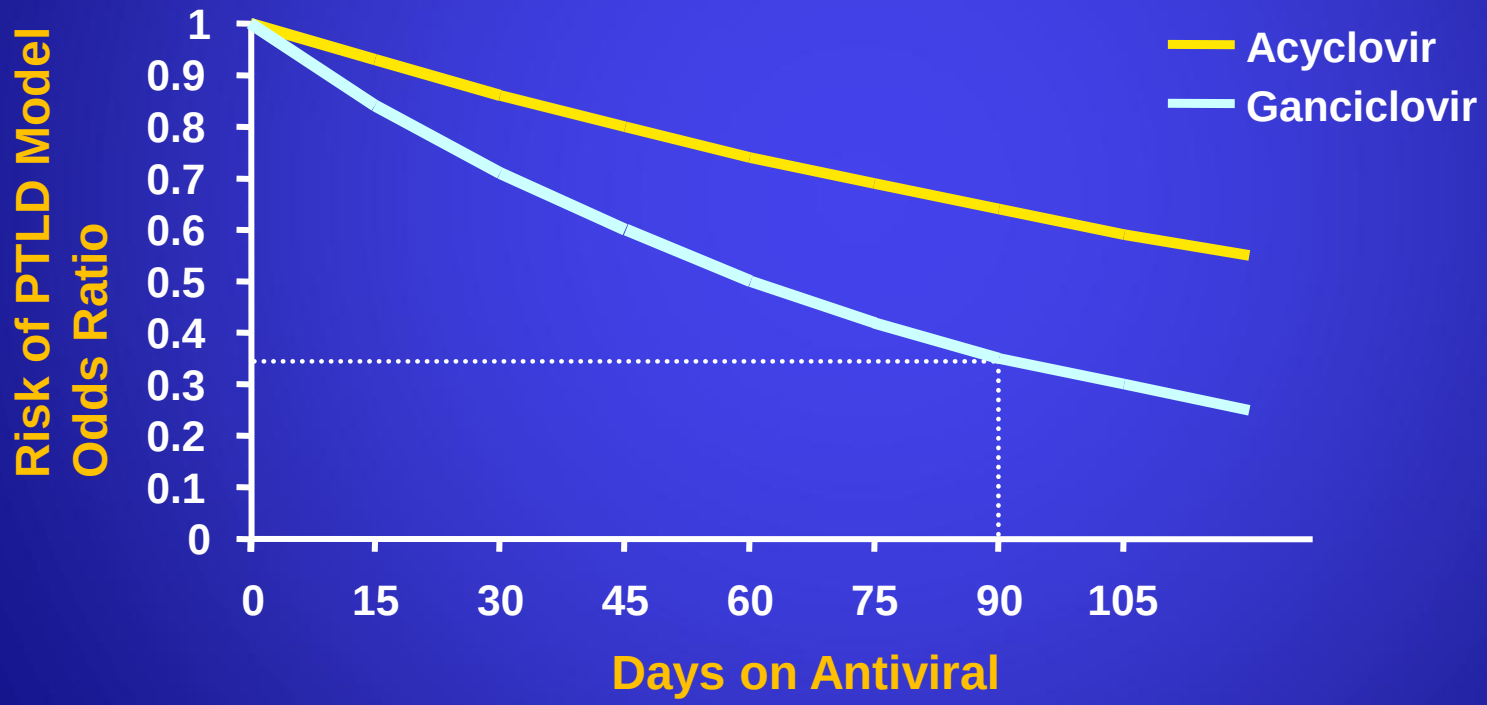
- Owing to its immunosuppressive effect, CMV has also been suggested as a risk factor for the development of ***post-transplant lymphoproliferative disorders (PTLDs)*** in solid organ recipients, a pathological condition that is associated strictly with EBV replication

Varani and Landini Herpesviridae 2011, 2:6

PTLD Risk with Days on Antiviral



PTLD: post-transplant lymphoproliferative disease

Funch D *et al.* *Am J Transplant* 2005; 5:2894-2900.

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Journal of Nephropathology

The impact of cytomegalovirus infection on new-onset diabetes mellitus after kidney transplantation: a review on current findings

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ABSTRACT

Context: New onset diabetes mellitus after transplantation (NODAT) increases the risk of cardiovascular disease, rate of infections, graft rejection and graft loss as well as decreases patient and graft survival rates. There is a controversy surrounding the impact of cytomegalovirus (CMV) infection in the development of NODAT. This meta-analysis aims to identify the role of CMV infection leading to the development of NODAT in kidney recipient patients.

Evidence Acquisitions: We searched several electronic databases, including PubMed, Embase, Medline, Scopus, Trip Database and Google Scholar for studies that completely fulfill our criteria between January 1990 and January 2014.

The incidence of NODAT varies from ***14.3% to 27.1%*** in these studies. ***Overall adj OR was 1.94*** [exp (0.66)] with a 95% CI of 1.26-2.98 [exp (0.23) and (1.09)].

Conclusions: Our study showed that CMV infection is a risk factor for increasing incidence of NODAT. Thus, prophylaxis against CMV infection after kidney transplantation is strongly suggested. However, further clinical trials and cohorts are needed to confirm this association.

Review

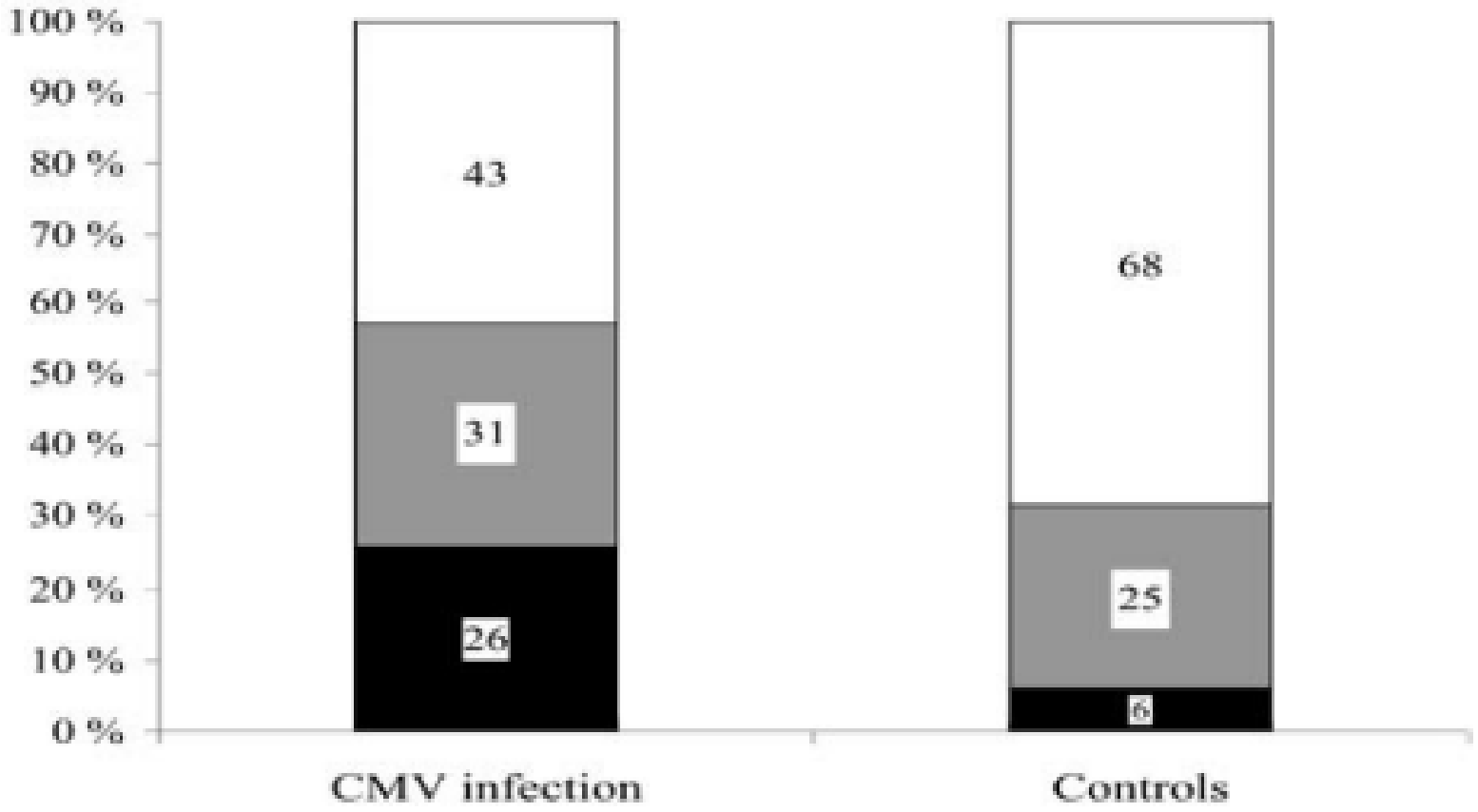


Figure 1.12 Relative proportions of patients with varying degrees of glucose tolerance according to CMV status

A significantly higher proportion of patients with CMV infection developed NODAT (p=0.003) and Impaired Glucose Tolerance (p=0.008) compared with controls.

CMV infection (*n*=61), patients without CMV infection (controls, *n*=63). White: Normal Glucose Tolerance, Grey: Impaired Glucose Tolerance, Black: Post-Transplant Diabetes Mellitus [143].

Increased risk for post-transplant diabetes mellitus

- Although the most important cause of PTDM is the effect of immunosuppressive drugs on glycemia control, CMV infection has also been identified as a risk factor for this entity.

Smith R. Diabetologia. 2004;47:1473-5.

Increased risk for post-transplant diabetes mellitus

- Clinical evidence suggests that asymptomatic CMV infection and CMV disease are ***independent risk factors for early-onset*** diabetes mellitus in recipients of renal transplant (PTDM).

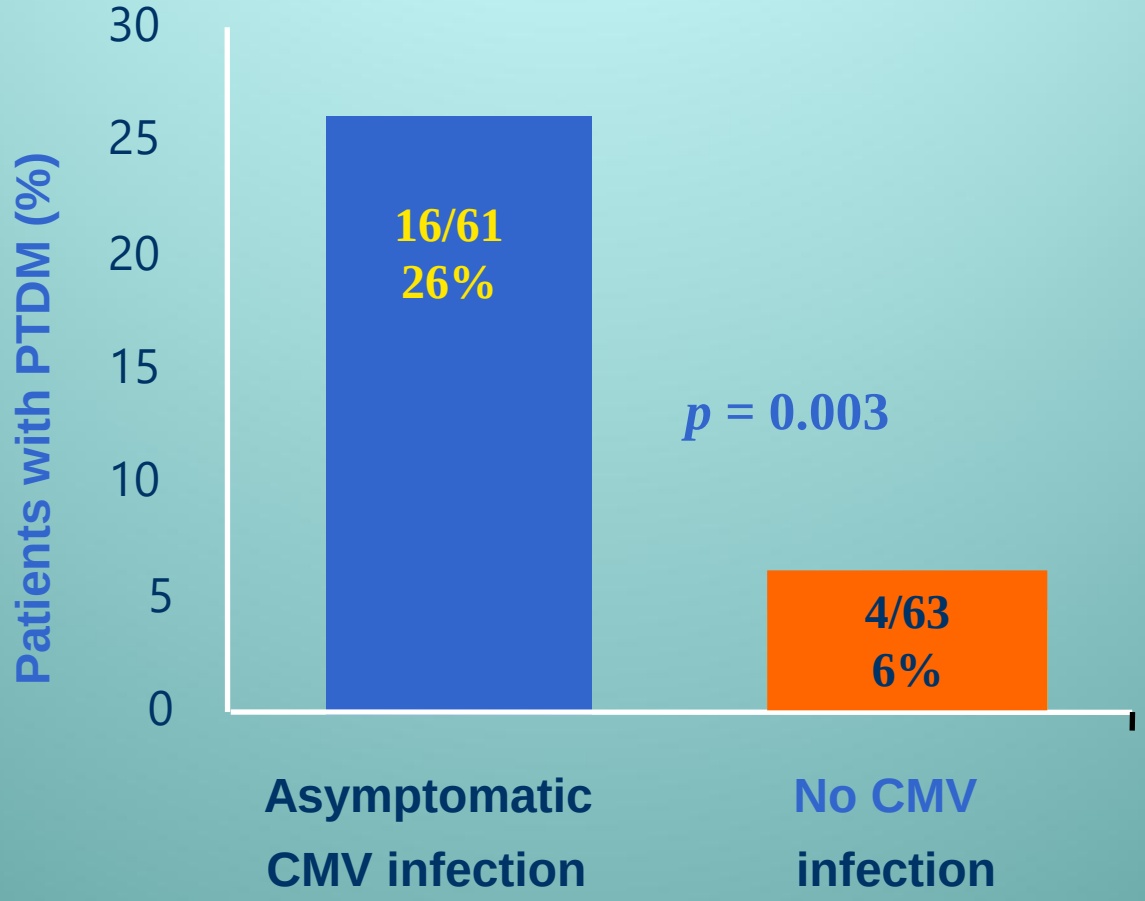
Hjelmesaeth et al. Diabetologia 2004, 47:1550-6.
Hjelmesaeth et al. Transplantation 1997, 64: 979-983.

Increased risk for post-transplant diabetes mellitus

- ***CMV donor-positive/recipient-negative serostatus*** is a risk factor for the development of PTDM in pediatric renal transplant patients.

Burroughs et al. Transplantation 2009, 88: 367-373.

Low-Level CMV Replication is Associated with PTDM



Hjelmesaeth J et al. *Diabetologia* 2004; 47:1550-6.

Increased risk for post-transplant diabetes mellitus

- The incidence of PTDM has ***declined significantly*** since the introduction of ***preemptive anti-CMV regimens***, supporting the link between CMV and PTDM.

Valderhaug et al. Transplantation 2007, 84:1125-30.

Increased risk for post-transplant diabetes mellitus

- ***CMV damages β-cells by direct viral infection*** (the pancreas is a target organ of CMV infection), through the cytotoxic effects of activated effector lymphocyte infiltrates, or the induction of proinflammatory cytokines.

Kamalkumar et al. Clin Exp Nephrol 2009, 13: 389-91.
Hjelmesaeth et al. Nephrol Dial Transplant 2005, 20: 2311-5.

Possible role of MBL deficiency in CMV diases and post transplant diabetes

Association Between Mannose-Binding Lectin Deficiency and Cytomegalovirus Infection After Kidney Transplantation

Oriol Manuel,[1] Manuel Pascual,[2] Myriam Trendelenburg,[3] and Pascal R. Meylan[1,4]

Low Serum Mannose-Binding Lectin as a Risk Factor for New Onset Diabetes Mellitus After Renal Transplantation

Montserrat Vamvakas,[1] Francesc Moreso,[2] José M. Morena,[1] Oriol Bestard,[1] Josep M. Cruzado,[2] Josep M. Grinyó,[2] Wilfredo Rivera,[2] José M. Fernández-Real,[3] and Daniel Serón[1,2]

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Cytomegalovirus infection and new-onset post-transplant diabetes mellitus

Leung Ki E-L, Venetz J-P, Meylan P, Lamoth F, Ruiz J, Pascual M.
Cytomegalovirus infection and new-onset post-transplant diabetes mellitus.
Clin Transplant 2008: 22: 245–249. © 2008 Blackwell Munksgaard

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CMV induced renal disease

- Rejection associated with CMV viremia
- CMV infection associated with RAS
- CMV associated with HUS/TTP
- CMV induced transplant glomerulopathy

Conclusions

- The indirect effects of CMV in transplant recipients are due to survival mechanisms of the virus:
  - Immunosuppressive effects: to avoid recognition by the immune system
  - Proinflammatory effects: to replicate and disseminate
- The stronger clinical evidence of the immunomodulatory effects of CMV is the reduction of other infections and acute rejection with the introduction of universal antiviral prophylaxis (3-6 months)


Thank you
all for your
attention