CMV DISEASE IN TRANSPLANT RECIPIENTS: EVALUATION AND MANAGEMENT

Emily A. Blumberg, MD
Professor of Medicine
Perelman School of Medicine of the University of Pennsylvania

Cytomegalovirus: Then and Now

1979*

- Most common opportunistic infection following SOT
- Clinical infection 67% renal transplant patients
- Diminished long term patient and graft survival (<80% 2yr survival)

2015**

- **Most common opportunistic infection following SOT**
- **Clinical infection common - >20% D+R- with prophylaxis**
- **Diminished long term patient and graft survival**

*Rubin, et al. J Infect Dis 1979;139:728-34 , **Fishman, NEJM 2007;357:2601-14; Humar, et al. Am J Transplant 2010;10:1-10

Why are we still talking about CMV?

- Improved prevention strategies
  - Understand the at risk population
  - More effective diagnostics
  - More potent antivirals for prevention and treatment
- *But….*
  - *More potent immunosuppression*
    - *T cell depleting agents*
  - *More challenging transplants*
    - *Including patients at higher risk of rejection*

Outline

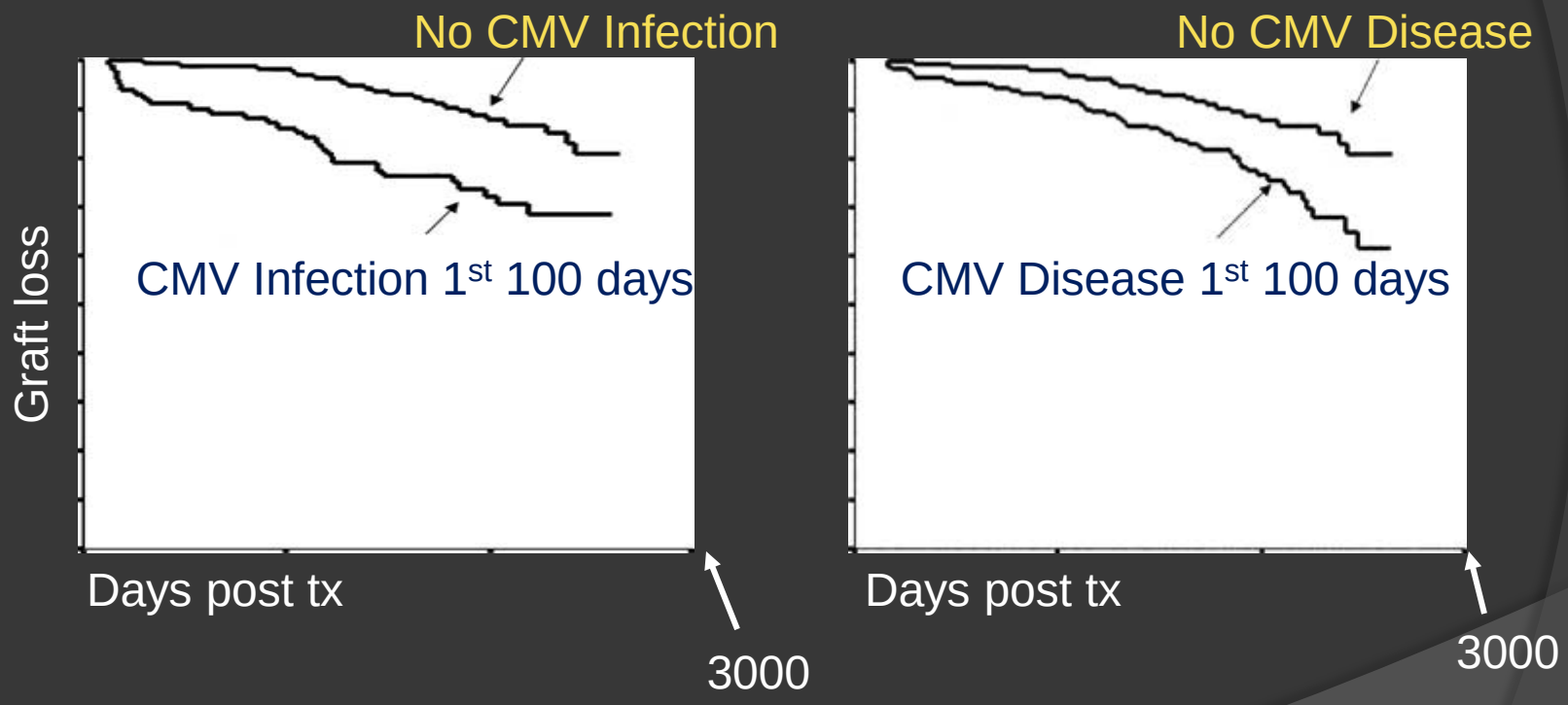
- Impact of CMV
  - Direct effects
  - Indirect effects
- Prevention 2013
- Diagnosis in the era of molecular diagnostics
- Treatment of Sensitive and Resistant Virus
- The Future

Definitions

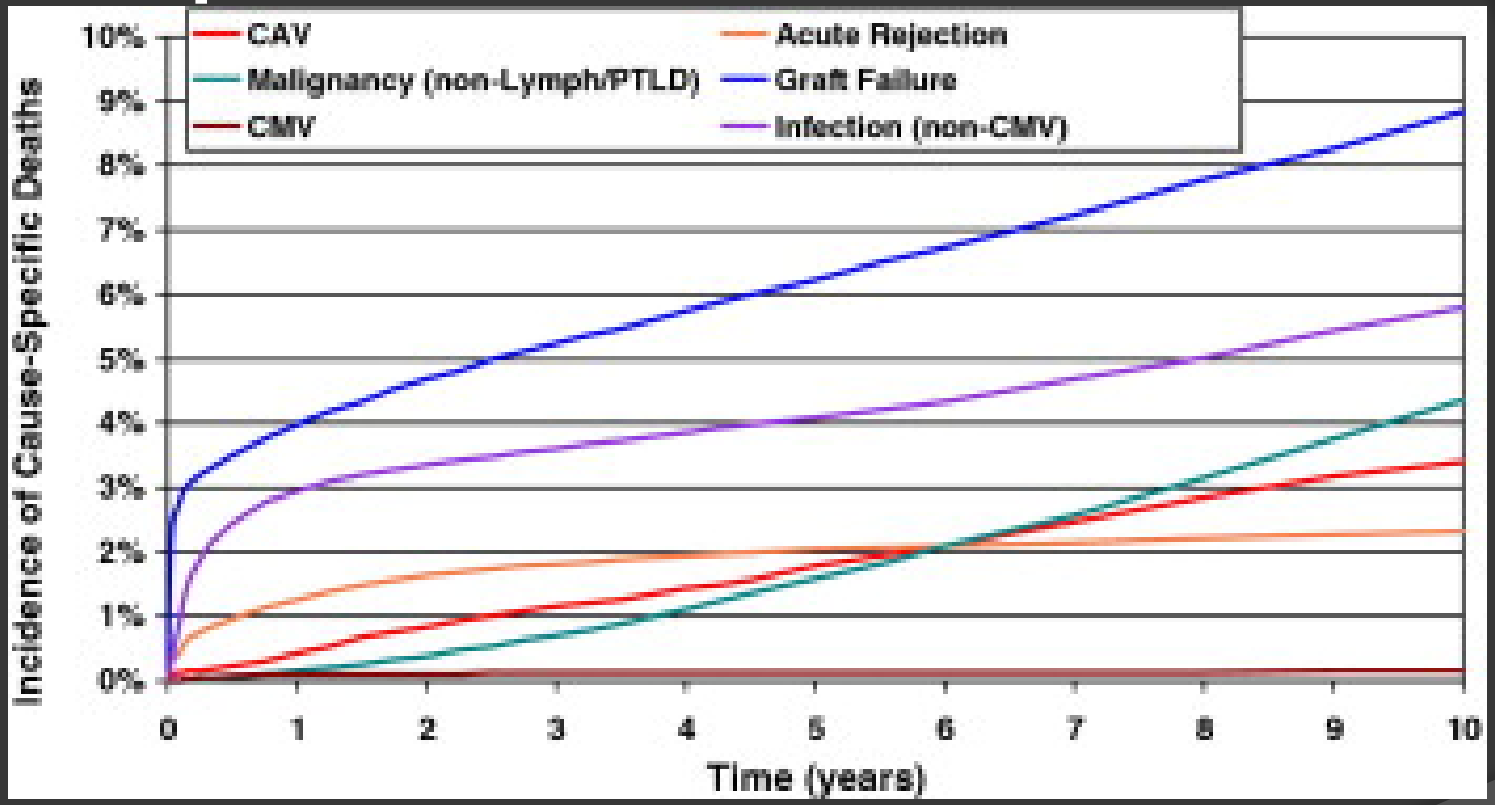
- Latent CMV
  - Positive serology without evidence of active infection
- CMV Infection
  - Evidence of CMV replication regardless of symptoms
- CMV Disease
  - Evidence of infection with attributable symptoms
    - CMV syndrome
    - Tissue invasive disease

Graft Survival in Kidney Transplant: Impact of CMV

Sagedal , et al., Kidney International 2004

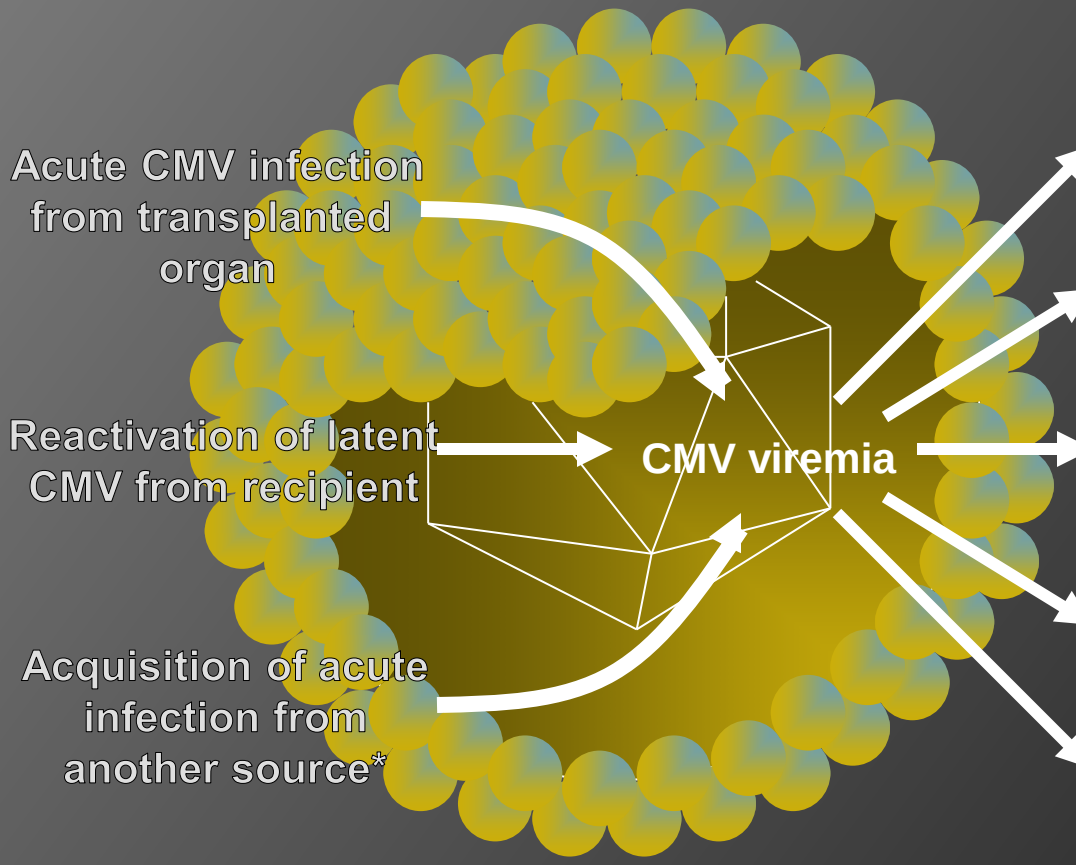


Mortality in Heart Transplant Recipients



Taylor, et al. J Heart and Lung Transplantation 10:1007, 2009

Reactivation or acquisition of CMV



Potential effects of CMV on liver transplant recipient

CMV syndrome
- Fever
- Leukopenia
- Thrombocytopenia

CMV tissue-invasive disease
- End-organ damage (such as enteritis, colitis, gastritis, esophagitis, hepatitis)

Direct Effects

Allograft rejection

Immunosuppression‡

Increased hepatitis C viral replication

Indirect Effects

*Person-to-person transmission or transfusion of contaminated blood products

‡CMV has been associated with increased risk of bacterial, fungal, and protozoal infections

Indirect Effects of CMV

Graft/Patient	Infection	Miscellaneous
• Acute rejection • Chronic allograft dysfunction • Hepatic artery thrombosis (Liver) • Vasculopathy (Heart) • Bronchiolitis obliterans (Lung) • Mortality	• Bacterial • Fungal (including PCP) • Viral • Accelerated HCV	• Post transplant lymphoproliferative disorder • Cardiovascular • New onset diabetes • Immunosenescence

Immunosuppressive Mechanisms of CMV Infection

Adapted from Freeman, Am J Transplant 2009;9:2453-58

- CMV evades the host immune system by downregulating innate and adaptive immunity
  - ↓ HLA expression
  - HLA class I homologue
  - ↓ Antigen presentation
  - ↓ T-cell proliferation
  - ↓ Production of IL-2, INF-c, PD-1
  - ↑ Fc receptor expression
  - Fc receptor homologue
  - ↑ Complement inhibitors
  - ↓ Macrophage migration
- This leads to an increased susceptibility to infection

Preventing CMV: Prophylaxis vs Preemption

- Prophylaxis

Administration of antiviral to at risk population during risk period (typically months 1-4)

  - Usual antivirals – Valganciclovir, Ganciclovir, or Valacyclovir

- Preemptive Therapy

Monitor for viral replication and administer antiviral when replication reaches threshold

  - Usual antiviral – Ganciclovir or Valganciclovir

- Hybrid Approach

Prophylaxis for limited time followed by period of monitoring

Preemptive vs Prophylactic Strategies

Zhang, et al. Transplant Infect Dis 2011;13:622-32

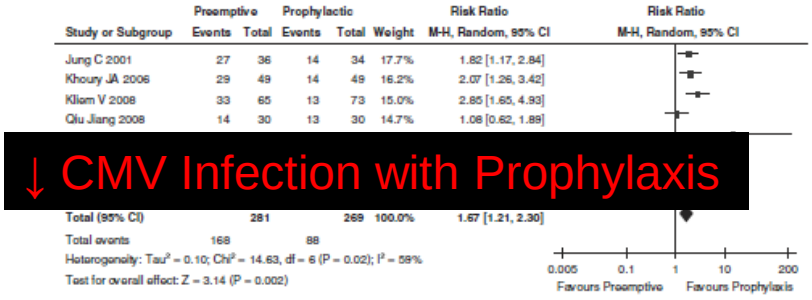


Fig. 3. Cytomegalovirus infection after renal transplantation on preemptive and prophylactic therapy. CI, confidence interval.

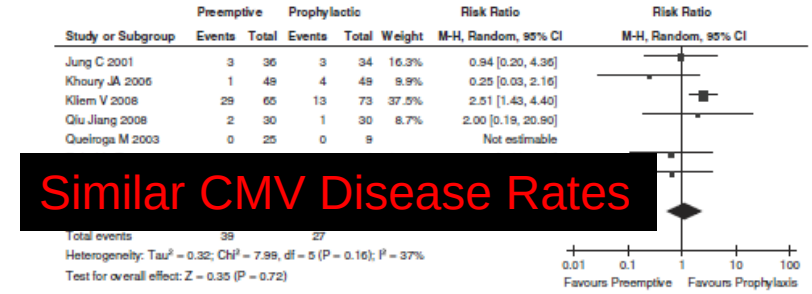


Fig. 4. Cytomegalovirus disease after renal transplantation on preemptive and prophylactic therapy. CI, confidence interval.

Fig. 5. Mortality after renal transplantation on preemptive and prophylactic therapy. CI, confidence interval.

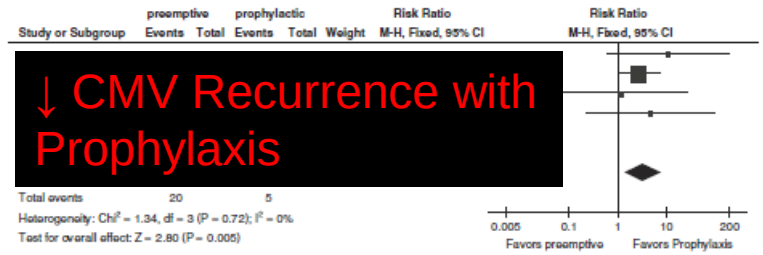


Fig. 6. Recurrence rates of cytomegalovirus infection after renal transplantation on preemptive and prophylactic therapy. CI, confidence interval.

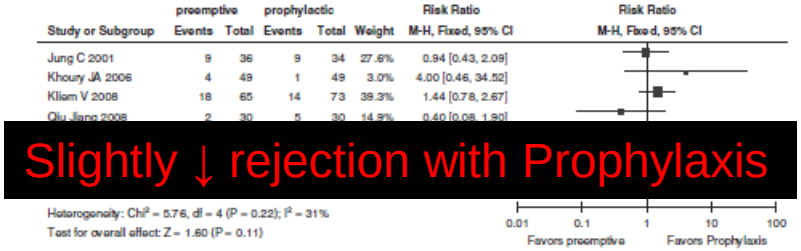


Fig. 7. Rejection episodes after renal transplantation on preemptive and prophylactic therapy. CI, confidence interval.

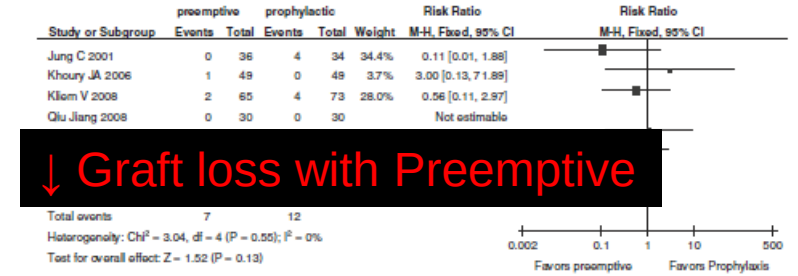
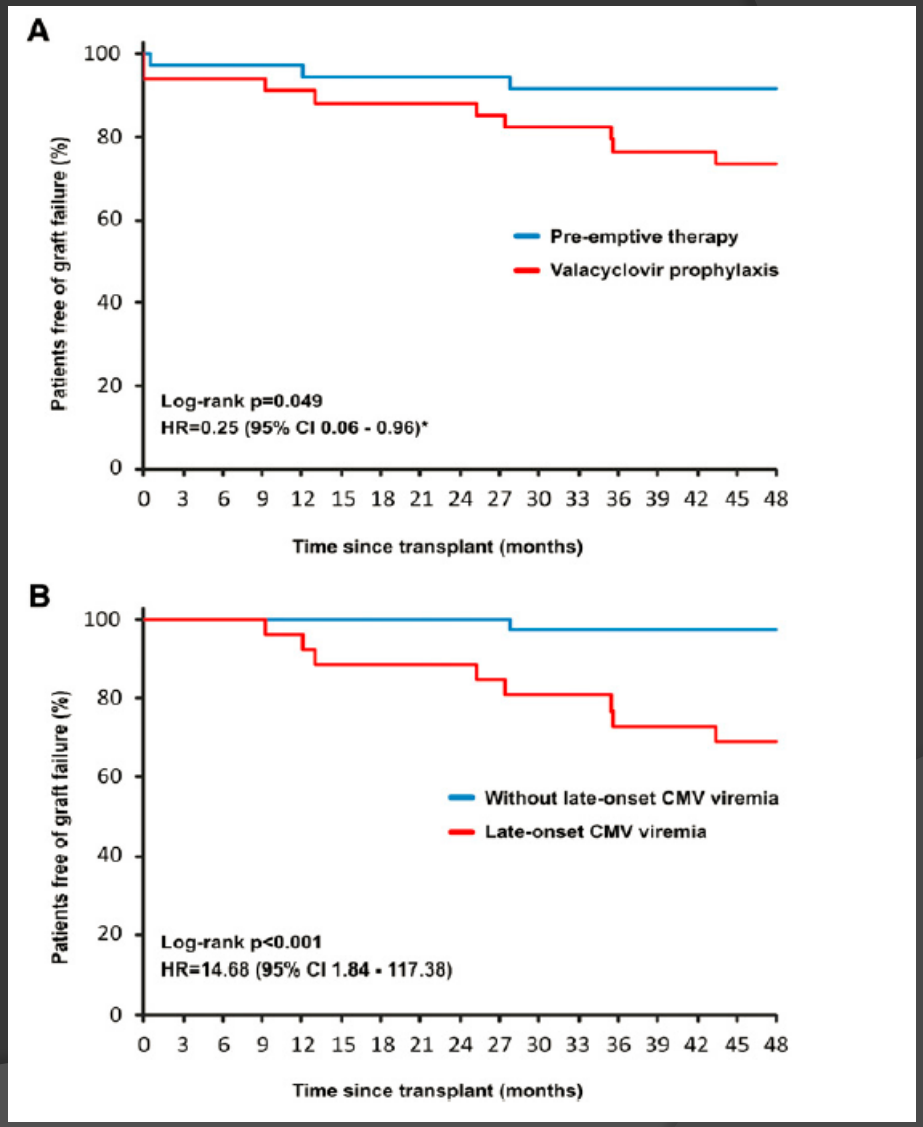


Fig. 8. Graft losses after renal transplantation on preemptive and prophylactic therapy. CI, confidence interval.

Long Term Outcomes: Preemptive Valganciclovir vs Valacyclovir Prophylaxis

Reischig, et al. JASN 2012;23:1588-97

- Comparison of VGCV preemptive vs 3 mos VACV prophylaxis (Kidney)
  - Majority D+R+
- Similar CMV disease rates
- Increased graft failure due to late CMV disease in VACV
- Does early viremia allow for development of protective immune response or is this reflection of VGCV activity?



Comparing Prophylaxis to Preemptive Therapy

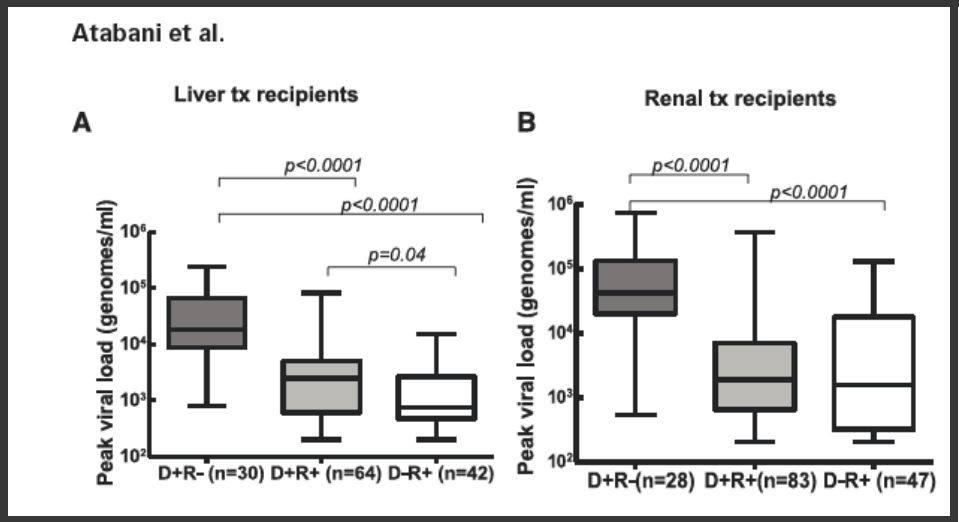
Kotton, et al. Transplantation 2013;96:333-60

TABLE 5. Comparison of prophylaxis versus preemptive therapy

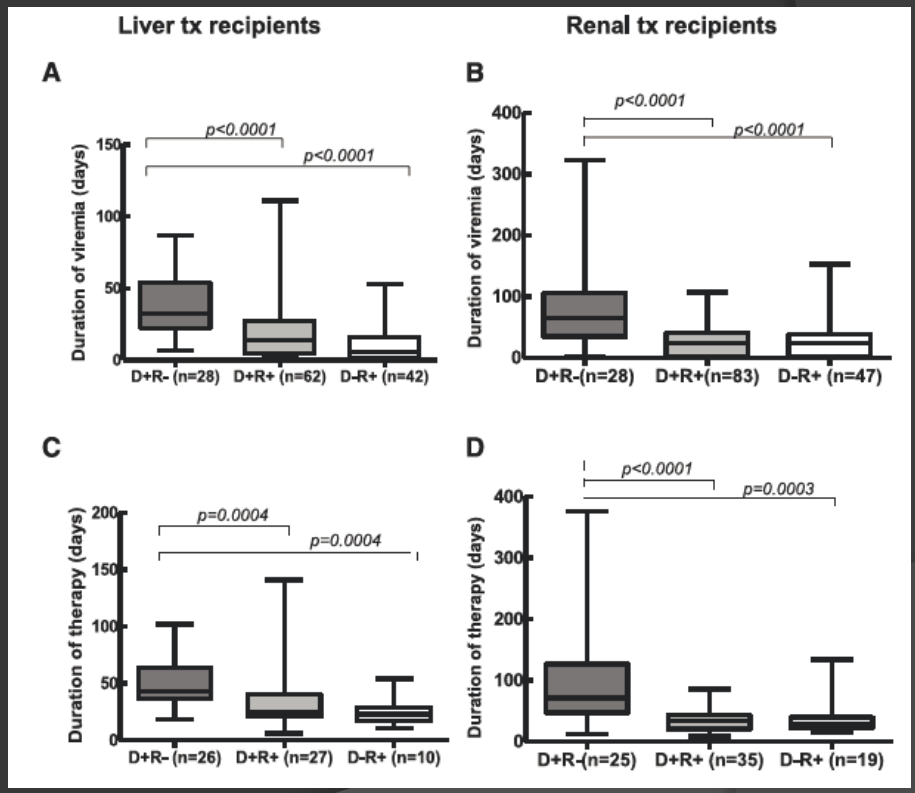
	Prophylaxis	Preemptive therapy
Early CMV DNAemia	Rare	Common
Prevention of CMV disease	Good efficacy	Good efficacy (less optimal in high-risk populations)
Late CMV (infection/disease)	Common	Rare
Resistance	Uncommon	Uncommon
Ease of implementation	Relatively easy	More difficult
Other herpes viruses	Prevents 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

Pre-emption and Risk Status

Atabani, et al. Am J Transplant 2012; 12:2457-64



D+ R- patients have higher viral loads



D+R- patients have longer duration of viremia

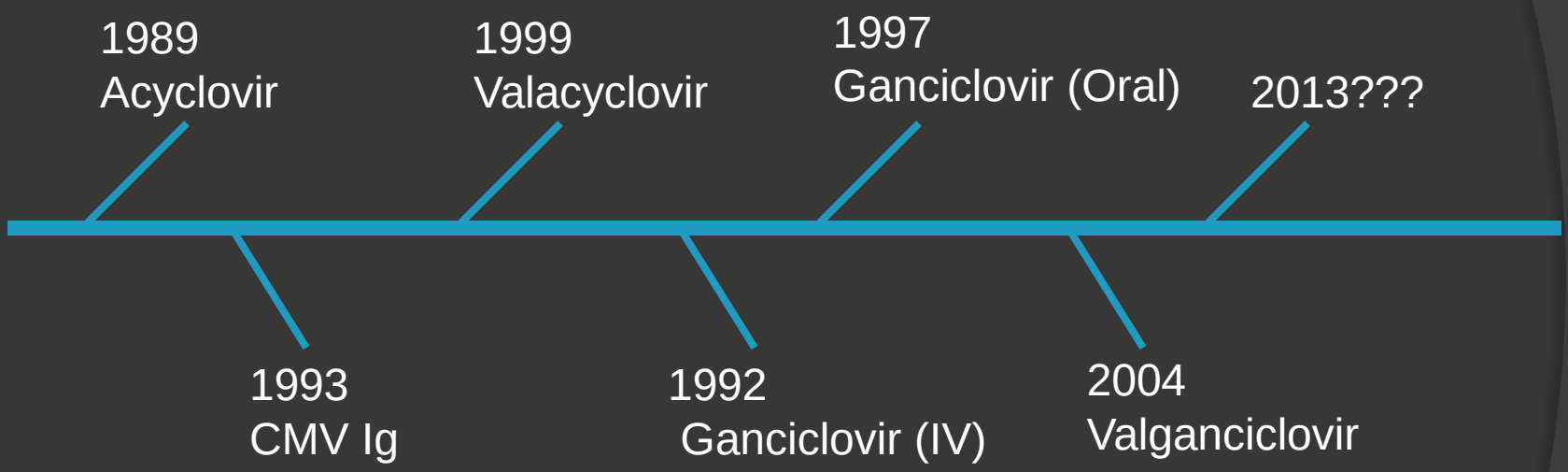
CMV Resistance in D+R- Kidney Recipients Receiving Preemptive Therapy

Couzi, et al. Am J Transplant 2012; 12:202-9

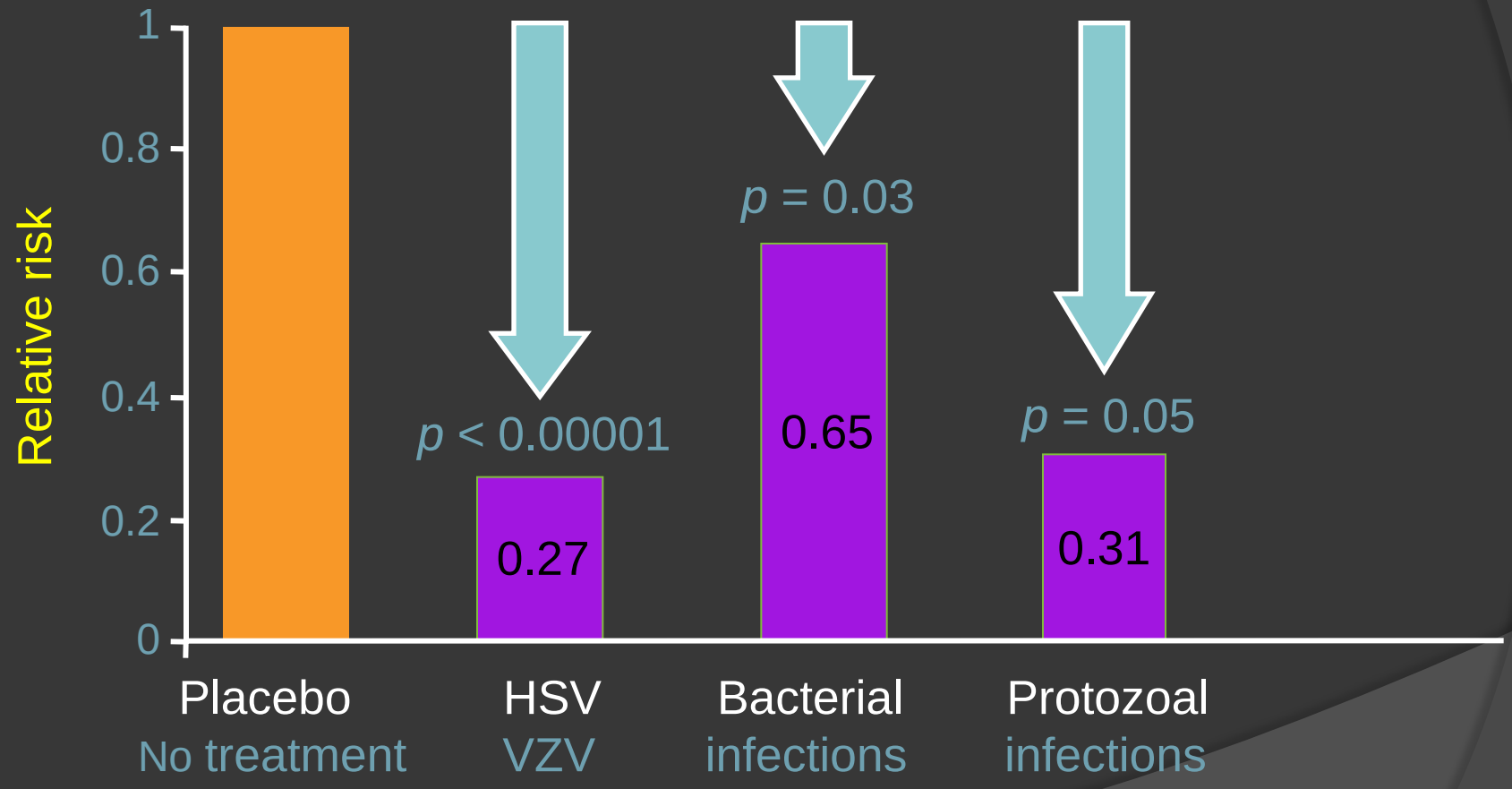
Table 2: Direct effects of CMV and anti-CMV treatment

	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
Anti-CMV drug resistance (%)	1 (3)	13 (16)	0.05

History of Prophylaxis

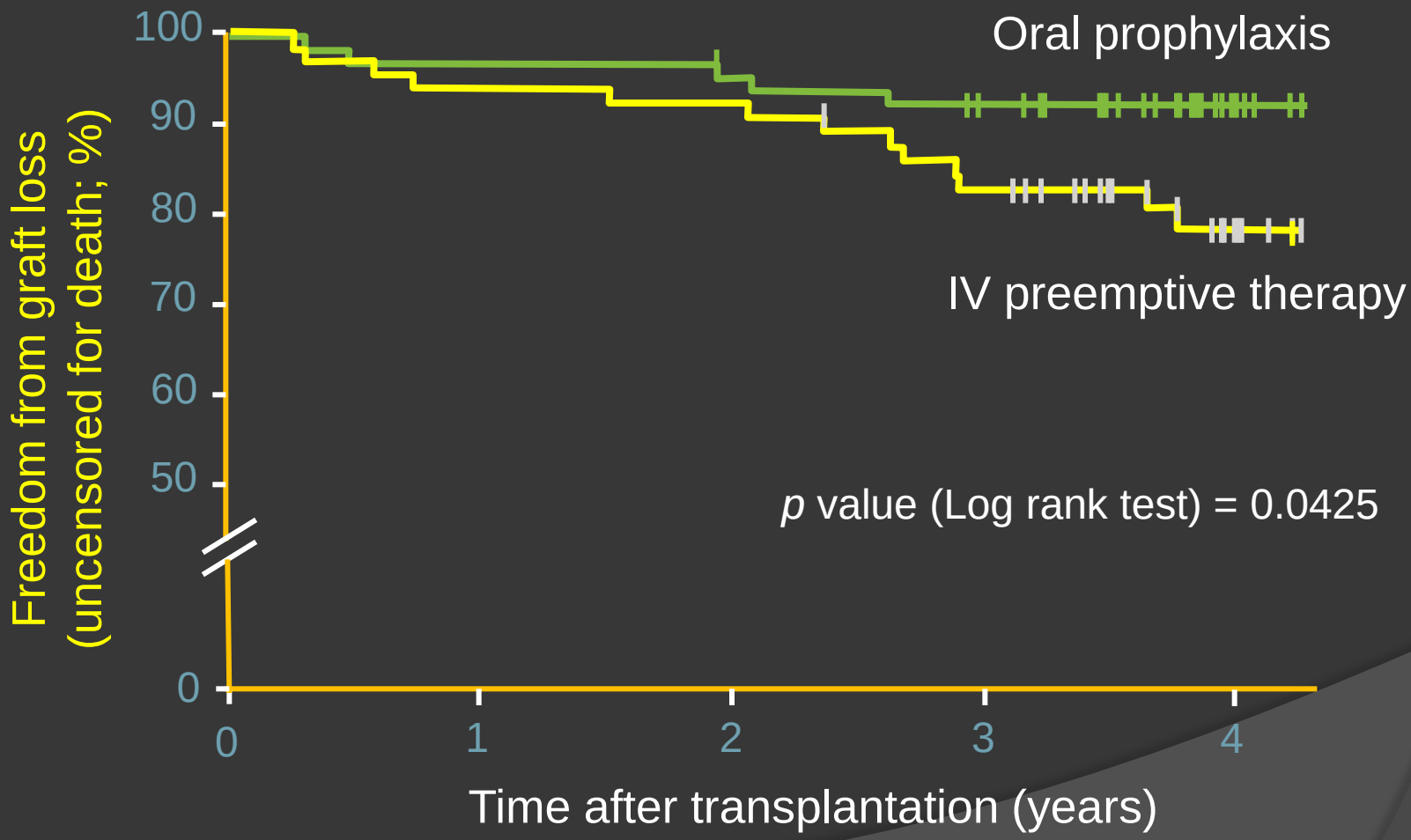


Effects of Anti-CMV Prophylaxis on Concomitant Infections



Hodson et al. *Cochrane Database Syst Rev* 2008: Issue 2. Art. No: CD003774.

Prophylaxis is Effective Against Indirect Effects



Kliem V et al. *Am J Transplant* 2008; 8:975-83.

Questions Regarding Prophylaxis

- Valacyclovir vs Valganciclovir
- Valganciclovir prophylaxis
  - Risk group specific prophylaxis
  - Organ specific issues
    - Liver transplantation and valganciclovir
- How long should we give this?
- What dose of valganciclovir should we use?

Table 2. Clinical outcome at 1 year after transplantation in D+/R− renal transplant patients with low-dose VACV (3 g/day) prophylaxis for a median of 90 days after transplantation ($n = 102$, 97 patients with a functioning graft).

	Uppsala	CTS	p-value
Graft function (creatinine in μmol/mL)			
<130	47 (48%)	1047 (52%)	NS
130–260	45 (46%)	873 (44%)	
260–400	4 (4%)	68 (3%)	
>400	1 (1%)	17 (1%)	
Mean (±SD)	153.8 ± 65.4	ND	
Median (range)	131 (74–485)	ND	
Biopsy-proven acute rejection (BPAR)	23 (22%)	400 (23%)	NS
CMV disease (all categories)	26 (25%)	ND	
CMV syndrome	8 (8%)	ND	
CMV disease (tissue invasive)	2 (2%)	ND	
CMV resistance (confirmed)	1 (1%)	ND	
Time to CMV disease (days)	124 (26–191)	ND	
Treatment (total days)	21 (14–150)	ND	
Successfully treated (no recurrences)	24 (92%)	ND	
Major neurotoxic adverse effects	2 (2%)	ND	

Values are expressed as median (range) unless stated otherwise. Graft function and rejection are compared to CTS data ($n = 2005$). NS, $P > 0.05$; ND, no data.

Valcyclovir 73% GCV/VGCV)

Sund, et al. Nephrol Dial Transplant 2013;28:758

Summary of CMV disease up to 12 months (EC, ITT population): Valganciclovir vs Oral Ganciclovir

Paya, et al, Am J Transplant 2004

	Valganciclovir (n=239)	Ganciclovir (n=125)	Total (n=364)
All Organs	17.2% (41 pts)	18.4% (33 pts)	17.6% (64 pts)
Heart	11.4% (4)	19.0% (4)	14.3% (8)
Liver	20.3% (24)	13.6% (8)	18.1% (32)
Kidney	16% (13)	25.6% (10)	19.2% (23)
Kidney Pancreas	0	16.7% (1)	9.1% (1)

CMV Risk: Organ and Donor/Recipient Status

Emery, et al. J Clinical Virology 2012;54:125-9

Table 3
Incidence of CMV disease (including syndrome) in different organ transplant recipients according to their donor and recipient serostatus for CMV for patients with 2 year follow-up data, who lost their graft or died during the 2 year period.

	D+R−		D+R+		D−R+		D−R−		Unknown	
Transplant group	*N*	CMV disease (%)	*N*	CMV disease (%)	*N*	CMV disease (%)	*N*	CMV disease (%)	*N*	CMV disease (%)
Renal	143	21.5	203	12.8	144	4.9	178	0.6	56	3.6
Liver	73	20.5	141	5.7	142	2.8	104	0.0	19	0.0
SPK	12	25.0	1	0.0	11	0.0	18	0.0	3	33.3
Heart	33	6.1	16	0.0	22	18.2	31	0.0	0	0.0
Lung(s)	17	29.4	18	22.2	26	19.2	19	0.0	6	0.0
Totals	278	20.5	379	8.1	345	9.0	350	0.1	84	7.4

Key: SPK = simultaneous pancreas and kidney and (includes 1 pancreas only transplant).

- Patients received valganciclovir prophylaxis (varying doses) vs preemptive approach based on organ, risk category, center
  - D+R- typically received high dose valganciclovir for 90 days

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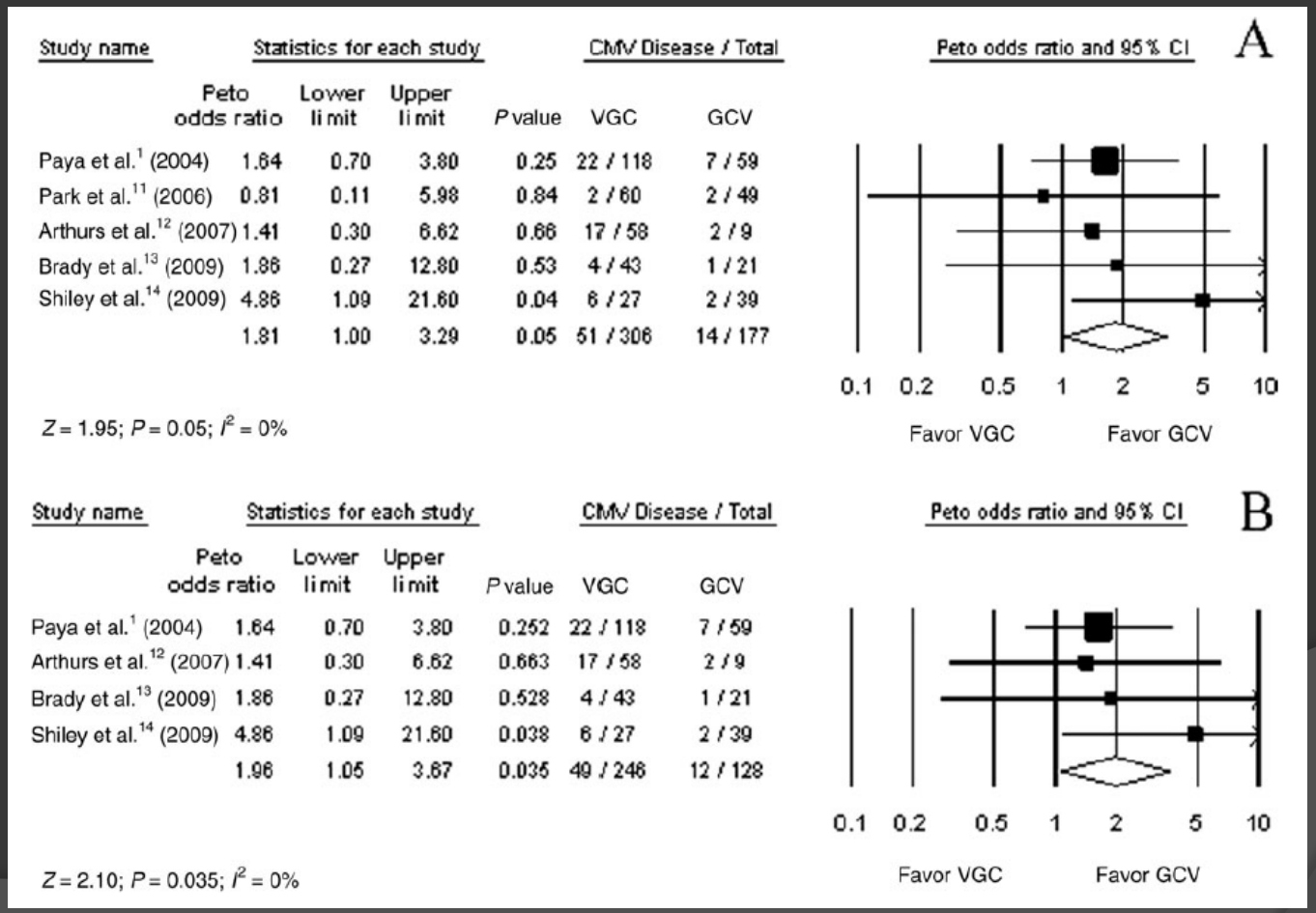
Valganciclovir Prophylaxis in Liver Transplantation – A Metaanalysis

Kalil, et al. Liver Transplantation 2012;18:1440-47



A

Study name	Peto odds ratio	Lower limit	Upper limit	*P* value	CMV Disease / Total VGC	GCV
Paya et al.[1] (2004)	1.64	0.70	3.80	0.25	22 / 118	7 / 59
Park et al.[11] (2006)	0.81	0.11	5.98	0.84	2 / 60	2 / 49
Arthurs et al.[12] (2007)	1.41	0.30	6.62	0.66	17 / 58	2 / 9
Brady et al.[13] (2009)	1.86	0.27	12.80	0.53	4 / 43	1 / 21
Shiley et al.[14] (2009)	4.86	1.09	21.60	0.04	6 / 27	2 / 39
	1.81	1.00	3.29	0.05	51 / 306	14 / 177

$Z = 1.95$; $P = 0.05$; $I^2 = 0\%$

B

Study name	Peto odds ratio	Lower limit	Upper limit	*P* value	CMV Disease / Total VGC	GCV
Paya et al.[1] (2004)	1.64	0.70	3.80	0.252	22 / 118	7 / 59
Arthurs et al.[12] (2007)	1.41	0.30	6.62	0.663	17 / 58	2 / 9
Brady et al.[13] (2009)	1.86	0.27	12.80	0.528	4 / 43	1 / 21
Shiley et al.[14] (2009)	4.86	1.09	21.60	0.038	6 / 27	2 / 39
	1.96	1.05	3.67	0.035	49 / 246	12 / 128

$Z = 2.10$; $P = 0.035$; $I^2 = 0\%$

Valganciclovir Prophylaxis in Liver Transplantation

- Possible reasons for suboptimal performance
  - Insufficient esterases preventing early conversion of valganciclovir to ganciclovir due to
  - Hepatic dysfunction
  - Bowel dysfunction
  - Competition with mycophenolate
  - Malabsorption due to diarrhea, bowel dysfunction
  - Inadequate dosing due to volume of distribution issues related to obesity, ascites
  - Reduced or missed doses due to adverse effects including cytopenias
- Nevertheless, in the absence of oral ganciclovir, most centers use valganciclovir prophylaxis

CMV in D+R- Kidney Recipients Receiving Valganciclovir

Humar, et al Am J Transplant 2010;10:1-10; Humar, et al. Transplantation;2010;90:427-31

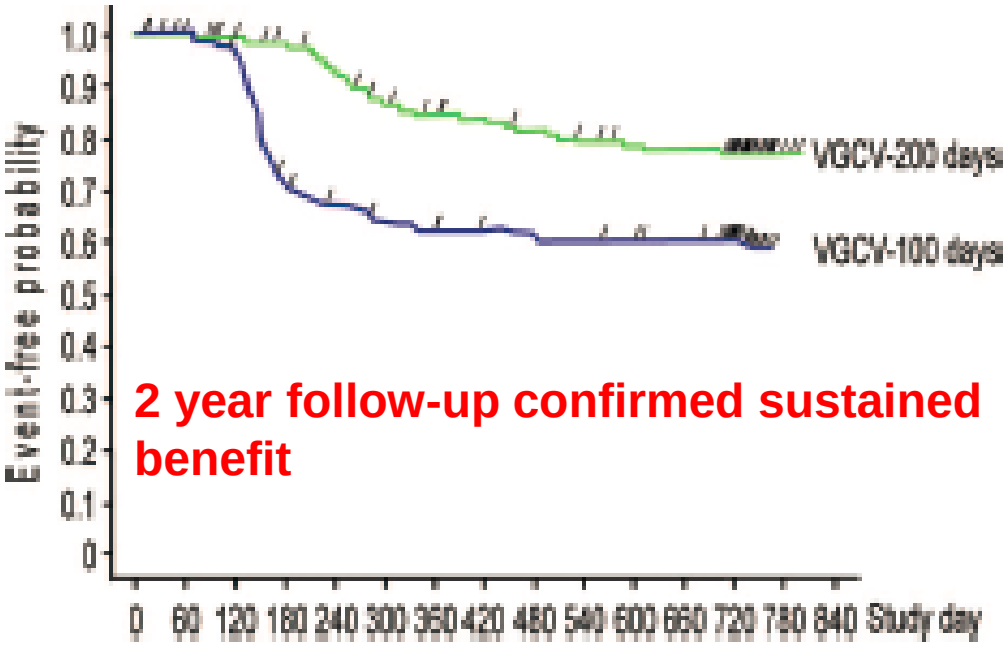
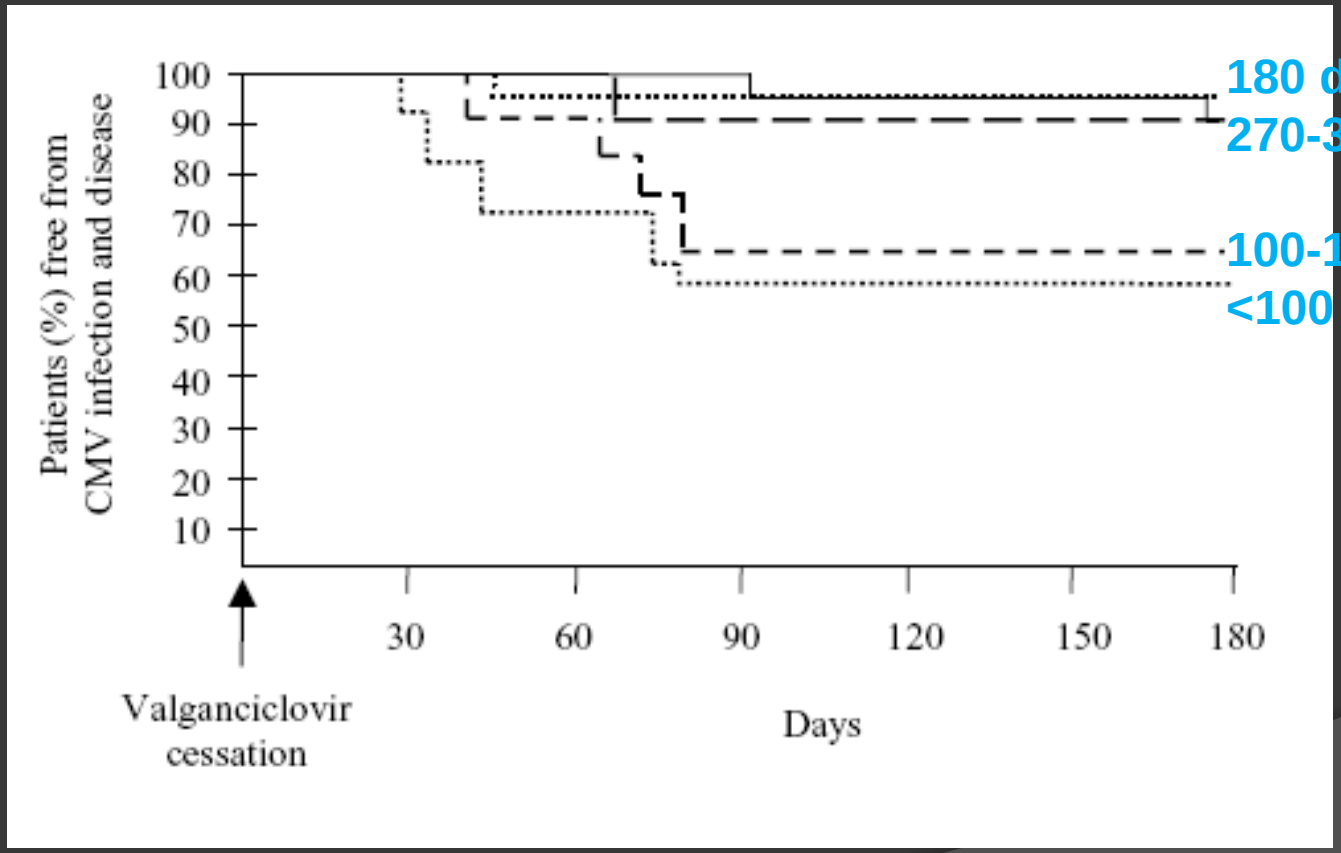


FIGURE 1. Time to cytomegalovirus disease up to 2-year posttransplant. VGCV, valganciclovir.

Trend towards decreased allograft loss in the 200 day arm

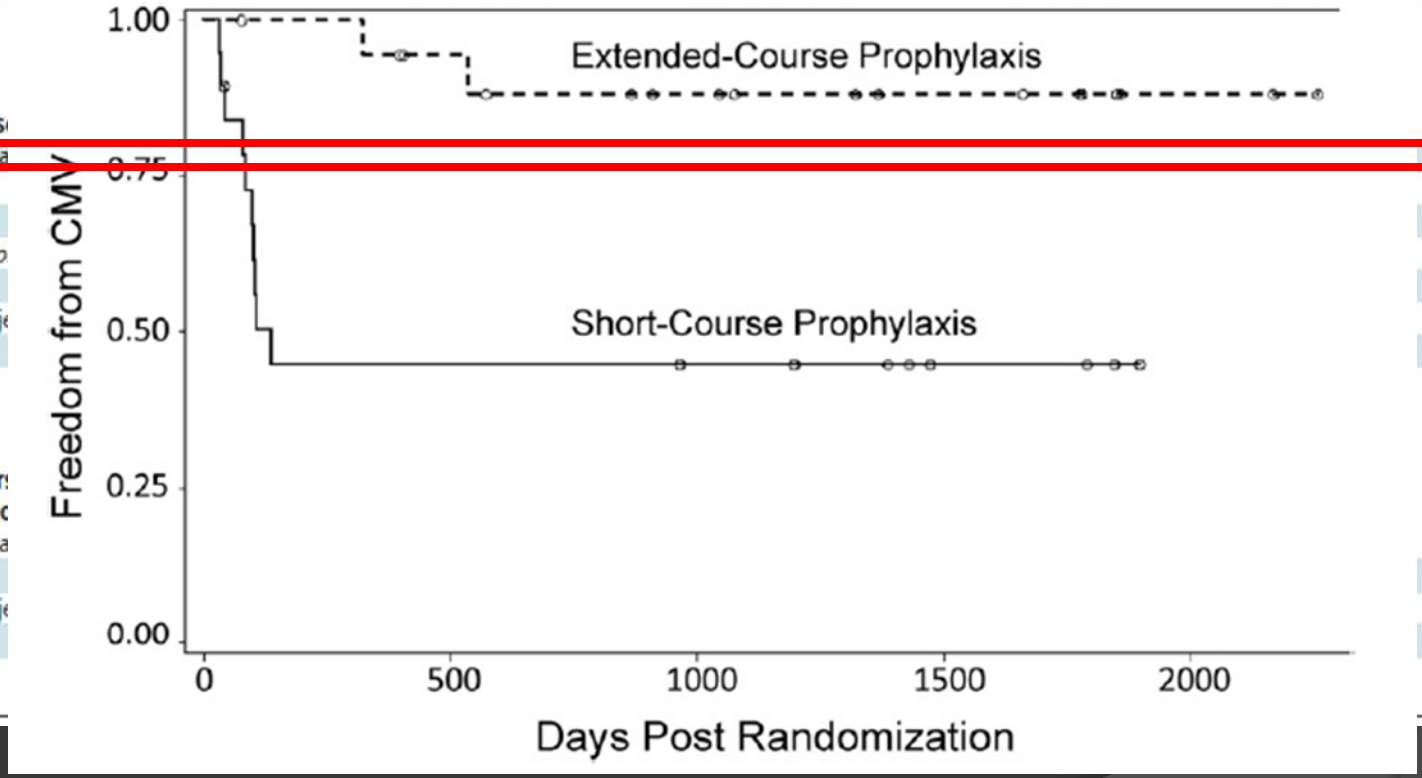
Impact of Duration of Valganciclovir Prophylaxis on CMV in Lung Transplantation Zamora, et al. Am J Transplant 2004;4:1635-42



Prolonged Valganciclovir Prophylaxis and Lung Transplantation

Table 2. Clinical Outcomes, by Treatment Group

Variable		P Value†
Rates for primary and s		
CMV syndrome or disea		<0.001
Invasive disease		0.001
CMV syndrome		0.004
PCR at diagnosis, *cop*		0.009
Any CMV infection§		<0.001
Biopsy-proven acute reje		0.09
Non-CMV infection		0.74
		P Value
Effect of extended-cours for primary and sec		
CMV syndrome or disea		0.001
Any CMV infection¶		<0.001
Biopsy-proven acute reje		0.06
Non-CMV infection**		0.79
Death††		0.79



Palmer, et al. Ann Intern Med 2010; 152:761-9; Finlen-Copeland, et al. J Heart Lung Transplant 2011;30:990-6

Cost Effectiveness of 200 Days of Valganciclovir

Blumberg, et al. Transplantation 2010;90:1420-6

TABLE 1. Cost-effectiveness results—base case (US$)

	100 d	200 d	Incremental	ICER
5-yr horizon				
Cost per 10,000 patients	624,433,251	635,849,658	11,416,407	14,859
QALY per 10,000 patients	29,581	30,349	768	
10-yr horizon				
Cost per 10,000 patients	1,065,150,672	1,063,405,609	−1,745,063	−733
QALY per 10,000 patients	47,639.9	50,020.3	2380.5	

QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Downsides to prolonged prophylaxis

- Toxicity
  - Leukopenia
  - Elevated liver enzymes
  - Central nervous system effects
- Cost

Dosing of Valganciclovir

- Pharmacokinetic studies suggest equivalence of low dose (450 mg daily) to oral ganciclovir 1 gm 3 times daily
- Clinical trials do not support low dose in the highest risk populations (D+R-)
  - May consider in lower risk populations
- Dose adjustments for renal function NOT for toxicity

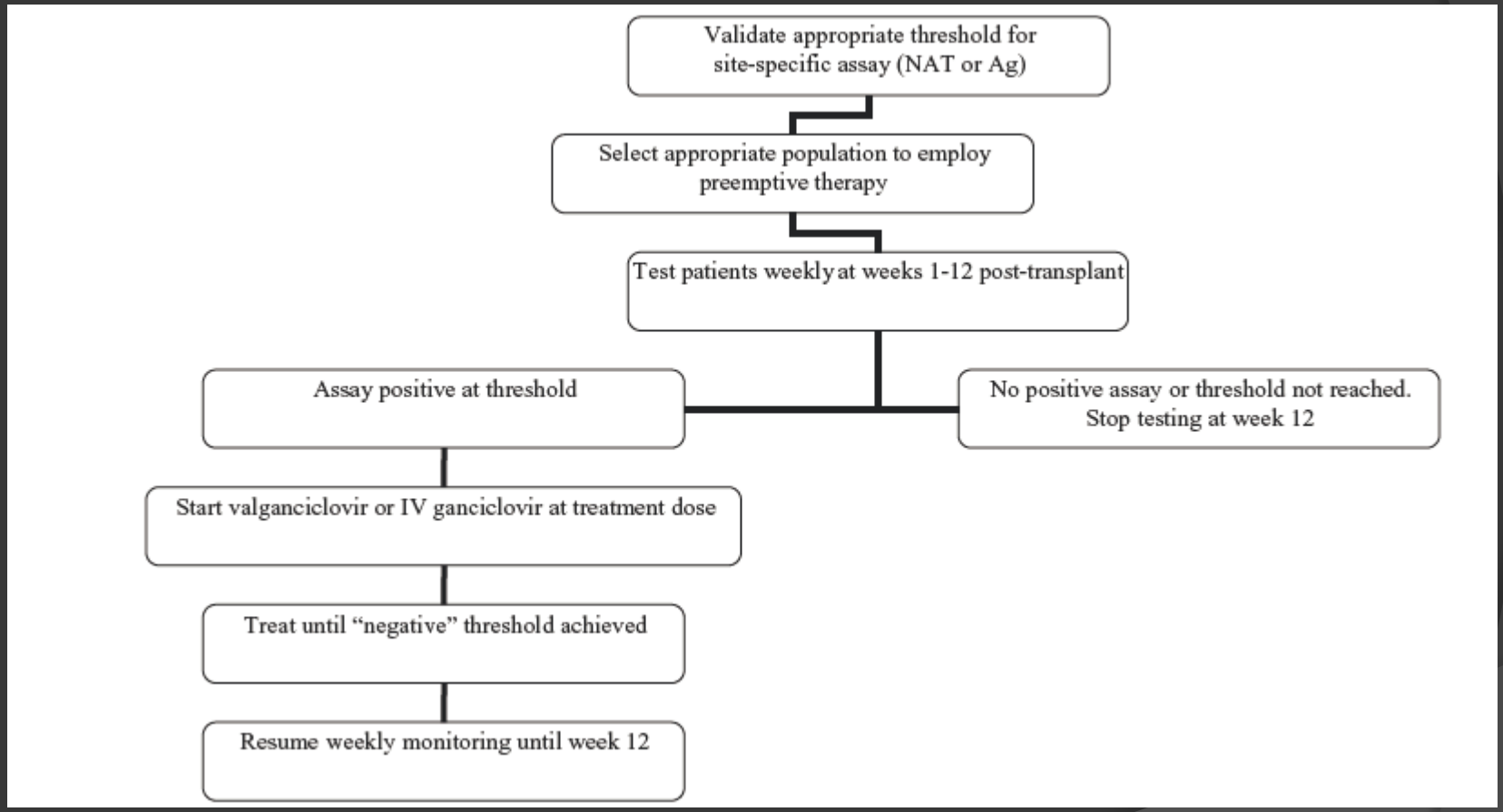
Current Recommendations

Kotton et al. Transplantation 2013;96:333-60; Razonable, et al. Am J Transplant 2013;13:S93-106

- Prophylaxis Recommended
  - D+R- all organs
  - R+ lung, heart-lung, intestine, vascular tissue composite allograft
- VGCV, GCV, VACYC (kidney only)
- Duration
  - 6 mos D+R- Kidney
  - 12 mos D+R- Lung
    - 6-12 mos R+ Lung
  - 3-6 mos all other D+R-, R+ intestine, composite
  - 3 mos all other R+
- Preemption Acceptable
  - D+R- Kidney, Liver
  - R+ Kidney, Liver, Heart, Pancreas

Strategy for Preemptive Therapy

Razonable, et al. Am J Transplantation 2013;13:S93-106



Despite prophylaxis, late CMV can still occur, especially in D+R-

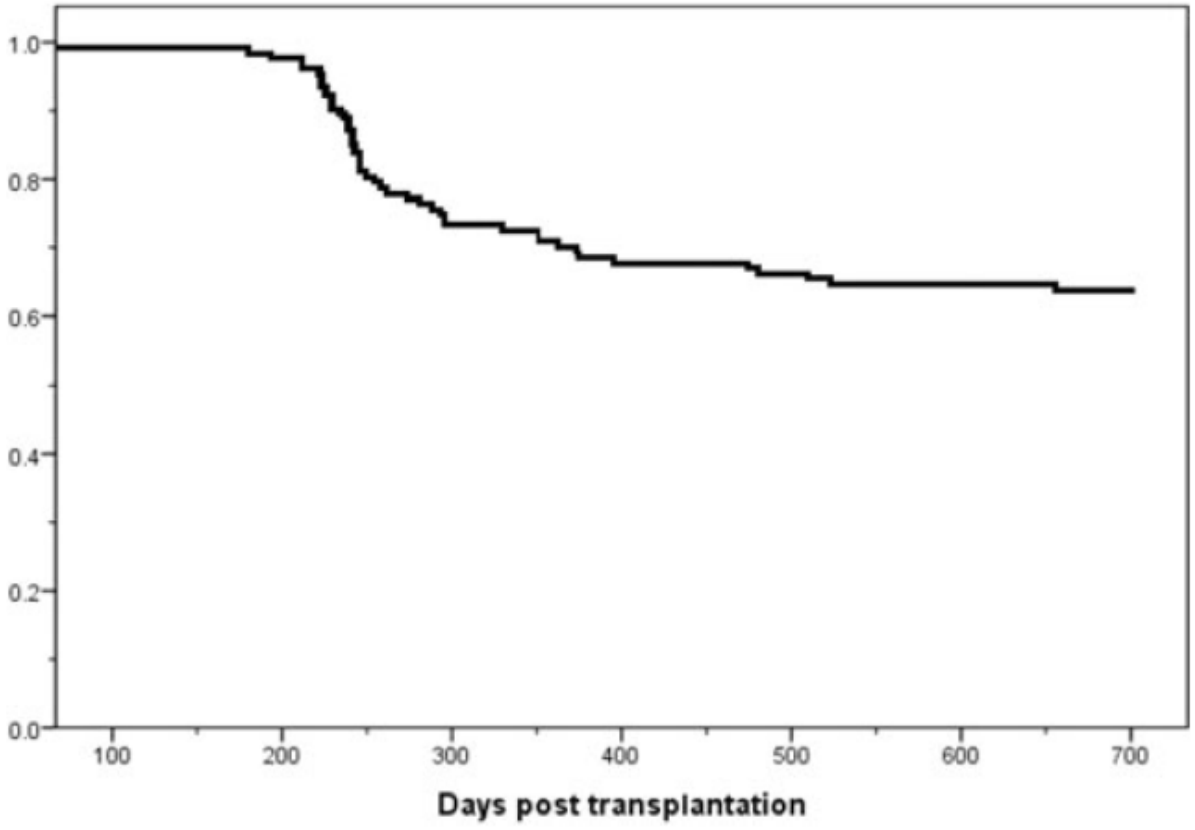


Figure 1: Description of the occurrence of late-onset primary CMV infections after 6 months of valganciclovir prophylaxis.

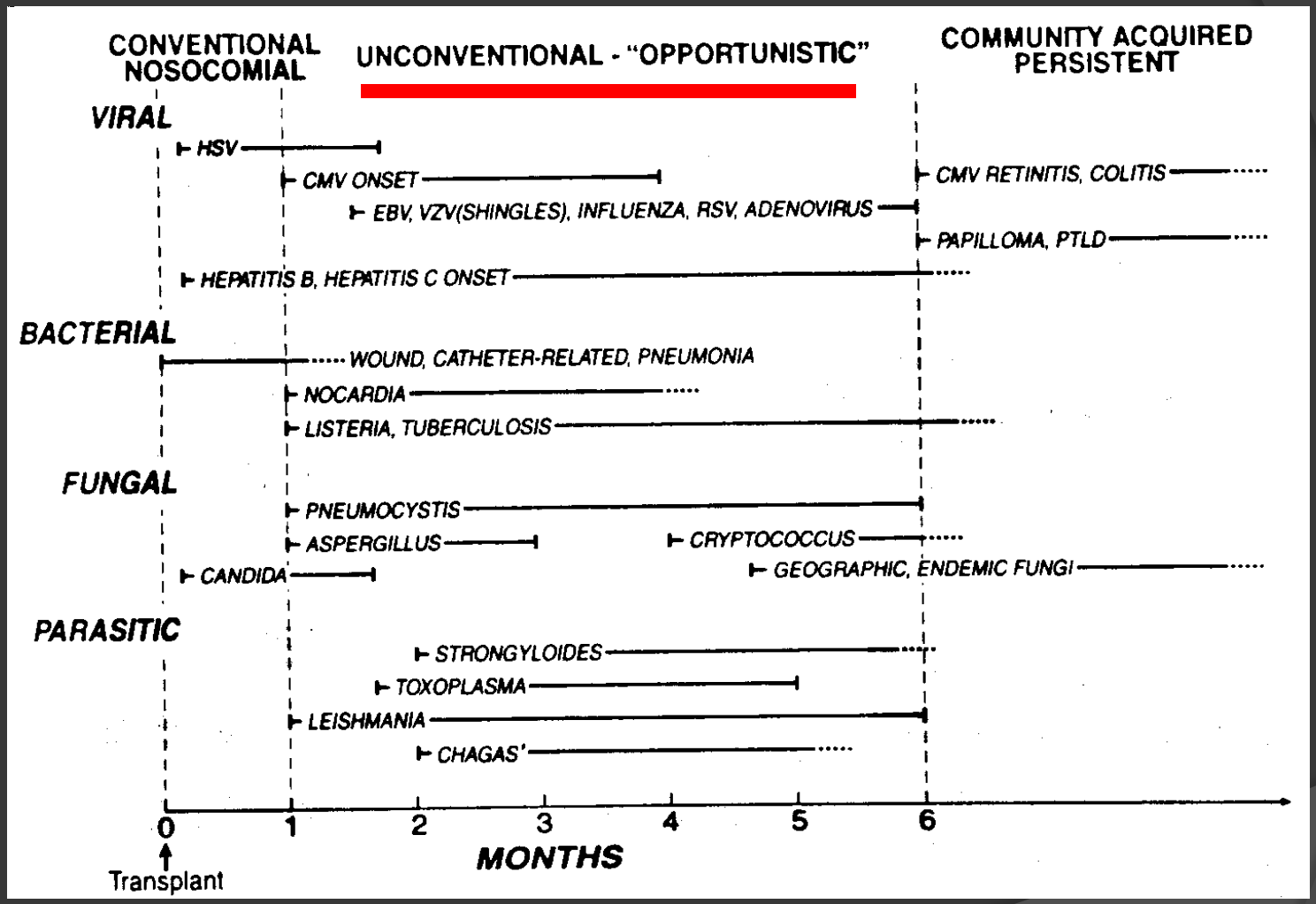
Recurrence rates 19%

Diagnosing CMV

- Recognition of clinical syndrome
  - Risk Group
  - Timing
- ~~Serologic Diagnosis~~
  - Useful for pre-transplant assessment of risk only
- Detection of viremia
  - Antigenemia
  - PCR
- ~~Viral culture~~
- Histopathology

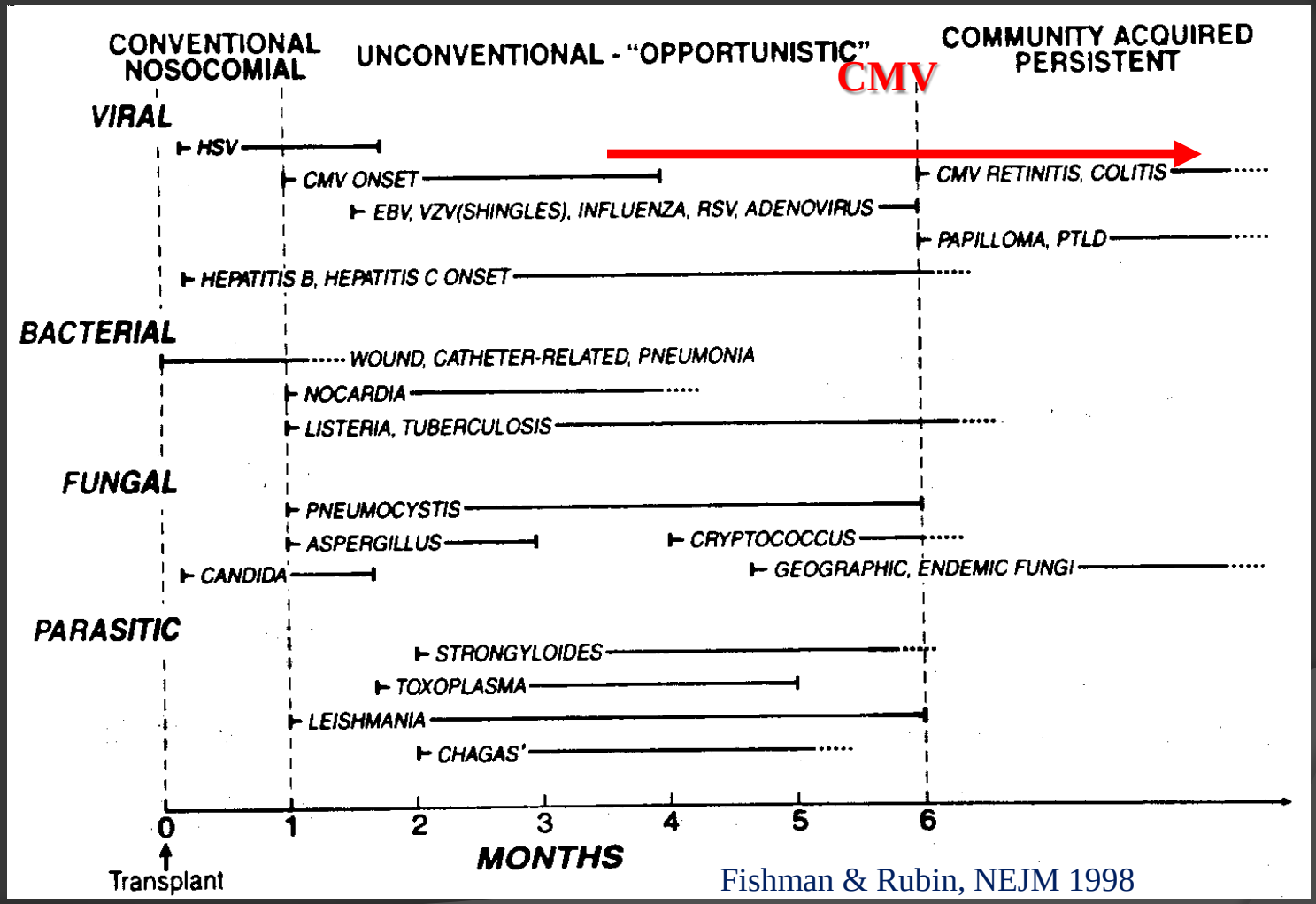
Risk Factors for CMV Following Transplantation

- CMV + Donor
  - Increased if CMV – Recipient
- Immunosuppressive regimen
  - Increased with Cytolytic therapies, Alemtuzumab
  - Decreased with IL 2 receptor antagonists
- Rejection
- Type of transplant
  - Especially heart lung and lung
- Co-infection with other viruses
- Hypogammaglobulinemia
- Absence of CMV antibody at 6 mos post transplant
- MHC mismatch
- Genetic polymorphisms (e.g.TLR 2, programmed death-1 receptor, etc)



Fishman & Rubin, NEJM 1998

Late CMV – CMV that occurs after 6 mos (after prophylaxis stops)



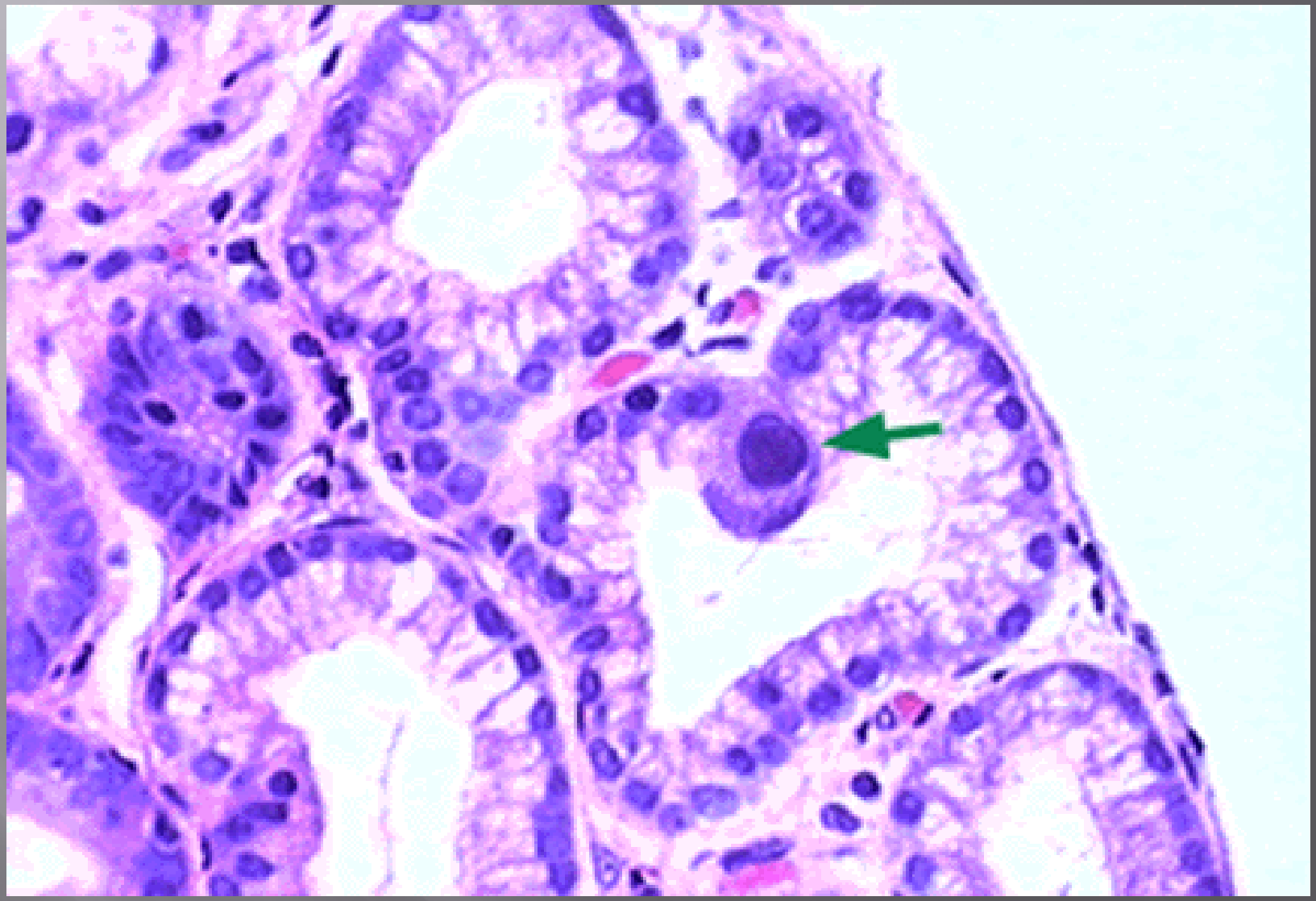
Fishman & Rubin, NEJM 1998

CMV Antigenemia

- Semiquantitative test
  - Higher numbers of infected cells correlate with disease
- Uses
  - Diagnosis
  - Monitoring response to treatment
  - Preemptive therapy
- Drawbacks
  - Lack of standardization
  - Difficulty interpreting if neutrophil count<1000
  - False negatives can occur with tissue invasive disease

PCR Assay for CMV

- Active versus latent virus
  - Similar results to antigenemia assay
    - Replacing antigenemia as increased access to technology
  - Qualitative vs quantitative test
  - Useful for diagnosis, monitoring, preemption
- Issues
  - Does not differentiate infection from disease (especially with BAL specimens, low viral loads)
  - May be negative with tissue invasive disease, especially intestinal
  - Laboratory variability in absence of international standard (just implemented)
    - Need to use same type of sample consistently (whole blood vs plasma)
  - Viral kinetics important to consider
  - High sensitivity leads to persistent low level positive results

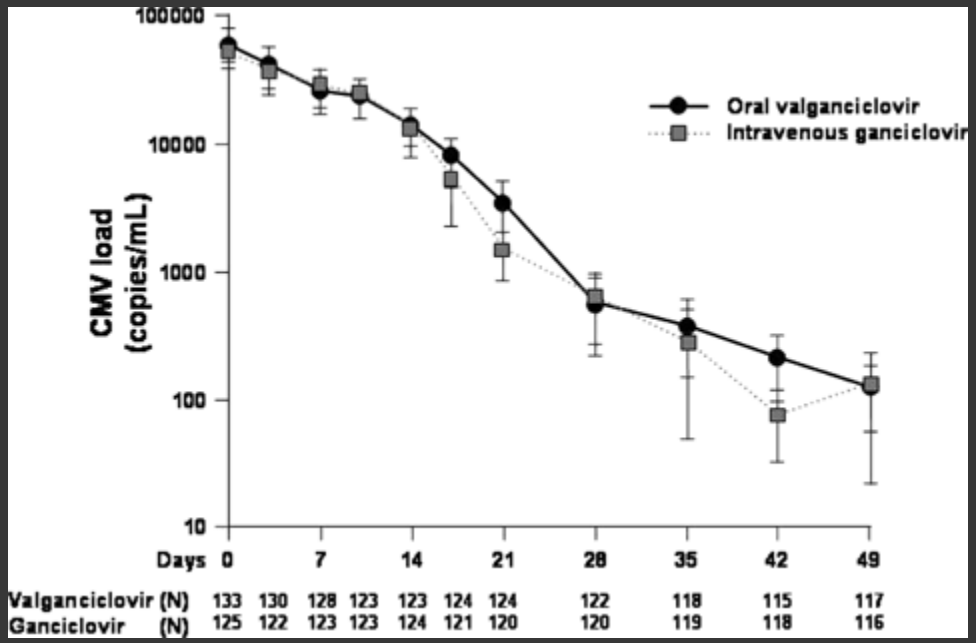


Treatment of CMV

- Reduction of immunosuppression
  - Which agent? – usually mycophenolate
  - To what degree?
  - How long?
- Treatment duration – minimum 3 weeks but….
  - Full resolution of all symptoms
  - Absence of viral shedding (by QNAT) (monitor weekly)
- Choice of agent
  - Intravenous ganciclovir
  - Valganciclovir
  - Foscarnet, cidofovir for resistant virus
  - Newer agents in development
  - Consider immunoglobulin preparations for refractory or resistant infection +/- hypogammaglobulinemia (NO data)

Treatment of CMV: Intravenous Ganciclovir vs Valganciclovir

Asberg, et al. American J of Transplantation 2007



VICTOR Study: Downsides

- Standard treatment plan did not allow for maintenance of treatment dose for patients with prolonged viremia
  - 21 days high dose followed by once daily VGC to day 49
- High relapse rates
  - 15% clinical, 30% virological
- Outcomes similar in both arms
  - 8/321 resistance developed
  - 20/321 died

KDIGO recommendations

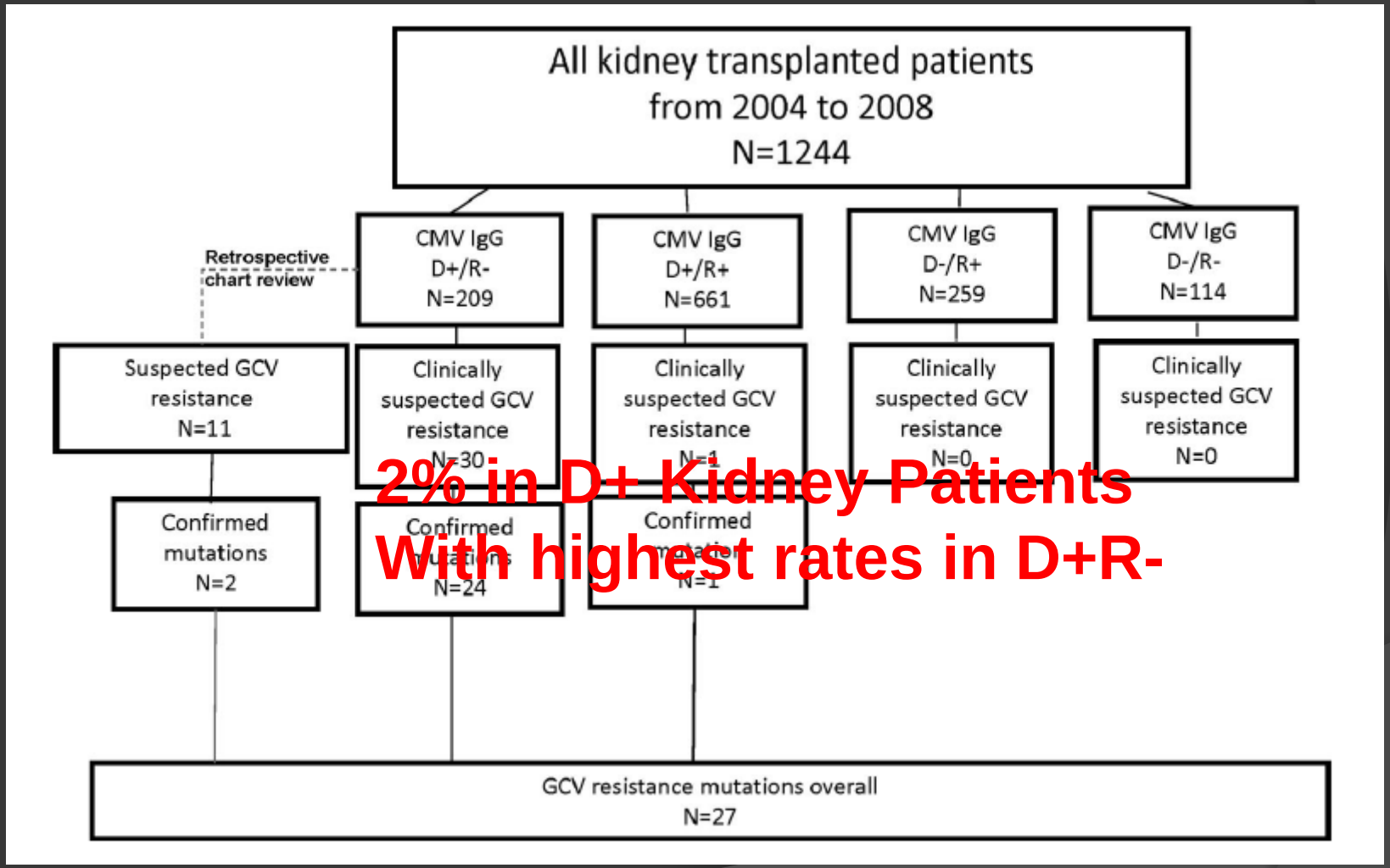
Reserve oral agent for mild to moderate disease without end organ involvement

Antiviral Resistance in CMV

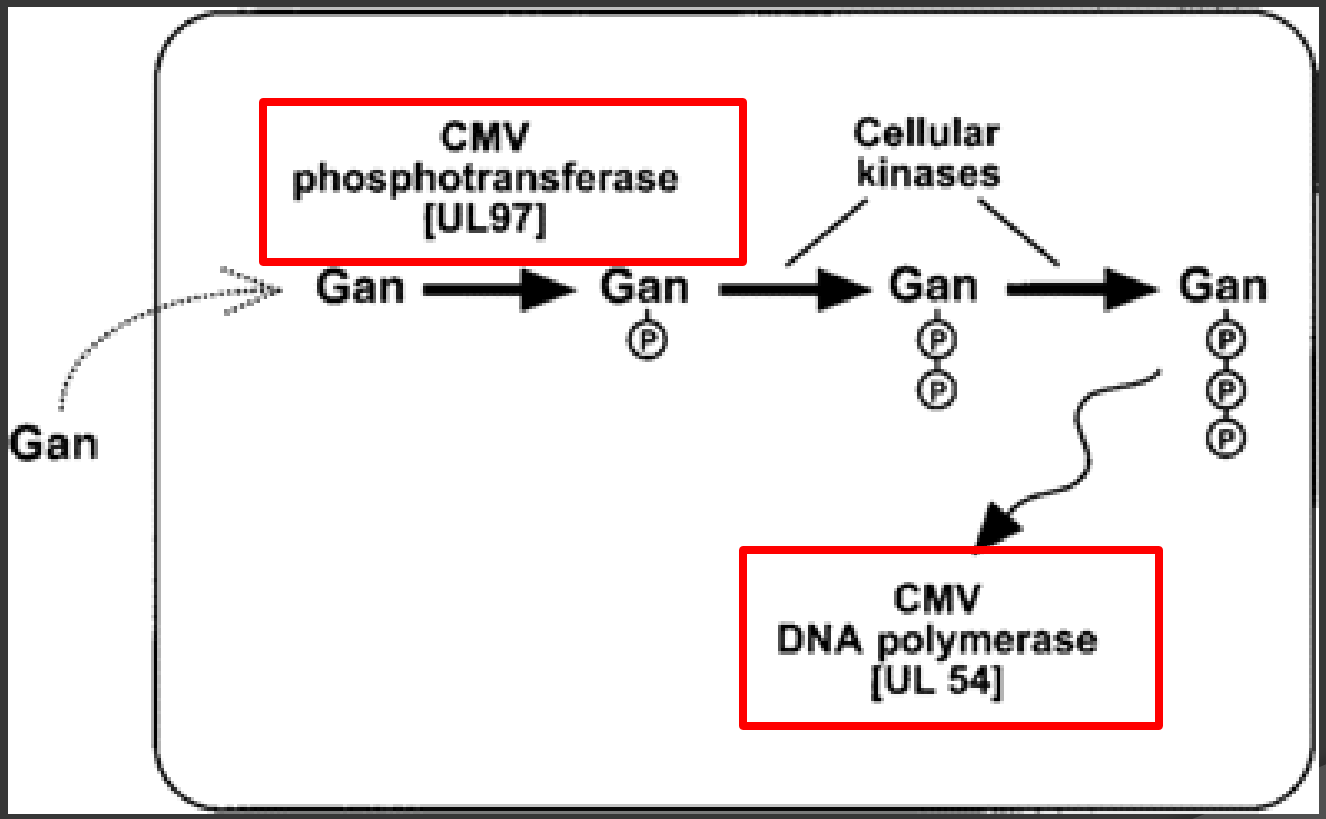
- Described in both transplantation and HIV
- In SOT major risk factors
  - CMV mismatch (D+R-)
  - Prolonged exposure to subtherapeutic ganciclovir exposure
  - Higher viral loads
  - Lung transplantation
  - Increased immunosuppression
- Correlates with worse outcomes both due to infection and toxicity of treatment

How Common Is Resistance?

Myrhe, et al. Transplantation 2011; 92:217-23

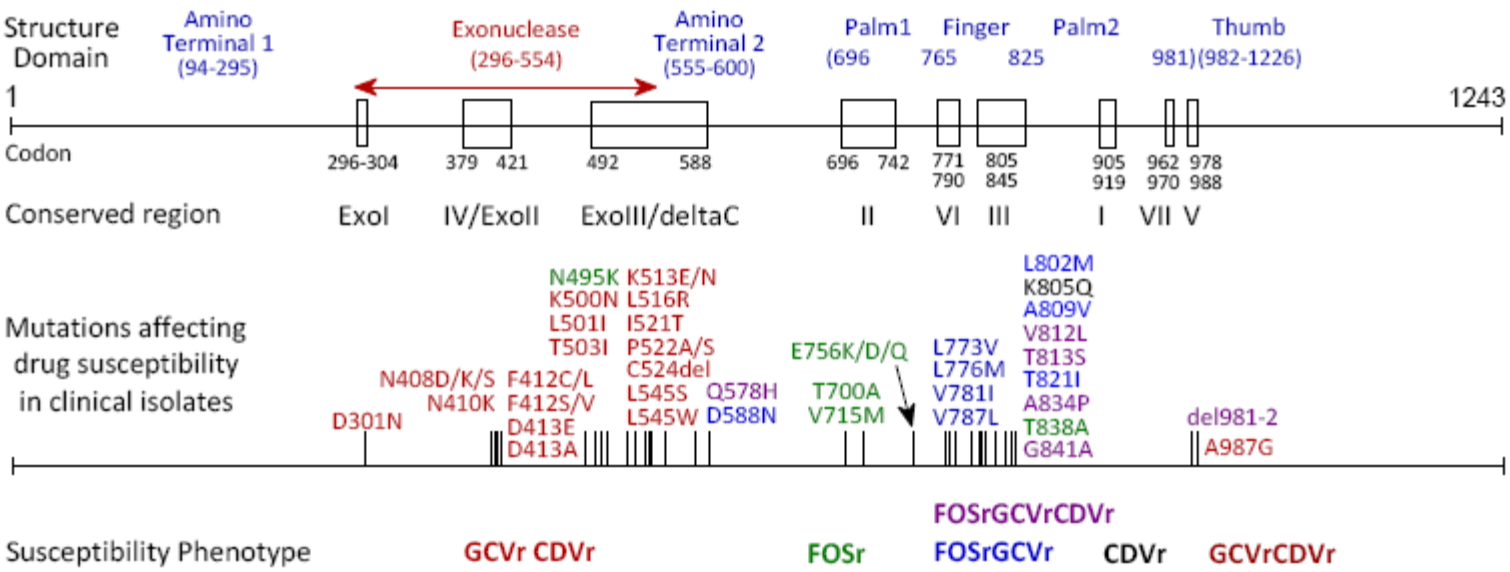


Diagnosis of Resistance: Genotypic Assay



CMV Resistance Genotypes

Kotton et al. Transplantation 2013;96:333-60



CMV Resistance Genotypes

Kotton et al. Transplantation 2013;96:333-60

Table 1. Ganciclovir resistance levels associated with UL97 genotypes

Genotype frequency	Fold change in ganciclovir EC50[a]		
	5-15x	2-5x	<2x
Most common	M460V/I, H520Q, A594V, L595S, C603W	C592G	
Less common at codons 460, 590-607	M460T, A594G, 595del[b], 596del, L595F/W, K599T, C603R, C607Y, del(≥3)[c]	A594E/T, E596G, C603S, 600del2[b], C607F	A591V, N597D, K599E/R, L600I, 600del[b], T601M, D605E[d]

(a) Moderate resistance (5-15x), low-grade resistance (2-5x), or insignificant resistance (<2x)

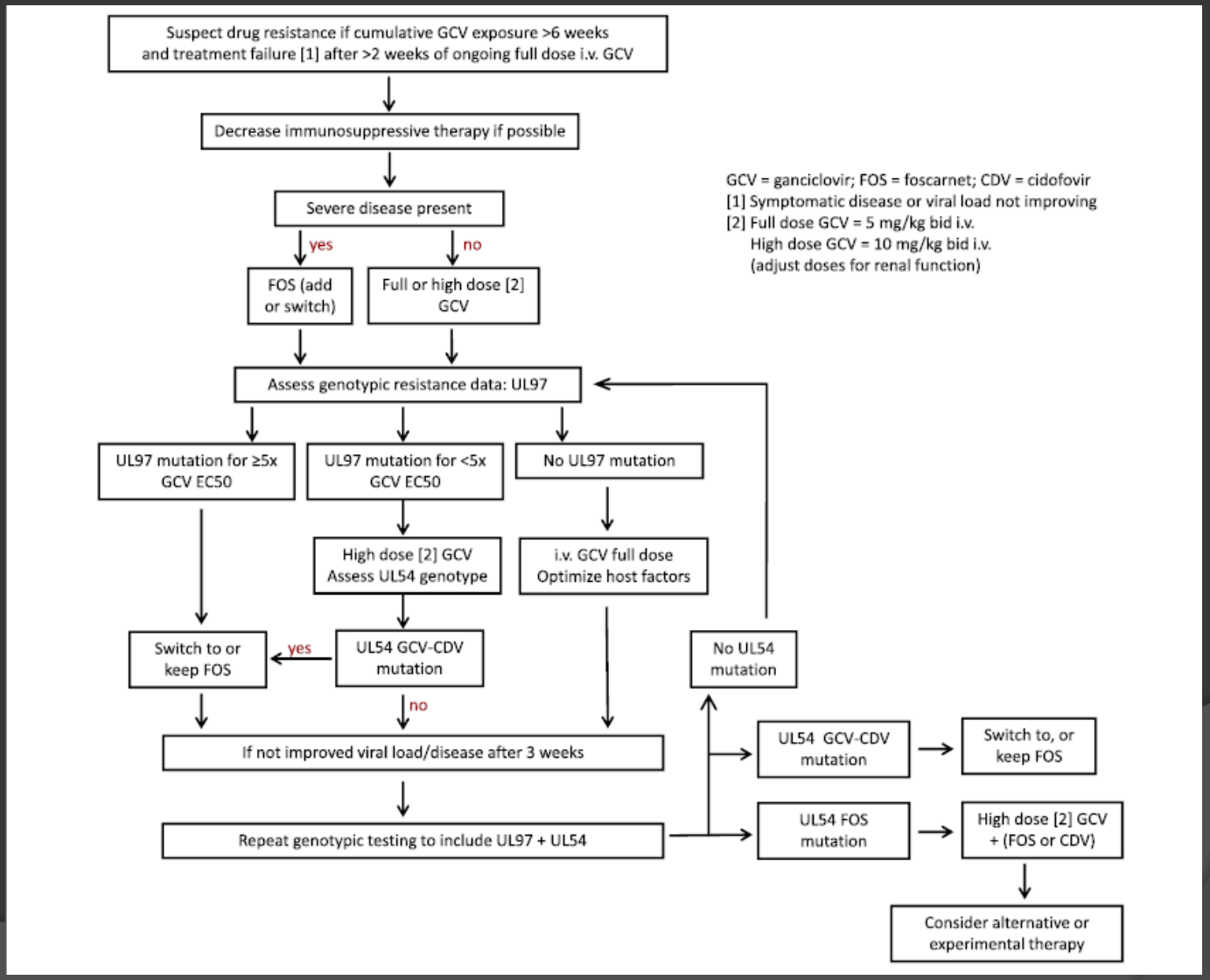
(b) del = in frame deletion of single codon; del2 = deletion of two codons

(c) In frame deletion of ≥3 codons in the 590-607 range can be assumed to confer moderate ganciclovir resistance although only a few examples have been phenotyped.
Deletion of less than 3 codons may confer varying degrees of ganciclovir resistance.

(d) D605E is a baseline sequence polymorphism common in east Asia, unrelated to drug resistance

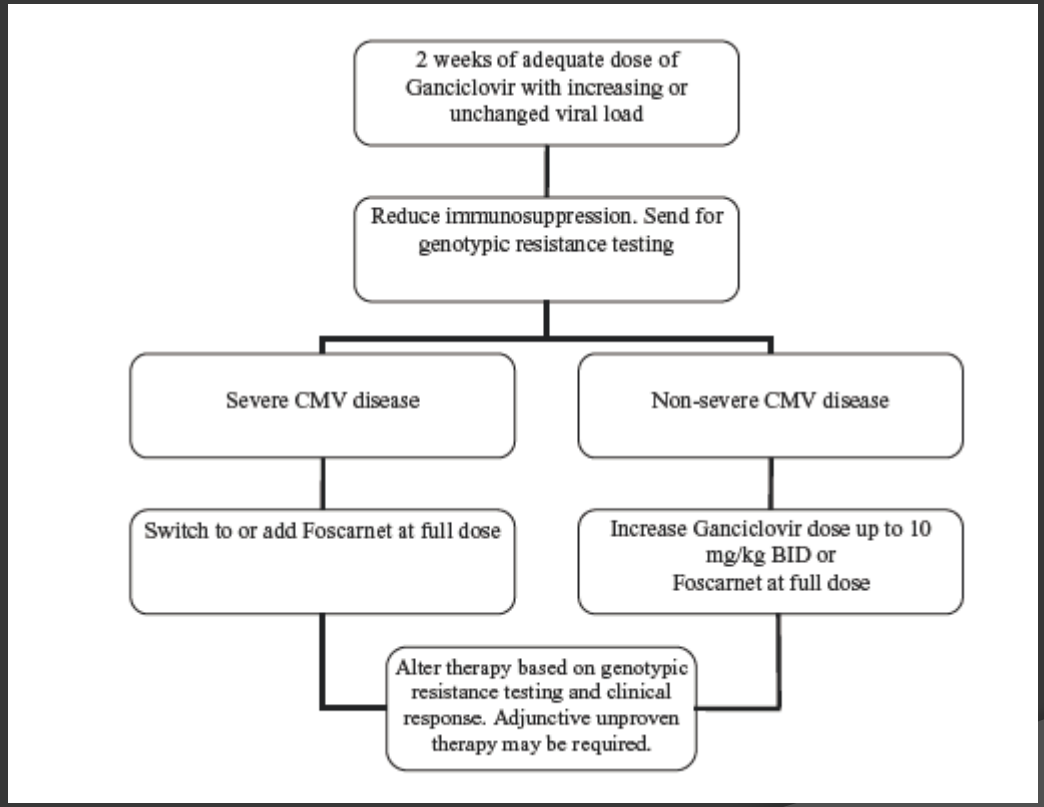
CMV Resistance Genotypes

Kotton et al. Transplantation 2013;96:333-60



Approach To Treating Ganciclovir Resistant CMV

Razonable, et al. Am J Transplant 2013:13:S93-106



The Future.....

- Will CMV ever be a minor event post transplant???????

The Near Future

- Prevention
  - Greater use of immune based assays to assess risk and need for ongoing treatment
    - Measurements of CMV specific immune responses
  - Vaccines
- Treatment options
  - New antivirals in development