CMV infection and prevention in renal transplantation

Morgyn Warner

South Australia

Cytomegalovirus

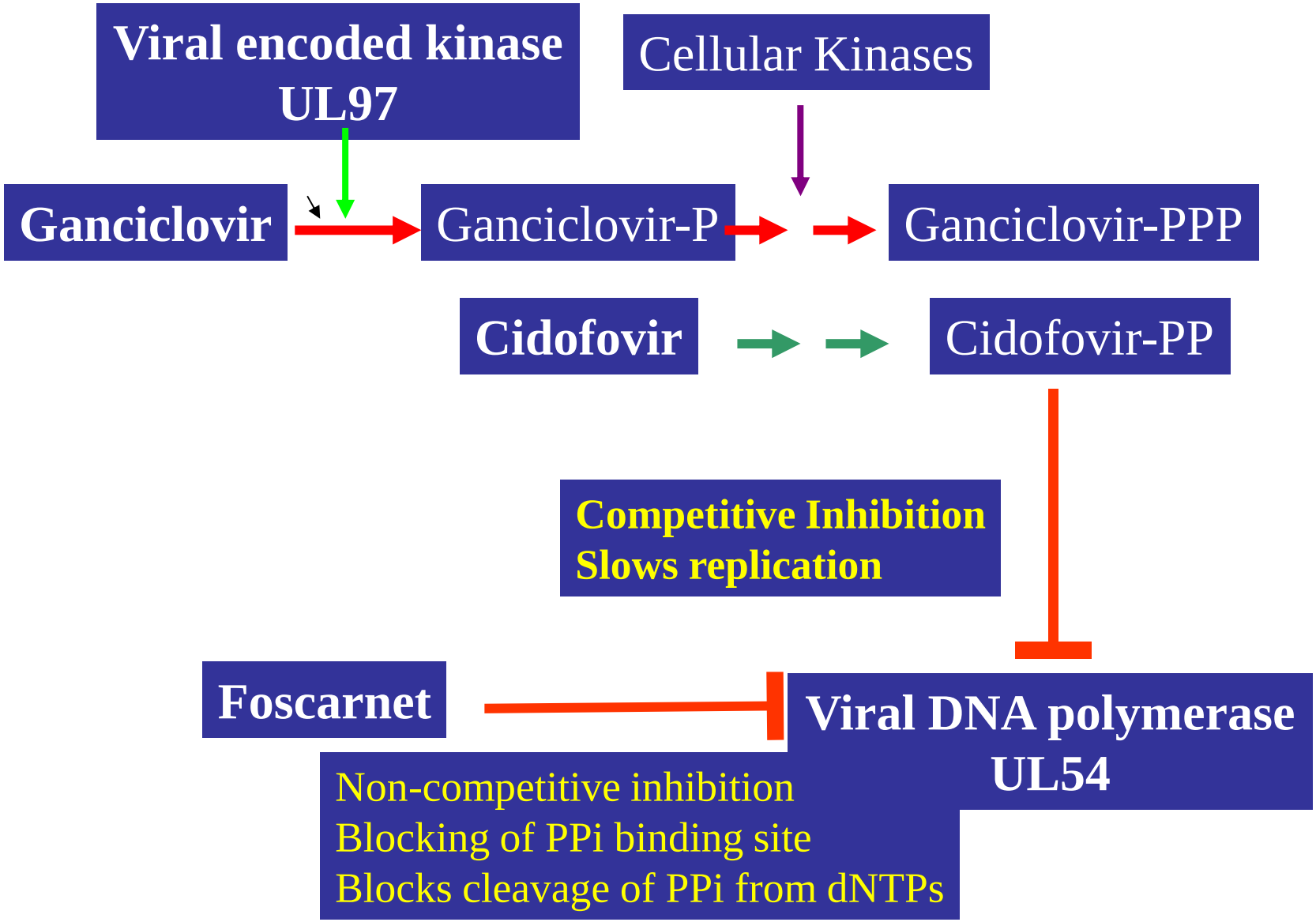
- Risk of CMV disease is dependant on
  - Donor & recipient serostatus
  - use of T-cell–depleting antibodies
  - Release of tumor necrosis factor (TNF-α)
  - Allo-response to organ (worse with more HLA mismatch)
- Disease manifestations
  - Asymptomatic CMV viremia
  - CMV syndrome
  - End organ disease
  - Indirect/immunologic effects (rejection)
  - Depends upon immune response and prophylaxis used

CMV disease in renal transplant patients

Risk factors

- Highest among:
  - CMV IgG negative recipients of (R-) of organs from CMV IgG+ donors (D+)
    - Without prophylaxis, 40%–58% of CMV D+/R kidney transplant recipients develop CMV disease, usually during the first 3 months after transplantation
  - Patients receiving lymphocyte depleting antibody therapy (thymoglobulin, ATG, OKT-3, alemtuzumab)

CMV Anti-Virals : Mechanisms



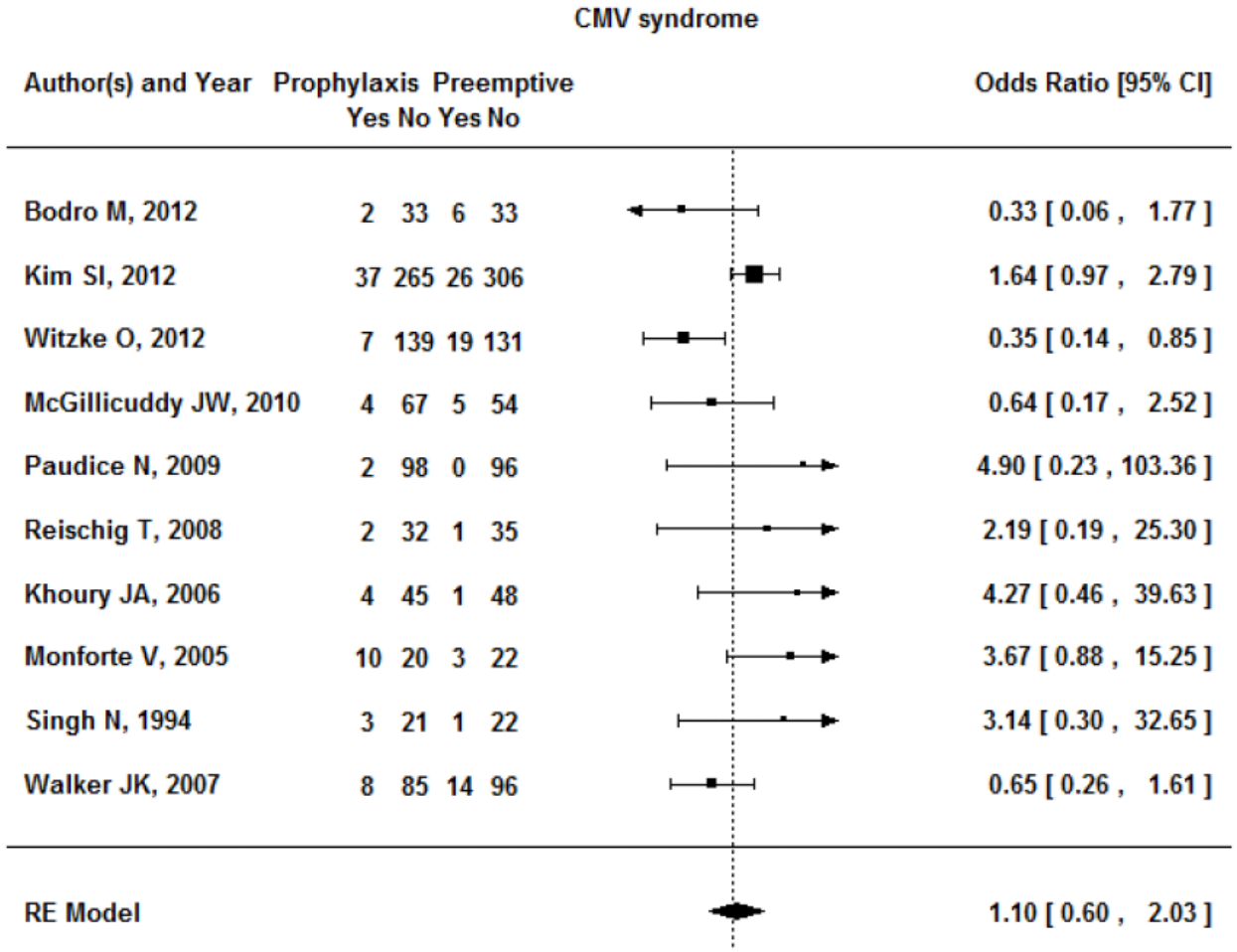
CMV: *Prevention*

- **Prophylaxis**
  - ***Positives***
    - Good efficacy (large RCTs)
    - Lower rate of CMV disease
    - Lower rejection & graft loss
    - Easy to coordinate
    - No viral load monitoring while on therapy
  - ***Negatives***
    - Drug costs
    - Drug toxicity
    - Late onset CMVin D+/R-
    - Resistance

- **Pre-Emptive**
  - ***Positives***
    - Efficacy (fewer trials, less D+/R-)
    - Low drug costs
    - Low toxicity
    - Much less late onset CMV
  - ***Negatives***
    - More CMV
    - Standard threshold for treatment not established
    - Infection may occur if no monitoring occurs
    - Difficult to coordinate
    - Resistance

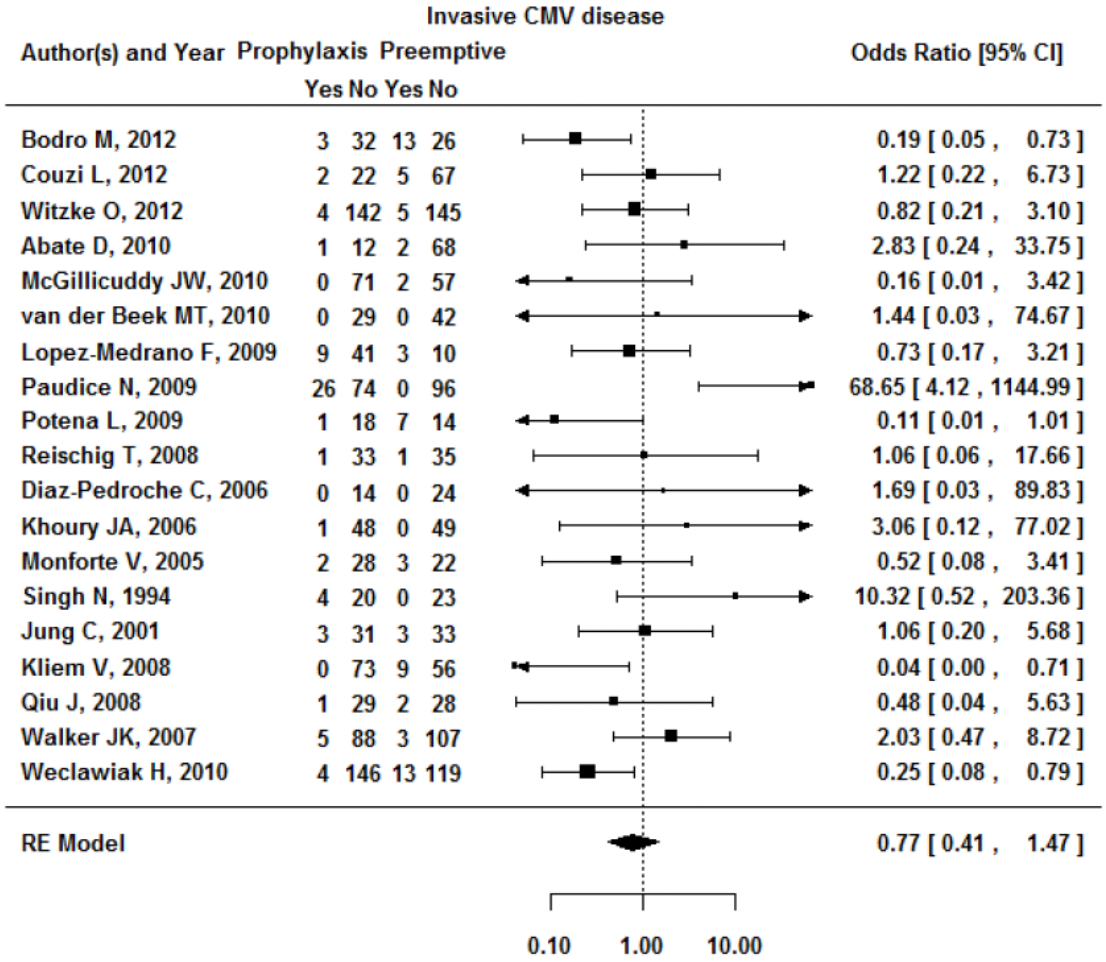
Adapted from Razonable, R et al, Am J Transplant 2013; 13:93

CMV viraemia



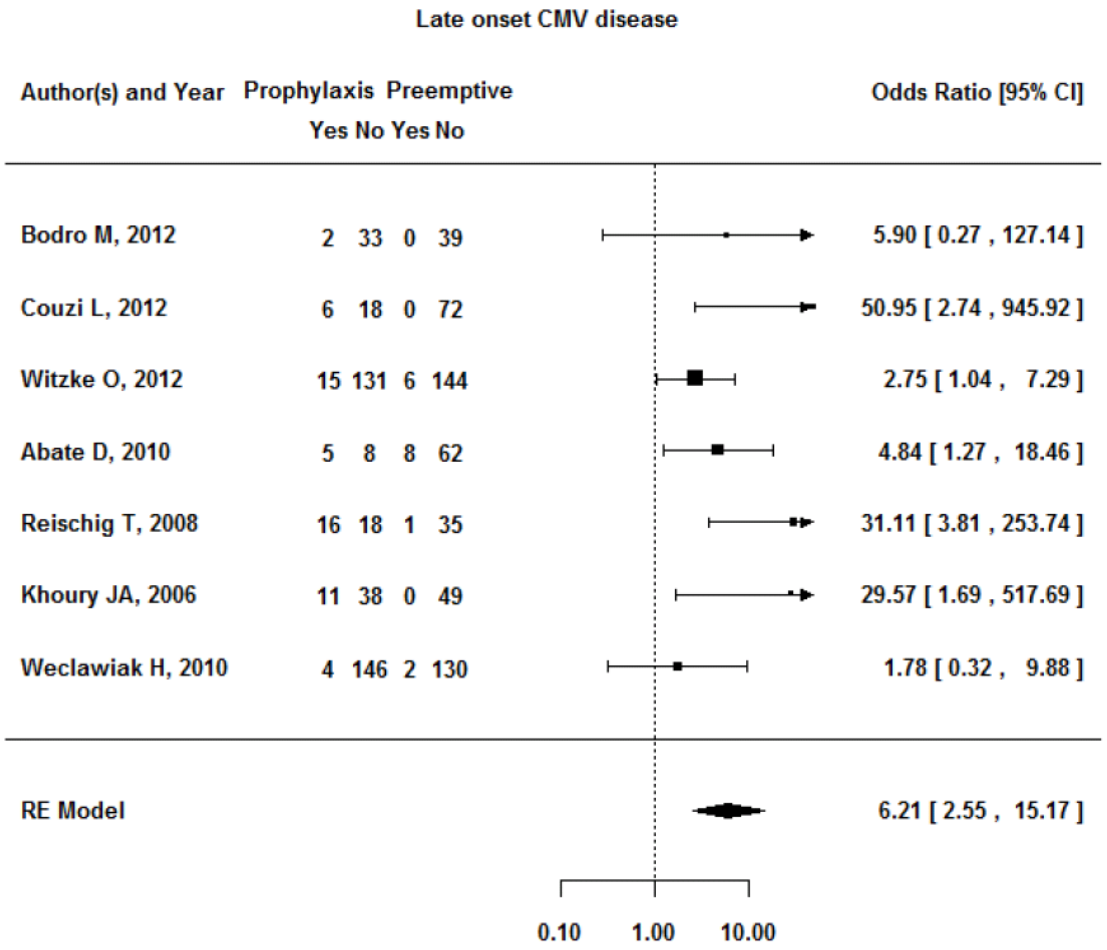
Florescu et al
The Clash Of The Titans: Prophylaxis Vs. Preemptive Strategies For CMV Infections After Solid Organ Transplantation. A Meta-analysis. ID Week 2013 abstract 1668

Risk of invasive CMV disease



Diana Florescu et al
The Clash Of The Titans: Prophylaxis Vs. Preemptive Strategies For CMV Infections After Solid Organ Transplantation. A Meta-analysis. ID Week 2013 abstract 1668

Late onset CMV disease



Diana Florescu et al
The Clash Of The Titans: Prophylaxis Vs. Preemptive Strategies For CMV Infections After Solid Organ Transplantation. A Meta-analysis. ID Week 2013 abstract 1668

Other findings prophylaxis vs pre-emptive

- No differences between prophylaxis and pre-emptive strategy for:
  - Graft loss (OR 0.88; p=0.78)
  - Graft loss censored for death (OR 0.73; p=0.78)
  - Acute rejection (OR 0.93, p=0.64)
  - Mortality OR 0.8, p=0.22)
- More patients on prophylaxis had leukopenia (OR 1.97, p=0.0001)
- Neutropenia (OR 2.07, p=0.02)
- Odds for other infections (VZV, HSV, bacterial, fungal infections not different between 2 strategies

Florescu et al ID Week 2013 abstract 1668

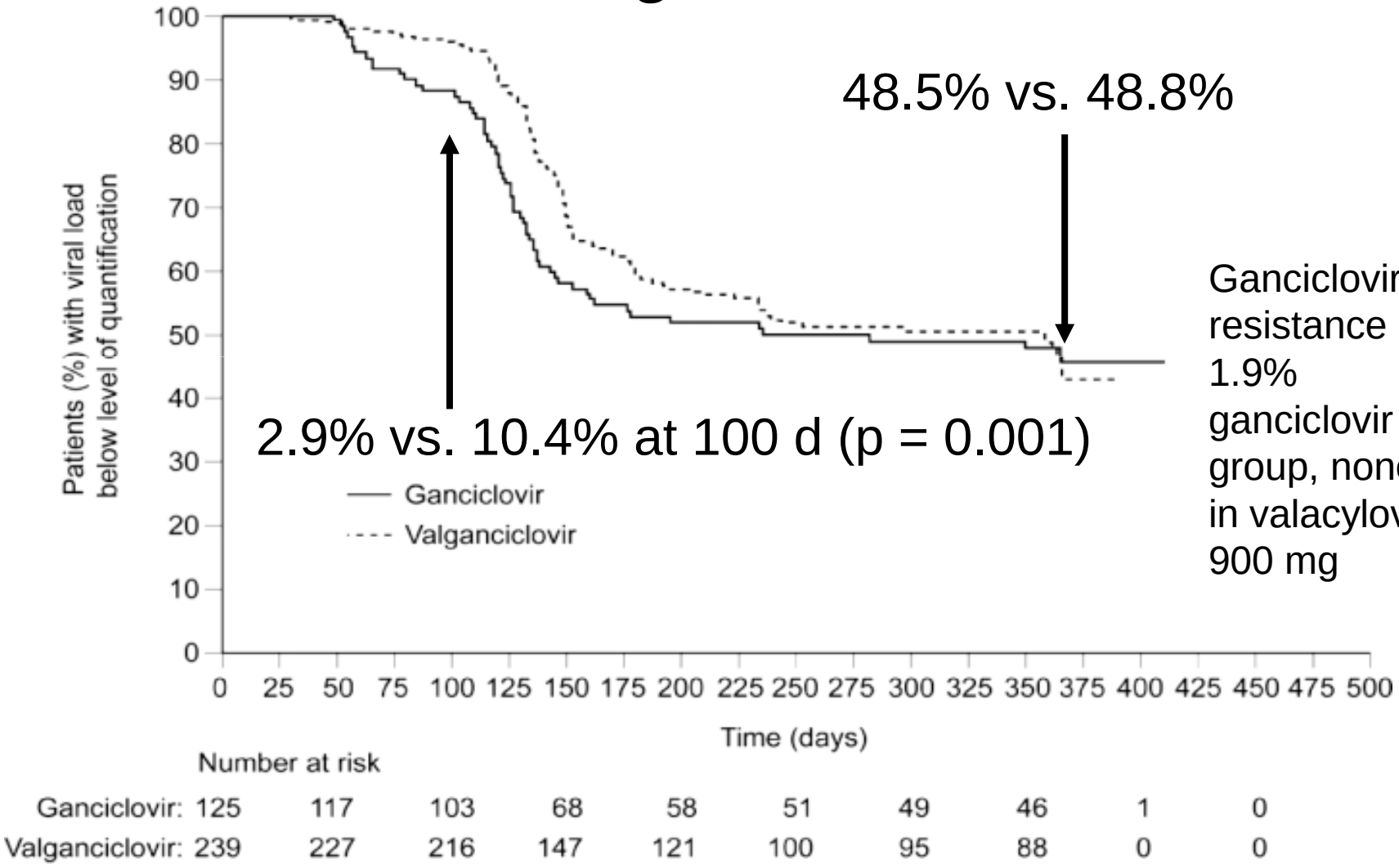
CMV prophylaxis regimens

	D+/R-	R+	D-/R-	Receipt of lymphocyte depleting rx	Other
SA (CALHN)	**90 days** valganciclovir 450 mg daily	**None-** preemptive strategy (unless receive lymph depl tx)	None	valganciclovir 450 mg daily **(even D-/R-)**	
WA (Royal Perth)	**180 days** valganciclovir 900 mg daily	**90 days** Valganciclovir 900 mg daily	None	**90 days** post receipt of tx	Monitoring two-weekly for 6 mo after cessation of prophylaxis
NSW (Hunter)	**180 days** CMV Ig at induction Initially ganciclovir 1.25mg/kg 3x/week iv then valganciclovir 450 mg daily	**100 days** **Initially ganciclovir 1.25mg/kg 3x/week iv** then valganciclovir 450 mg daily	None	**90 days** post receipt of tx valganciclovir 450 mg daily	
QLD **(QLD transplantation service)**	**180 days** Valganciclovir 900 daily (GFR >60)	**90 days** Valganciclovir 900 mg daily (GFR >60)	None		
VIC (Austin Health)	180 days Valganciclovir 450-900 mg daily	?	?		

Dose adjustments renal failure

CrCl (ml/min)	Product information	SA	QLD	NSW
≥60	900 mg once daily	450 mg once daily	450 mg twice daily	450 mg once daily
40-59	450 mg once daily	450 mg once daily	450 mg once daily	450 mg once daily
25-39	450 mg every 2 days	450 mg every 2 days	450 mg Mon, Wed, Fri	Not specified
10-24	450 mg twice weekly	450 mg every 2 days	450 mg twice weekly (M,F)	450 mg every 2 days
<10	Not rec (powder 100mg po 3x/wk after dialysis)	450 mg 2-3 times/week post dialysis	Nil or 0.625 mg/kg ganciclovir post dialysis 2-3x/week	Ganciclovir IV post dialysis 2-3x/week

CMV: *Prophylaxis valganciclovir 900 mg vs oral ganciclovir*



Paya C et al. ***Am J Transplant***. 2004;4:611-620.

Target ganciclovir level?

- Erice et al. found that patients responded to treatment for CMV disease had mean GCV trough levels of 0.7 µg/ml, compared with 0.43 µg/ml in those with progressive CMV.
- GCV level that is required to avoid asymptomatic CMV viremia post-transplantation is uncertain

Erice et al 1987 JAMA 257:3082–3087.

Ganciclovir exposure in relation to renal function-what is an appropriate level?

Valganciclovir
450 mg daily

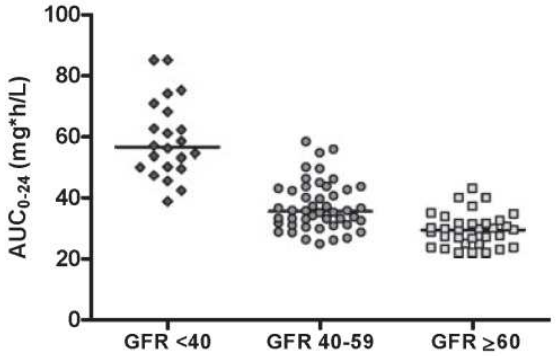


Fig. 1. Ganciclovir systemic exposure (area under the curve [AUC_{0-24}]) in patients receiving 450 mg of valganciclovir,

GCV trough levels
Therapeutic >0.6 mg/litre
Sub-therapeutic <0.6 mg/litre
Severely deficient <0.3 mg/liter

Parameter	GFR_{MDRD} 26–39 mL/min	GFR_{MDRD} 40–59 mL/min	GFR_{MDRD} ≥60 mL/min
Number of patients[a]	13	23	17
Number of samples	22	47	33
GFR_{MDRD}, mL/min, mean ± SD	33.6 ± 3.7	49.3 ± 5.4	69.4 ± 8.6
C_{trough}, mg/L, median (range)	1.29 (0.57–2.34)	0.55 (0.28–1.25)	0.38 (0.23–0.83)
$AUC_{0-24\,h}$, mg h/L, median (range)	59.3 (39.0–85.3)	35.6 (24.9–58.3)	29.6 (22.0–43.2)

$AUC_{0-24\,h}$, area under the curve; C_{trough}, ganciclovir levels at trough; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.
[a]Because the GFR was calculated for each sample, a patient could be included in more than one group depending on the evolution of the kidney function.

Manuel Clin Transplant 2010 DOI: 10.1111/j.1399-0012.2009.01205.x

AAC
Journals.ASM.org

Electronic Estimations of Renal Function Are Inaccurate in Solid-Organ Transplant Recipients and Can Result in Significant Underdosing of Prophylactic Valganciclovir

J. Trevillyan,[a] P. Angus,[b,e] E. Shelton,[b] J. Whitlam,[c] F. Ierino,[c,e] J. Pavlovic,[b] D. Gregory,[c] K. Urbancic,[a] J. Torresi,[a,e] A. Testro,[b,e] M. L. Grayson[a,d,e]

Infectious Diseases,[a] Gastroenterology,[b] and Nephrology[c] Departments, Austin Health, Heidelberg, Victoria, Australia; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia[d]; Department of Medicine, University of Melbourne, Victoria, Australia[e]

In a prospective study of solid-organ transplant recipients ($n = 22$; 15 hepatic and 7 renal) receiving valganciclovir for cytomegalovirus (CMV) prophylaxis, electronic estimation of glomerular filtration rate (eGFR) underestimated the true GFR (24-h urine creatinine clearance) by >20% in 14/22 (63.6%). Its use was associated with inappropriate underdosing of valganciclovir, while the Cockroft-Gault equation was accurate in 21/22 patients (95.4%). Subtherapeutic ganciclovir levels (≤0.6 mg/liter) were common, occurring in 10/22 patients (45.4%); 7 had severely deficient levels (<0.3 mg/liter).

Inaccuracy of eGFR

- GCV concentrations of <0.6 mg/liter common (45.4% at some stage)
- several patients with severely low levels below the routinely reported 50% inhibitory concentration [IC50] for CMV

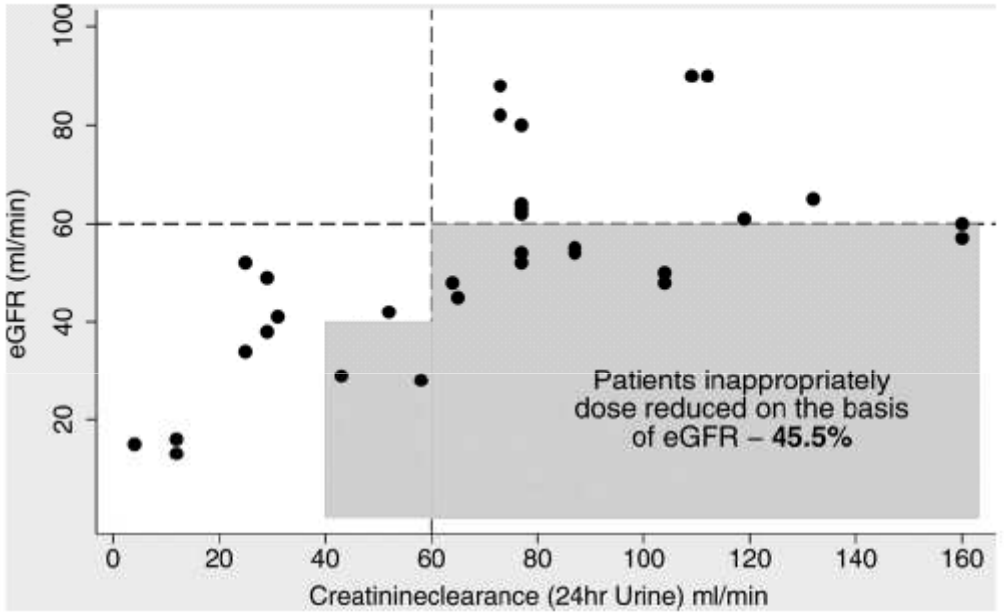


FIG 1 Comparison of estimated glomerular filtration rate (eGFR) and measured creatinine clearance (mCCl) from 24-h urine samples. $n = 31$ samples from 22 patients.

Trevillyan et al AAC 2013

Valganciclovir 900mg vs 450mg

Effectiveness of Valganciclovir 900 mg versus 450 mg for Cytomegalovirus Prophylaxis in Transplantation: Direct and Indirect Treatment Comparison Meta-analysis

Andre C. Kalil,[1] Cezarina Mindru,[2] and Diana F. Florescu[1]

[1]Infectious Diseases Division and [2]Hepatololgy Division, University of Nebraska Medical Center, Omaha, Nebraska

Kalil CID 2011:52
Avery CID 2011:53 (ed)

Findings:
Similar efficacy, 3 times increase in the risk of leucopenia and 2 times increase in the risk of rejection compared with VGC 450 mg
BUT: 900mg group included lung transplants, 450 mg did not
In PV16000 study the oral ganciclovir arm (which was said to be comparable to the 450-mg valganciclovir dosage group) included patients who developed ganciclovir-resistant CMV infection (1.9% of patients), whereas the valganciclovir group (which received the higher dosage of 900 mg/day) did not develop ganciclovir-resistant infection

- **Important Considerations for Prophylaxis for D+/R- Patients**
- Dosing of antiviral medication should be based on standard recommended dosing algorithms and adjusted for renal function.
- “Mini-dosing” strategies (i.e., valganciclovir 450 mg a day with normal renal function) are not recommended.

Kotton et al International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation *Transplantation* 2010;89: 779–795

CMV: *Late-Onset Disease*

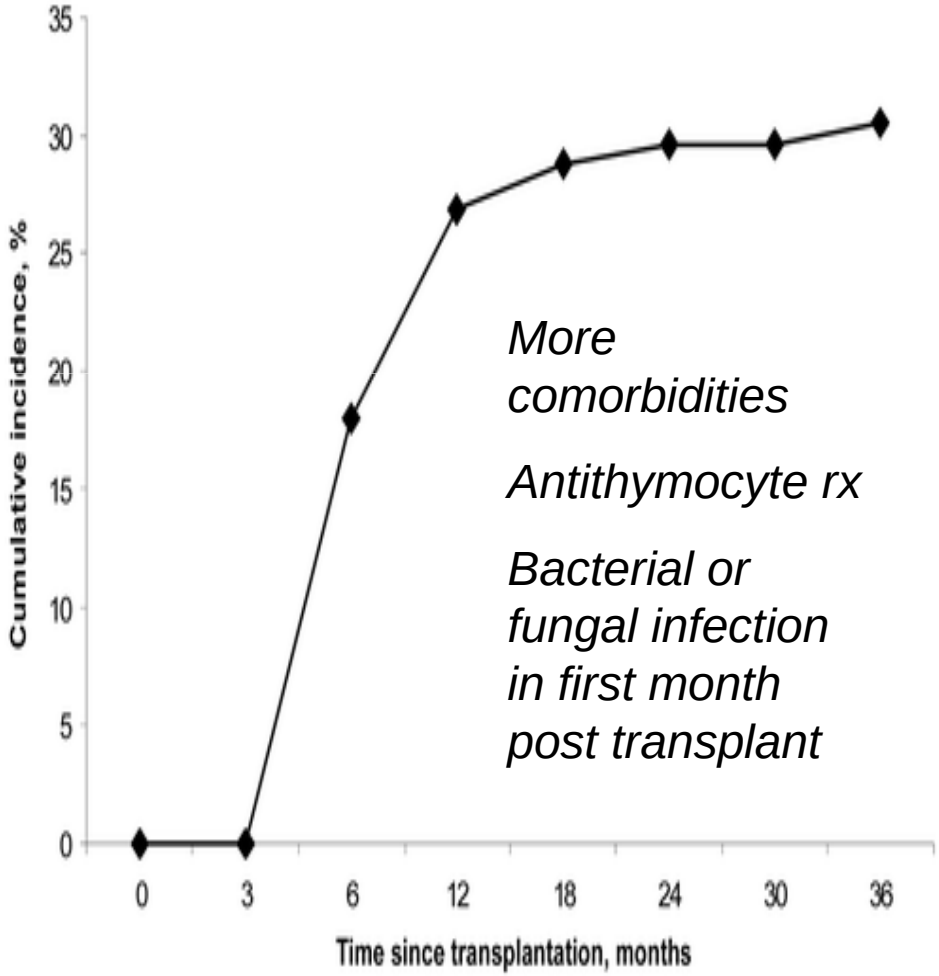


Table 2. Univariate Cox proportional hazard model for risk factors associated with delayed-onset primary cytomegalovirus disease after kidney transplantation.

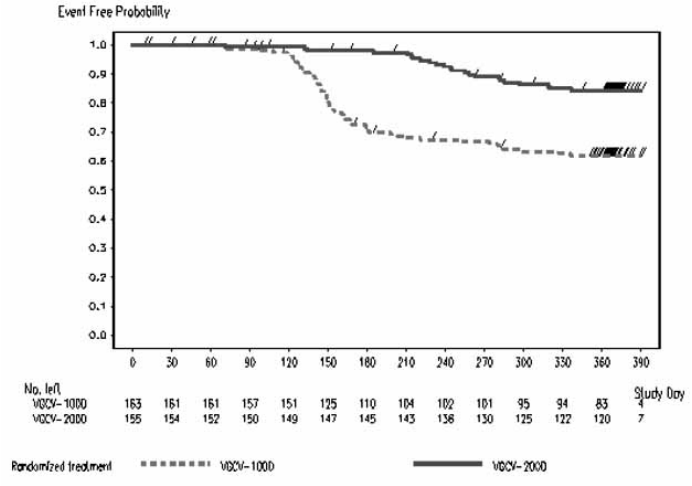
Risk factor	Hazard ratio (95% CI)	*P*
Age at time of transplantation	1.010 (0.989–1.032)	.339
Male sex	0.986 (0.555–1.752)	.963
Charlson comorbidity index (continuous variable)	1.049 (0.900–1.222)	.550
Charlson comorbidity index ⩾3	2.207 (1.155–4.218)	.017
Diabetes mellitus	0.820 (0.462–1.456)	.494
Induction immunosuppressive therapy		
Thymoglobulin	1.398 (0.714–2.734)	.328
Basiliximab	0.587 (0.211–1.634)	.308
Daclizumab	0.532 (0.0734–3.855)	.532
Combination of thymoglobulin, rituximab, intravenous immunoglobulin, and plasmapheresis	0.891 (0.353–2.248)	.808
Maintenance immunosuppressive therapy[a]		
Cyclosporine	0.580 (0.081–4.198)	.554
Sirolimus	0.908 (0.361–2.285)	.835
Tacrolimus	1.026 (0.438–2.406)	.951
Time of onset of bacterial infection after transplantation		
1 month	5.379 (2.386–12.125)	<.001
2 months	3.353 (1.608–6.992)	.001
3 months	1.845 (0.880–3.867)	.104
Time of onset of fungal infection after transplantation		
1 month	8.640 (1.144–65.275)	.034
2 months	3.859 (0.525–28.377)	.185
3 months	2.602 (0.356–19.046)	.346
Acute graft rejection	0.335 (0.120–0.933)	.036
Treated acute graft rejection[b]	0.292 (0.091–0.940)	.039

[a] Because almost every study subject was receiving mycophenolate mofetil and prednisone, these were not assessed for their association with delayed-onset primary cytomegalovirus disease.
[b] Treated acute graft rejection followed by 1–3 months of antiviral prophylaxis.

Arthurs *et al*. ***Clin Infect Dis***. 2008; 46: 840-846.

CMV: *Prophylaxis duration*

- IMPACT Study
  - Randomized 318 D+/R- kidney transplant recipients to valGCV 900mg QD for 100 vs. 200 days
  - Followed the patients to 1 year
    - CMV: 36.8% vs. 16.1% (p< 0.0001)
    - Rejection: 17.2% vs. 11% (p = 0.11)
    - Graft Loss: 1.8% vs. 1.9% (p = 0.9)



Helantera AmJ Trp 2010

CMV infection in 47/127 (37%) D+R- pts after 6 mo rx valgan

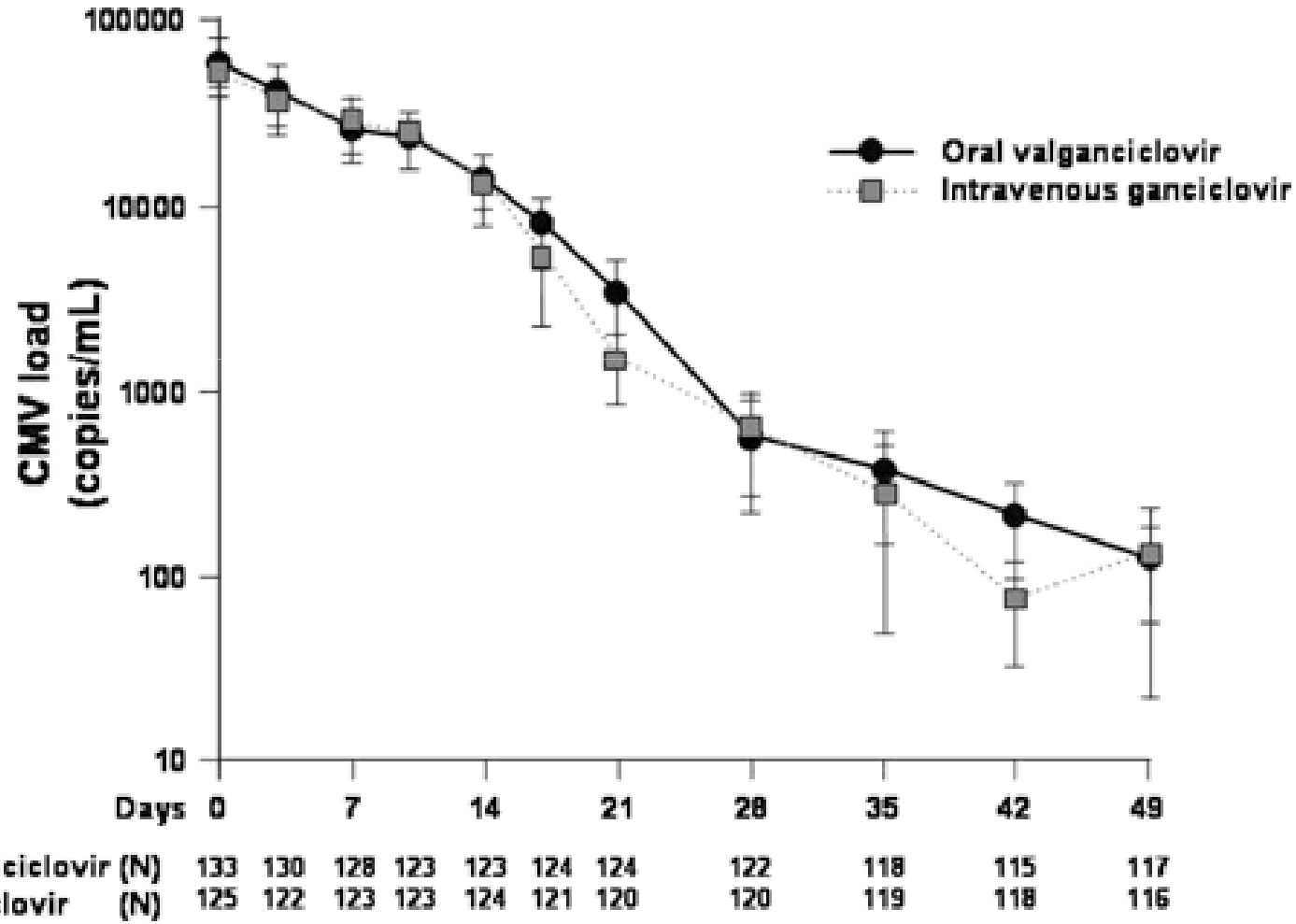
Humar*et al.* Am Transplant Congress 2009 (Boston): Abstract 201.

Timing of prophylaxis

- Usually within days of transplantation
- Small trial delayed long-term prophylaxis in (D+/R-) solid organ transplant recipients to 2 weeks post transplant
  - Saw decreased rates of CMV disease
  - CMV disease occurred in 7 of 26 patients (27%) receiving conventional prophylaxis compared with 1 of 18 patients (5.5%) receiving delayed prophylaxis ($p = 0.07$).
  - Furthermore, five patients (19%) receiving conventional prophylaxis developed CMV colitis, while none of the patients receiving delayed prophylaxis developed tissue-invasive disease ($p = 0.048$).
  - ? Transient exposure of immune system to CMV allowed development of partial protective immunity

San Juan, Clin Transplant 2009; 23 (5): 666-71

CMV: *Treatment*



Åsberg *et al*. ***Am J Transplt***. 2007; 7:2106.

Treatment-duration

- Recommended duration of therapy
  - Treat until CMV PCR is negative
  - Clinical evidence of disease has resolved
  - Minimum 2-3 weeks
    - Am J Transp 13(s4):93, 2013, Blood 113:5711, 2009

When is IV ganciclovir preferred over po valganciclovir as first line treatment?

- Patients with life-threatening disease
- High viral load (>100,000 IU/ml)
- Concern for inadequate gastrointestinal absorption
  - CMV colitis, diarrhoea

When to give secondary prophylaxis

- Patients recently treated with high dose immunosuppression (1-3 month course)
- Severe CMV disease
- Patients with >1 episode of CMV disease

Other considerations

- Dose reduction of antiviral treatment due to side effects such as leukopenia should be avoided as much as possible.
- A reduction of mycophenolic acid products, mammalian target of rapamycin inhibitors, azathioprine, and possibly also trimethoprim-sulfamethoxazole dosages should be considered before valganciclovir/ganciclovir reduction (III).

Kotton et al International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation *Transplantation* 2010;89: 779–795

When to consider ganciclovir resistance?

- Severe immunosuppression and high viral load
- Prolonged antiviral therapy (>6 weeks)
- Viral load fails to fall after 2 weeks of appropriate therapy

Algorithm for treatment of ganciclovir resistant CMV

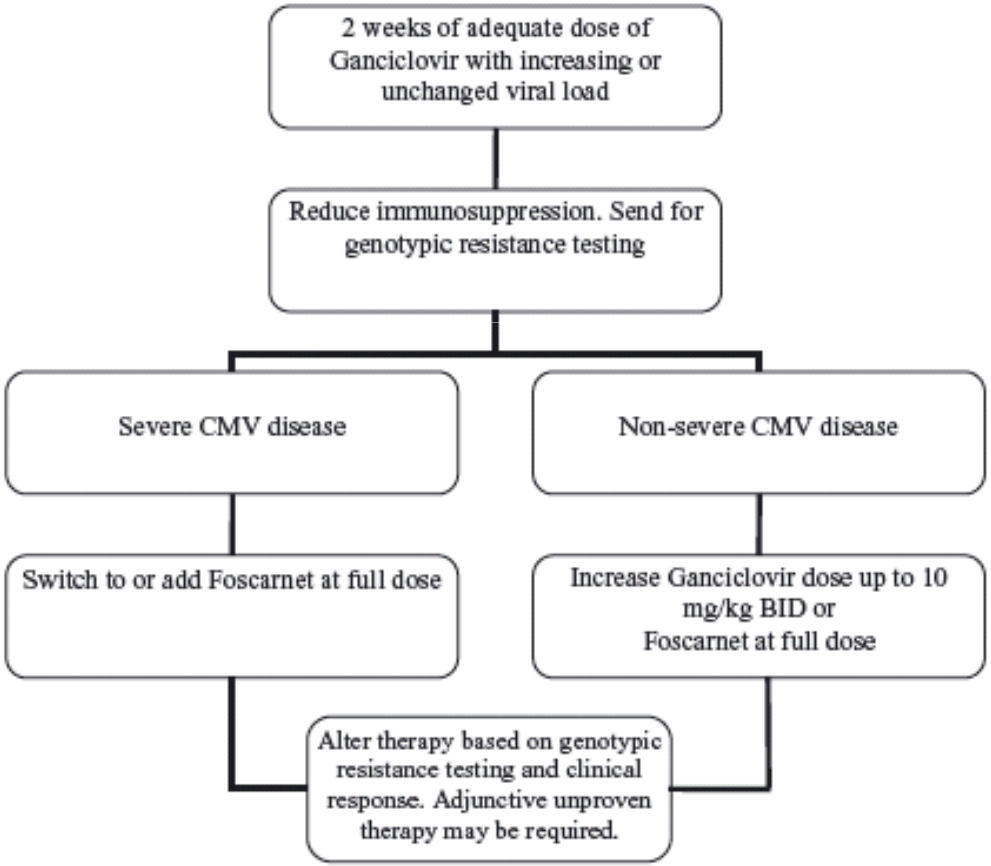


Figure 2: Algorithm for treatment of ganciclovir resistance.

Razonable, R et al, Am J Transplant 2013; 13:93

CMV: *Treatment summary*

- Can use valGCV for all cases except:
  - CMV Colitis/diarrhea
  - CMV pneumonitis
  - High CMV viral load (>100,000 copies)
- Always check a measured 24 hr CrCl
- Consider and test for resistance
- Expected response
  - Clinical improvement within 48-72 hours
  - A reduction of viral load within 1 week
- Treat until
  - Viremia has cleared (use the same lab)
  - No evidence of end organ disease
- 3 months of secondary prophylaxis then monitor

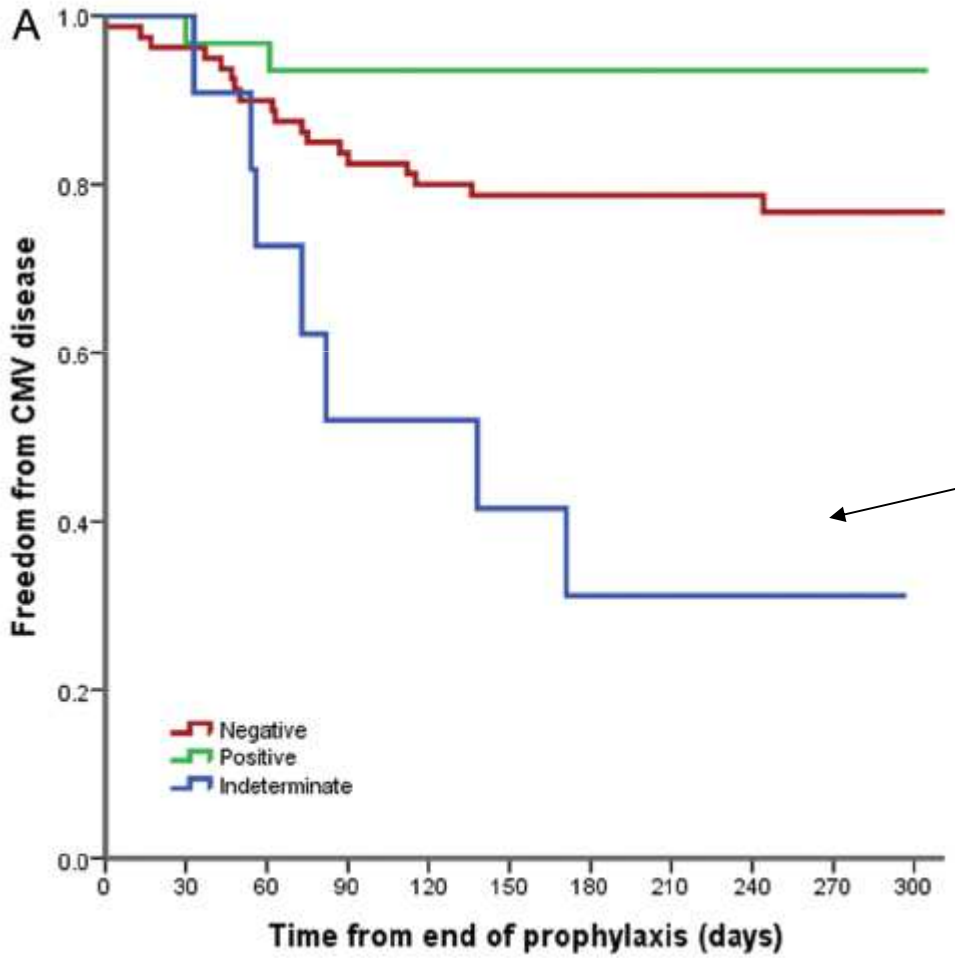
Adapted from slide by Ison (Transplant physician, Northwestern Medical center, Chicago IL)

Future directions

- Better assessment of immune function to predict likelihood of CMV disease
- CMV vaccines[1]
  - Lower rates of antiviral drug use and less degree of viraemia in vaccinees
- Alternative therapies for CMV

1. Griffiths, Lancet 2011; 377: 1256–1263.

CMV specific immunity as a predictor or CMV disease



CMV quantiferon assay

No response to mitogen

Manuel, Clinical Infectious Diseases 2013;56(6):817–24

Future/alternative drugs

- CMX001
  - Nucleoside phosphonate (converted intracellularly to cidofovir diphosphate)
  - Long intracellular half-life (dose twice weekly)
  - No myelosuppression
  - Not concentrated in renal tubules, unlikely to have renal toxicity
  - Active vs CMV, HSV, polyomaviruses, adenovirus
  - 400 times more potent than cidofovir against CMV
  - Limited by severe gastrointestinal side effects at higher doses

Marty et al NEJM 2013; 369:13

Future/alternative drugs

- Letermovir
  - Acts versus viral terminase
- Cyclopropavir
  - DNA polymerase inhibitor
- Leflunomide
- Artesunate
- Maribavir
  - Disappointing results liver and bone marrow transplants
- Sirolimus
  - Has some antiviral properties and associated with lower CMV risk

Considerations in indigenous transplant/remote locations

- Prophylaxis logistically preferred over preemptive strategy in CMV
- Longer duration of prophylaxis in high risk patients may need consideration
- Prospective analysis of CMV disease and associated risk factors, optimal duration of therapy
  - More data needed!