

**PUO in the
Immunocompromised Host:**

CMV and beyond

PUO in the immunocompromised host: role of viral infections

- Nature of host defect
 - T cell defects
 - Underlying disease
 - Treatment
- Nature of clinical presentation
 - Specific organ-related manifestations
 - “Disseminated” disease (viremia)
- Sensitivity/specificity of diagnostic tests
 - Infection v disease

Immunocompromised Hosts

- HIV/AIDS
- Lymphoma/leukemia
- Haematopoietic stem cell transplantation
- Solid organ transplantation
- Cytotoxic chemotherapy & immunotherapy
 - Neutropenic host

Pathogenesis of infections

- Reactivation latent/persistent viruses
 - DNA viruses
 - Herpesviruses
 - Adenovirus
 - Papovamaviruses
- Primary infection or reinfection
 - Common infections; multiple types

Cytomegalovirus

- CMV infection
 - isolation of virus, or
 - detection of viral proteins, or
 - detection of nucleic acid in any body fluid or tissue specimen.

- CMV disease
 - End-organ disease
 - CMV syndrome
 - documented presence of fever (temperature $>38^{\circ}\text{C}$ for at least 2 days within a 4-day period)
 - presence of neutropenia or thrombocytopenia
 - detection of CMV in blood

Prevention of CMV Disease

■ Prophylaxis

- High risk patients
- Valaciclovir, ganciclovir, valganciclovir
- First 100 days

■ Pre-emptive therapy

- Low risk patients
- Routine monitoring to detect CMV infection
- Ganciclovir followed by suppressive therapy until D100

CMV in HSCT: Pre-preventive strategies

Seropositive recipients of a graft from a seronegative donor:

- 60-70% develop CMV infection
- 20-30% of these develop end-organ disease

■ Seronegative recipients of a graft from a seropositive donor:

- 15-20% develop CMV infection

CMV in HSCT:

Post-preventive strategies

- 20% patients develop CMV disease
 - median 170 days (range 96-784 days)
 - 46% mortality
 - 40% survivors recurrence at median of 80 days
- Risk factors for late CMV disease:
 - chronic graft-versus-host disease (GVHD)
 - low CD4 counts ($< 50/\text{mm}^3$)
 - CMV infection before day 100.
- Not different for prophylaxis v pre-emptive approaches

CMV in solid organ transplants: Pre-preventive strategies

- Seronegative recipients of a graft from a seropositive donor (D+R-):
 - 40-60% develop CMV disease
 - CMV syndrome is most common manifestation
- Seropositive recipients irrespective of donor status (R+):
 - 25% develop CMV disease

CMV in SOT:

Post-preventive strategies

- 30% of D+R- patients and 5% of R+ patients developed CMV disease after antiviral prophylaxis was discontinued.
- No difference in the incidence, timing, or clinical manifestations of CMV disease in those who received either oral ganciclovir or valganciclovir prophylaxis
- No risk factors other than D+R- status for developing late CMV disease.

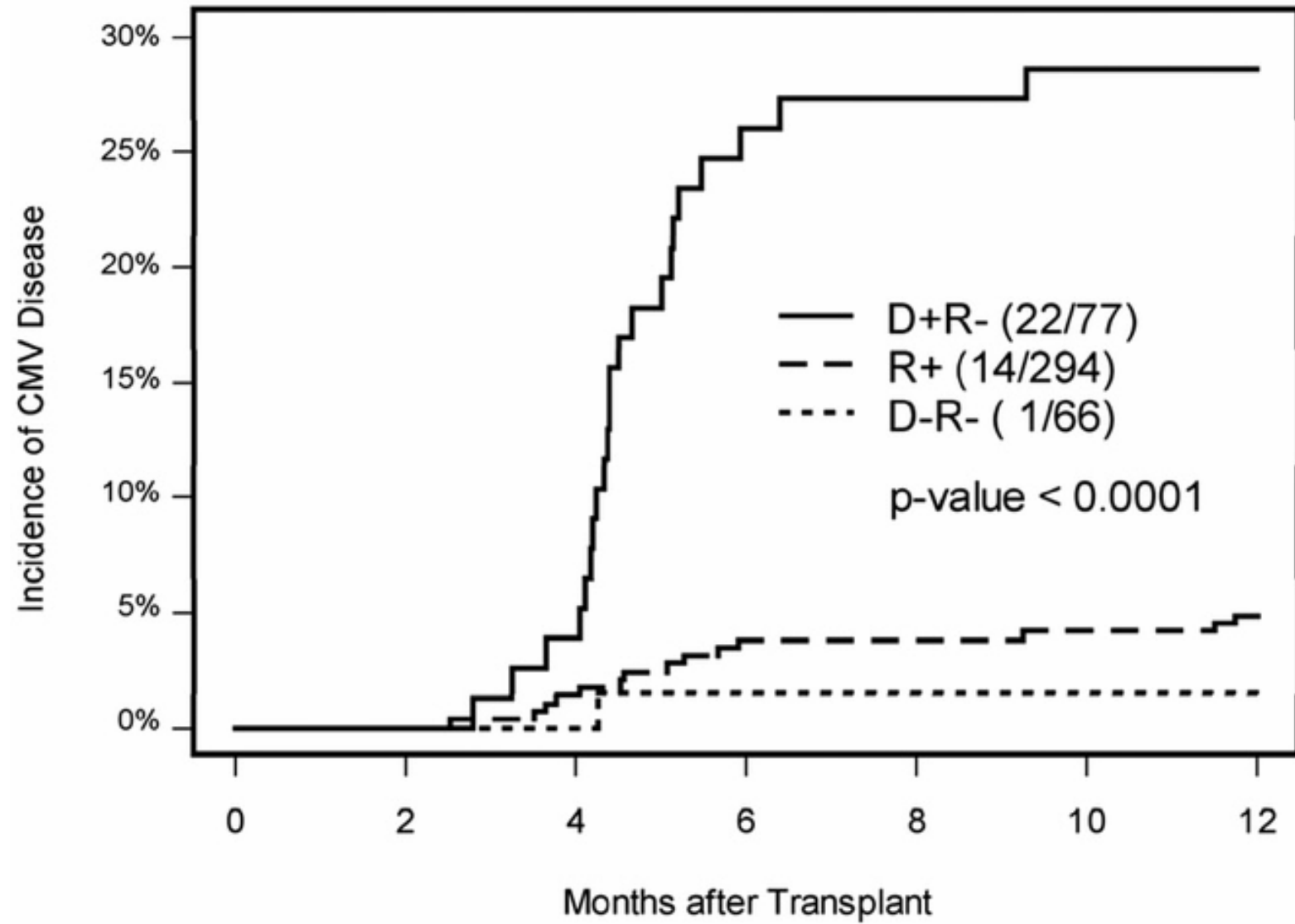


TABLE 2. Clinical presentation of CMV disease

	All	D+R-	R+	D-R-	<i>P</i> value
n	37	22	14	1	
Incidence	8.5%	28.6%	4.8%	1.5%	<i>P</i> < 0.001
95% confidence interval	(5.9%, 11%)	(18%, 39%)	(2.4%, 7.3%)	(0%, 4.5%)	
Median onset in months	4.5	4.4	4.8	4.3	
Range	(2.5, 12)	(2.8, 9.3)	(2.5, 12)	(4.3)	
Disease type					
Viral syndrome	19	9	9	1	
Tissue-invasive	18	13	5	0	
Hepatitis	6	5	1	0	
Pneumonia	5	4	1	0	
Enteritis	7	4	3	0	

Immunosuppressive/ Cytotoxic Chemotherapy

- Immunosuppressive therapy
 - Corticosteroids
 - Calcineurin inhibitors (cyclosporin, tacrolimus)
- Cytotoxic chemotherapy
 - Alkylating agents (cyclophosphamide)
 - Purine nucleoside analogues (fludarabine)
- Lymphocyte directed antibody therapy
 - Anti-thymocyte globulin
 - Anti-CD52

Fludarabine

- Purine nucleoside analogue
- CLL and NHL
- Overall OIs 50%; higher
 - combined with corticosteroids
 - previously treated
- Varicella zoster/Herpes simplex

Monoclonal Antibody Therapy

Antibody	Alemtuzumab	Rituximab	Bevacizumab	Cetuximab	Trastuzumab
Receptor	CD52	CD20	VEGF	EGFR	HER2
Infusion-related toxicity	+	+	-	+	+
Haematologic toxicity	+	+	-	+	-
OIs	+	+	-	-	-

Alemtuzumab (Campath)

- Humanised monoclonal antibody against CD-52
 - B & T lymphocytes, monocytes and NK cells
- T & B cell lymphocytic leukemia/lymphoma
- Risk of OIs
 - 25-80%
 - CMV viremia in 50%

Alemtuzumab in SOT

- Prevention and treatment of acute allograft rejection in SOT
- June 2006, Pittsburgh
 - 547 subjects receiving alemtuzumab
- 56 (10%) developed OIs
 - CMV 26% of all OIs (note routine CMV prophylaxis, except livers)
 - Median onset 145 days after SOT (85 days after therapy)
 - Higher risk when used for rejection therapy (21%)

.....and beyondHHV-6

■ HHV-6

- High prevalence of infection
 - 30-40% viremia within one month of transplant.
 - Lower in patients on CMV prophylaxis
- Most infections caused by B variant.
- In BMT, associated with organ disease especially encephalitis
- Possible co-factor in development of CMV disease in renal transplants

.....HHV-7

- 30% viremia in SOT; lower in patients on CMV prophylaxis (less effect than on HHV-6)

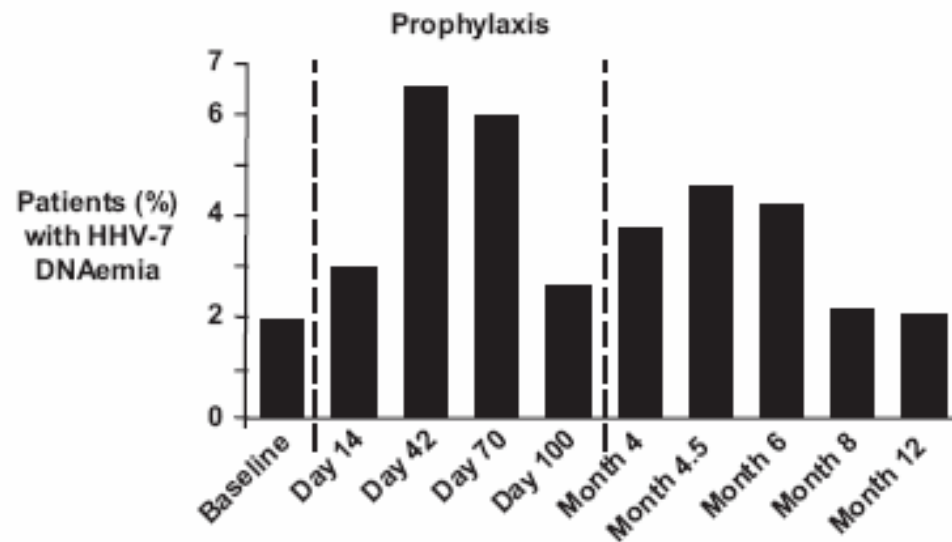


FIGURE 3. Incidence of significant HHV-7 DNAemia ($\geq 1,000$ copies/ml). The peak incidence of significant HHV-7 DNAemia ($\geq 1,000$ copies/ml) occurred around 6 weeks posttransplant while patients were still receiving cytomegalovirus prophylaxis.

Organ Transplant	Virus	Disease
Liver (n=46)	HHV-6	None
Liver, renal (n=32)	HHV-6	None
Liver (n=60)	HHV-6, 7	Rejection (HHV-6) None (HHV-7)
Renal (n=56)	HHV-6, 7	None (HHV-6) CMV disease (HHV-7)
Renal, pancreas (n=30)	HHV-6	Fever
Renal (n=52)	HHV-6, 7	None (HHV-6) CMV disease, rejection (HHV-7)
Renal (n=37)	HHV-6, 7	None (HHV-6) CMV disease (HHV-7)
Liver (n=51)	HHV-6	Graft dysfunction
Liver (n=33)	HHV-6, 7	CMV disease (HHV-6, 7)

Adenovirus in HSCT

- Higher incidence of infection in children
 - 20-30% in children
 - 10% in adults
- Primary infection v reactivation
 - Primary more likely in children
 - In adults, prior adenovirus is risk factor
- Earlier onset in children
 - Children within 30 days
 - Adults >90 days
- Organ-related disease
 - Hepatitis
 - Pneumonitis

Adenovirus in HSCT

- 2001, MD Anderson
 - 2889 adult BMT
- 85 (3%) adenovirus infection
 - 76 symptomatic infections
 - Organ-related disease
 - 13 patients with “disseminated” disease
 - Overall mortality 26% (higher in pneumonia and disseminated disease)

Adenovirus in SOT

- 7% viremia
 - Majority asymptomatic

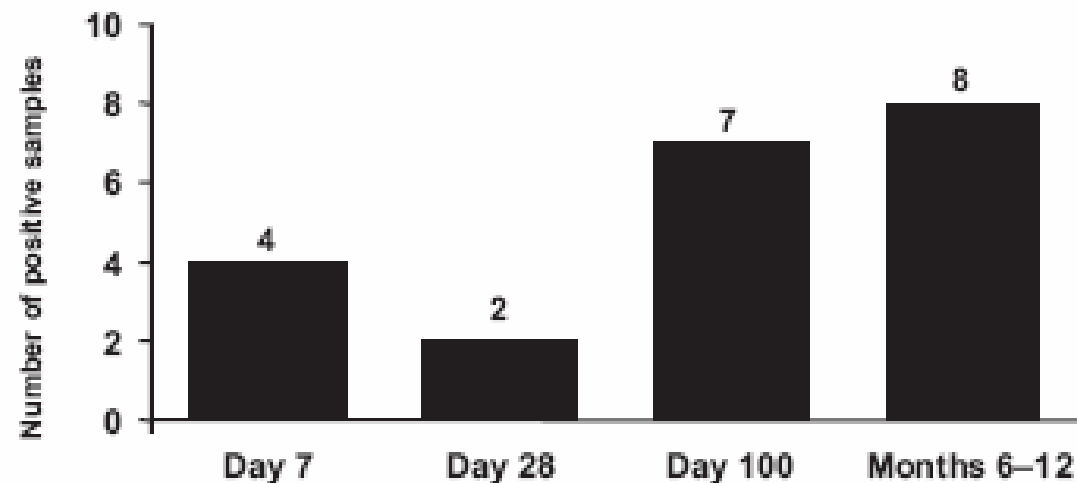


FIGURE 6. Time to detection of adenovirus viremia. Adenovirus viremia occurred throughout the 1-year evaluation period, both during and after discontinuation of cytomegalovirus prophylaxis.