

Viral Prophylaxis in Organ Transplant Patients

Michelle Slifkin, Shira Doron and David R. Snydman

Division of Infectious Diseases, Tufts-New England Medical Center, Boston, Massachusetts, USA

Contents

Abstract	2763
1. Prevention of Viral Infection	2765
2. Antiviral Prophylaxis	2766
3. Herpesviruses	2767
3.1 Cytomegalovirus (CMV)	2768
3.1.1 Prophylactic Regimens	2769
3.1.2 Pre-emptive Prophylactic Regimens	2776
3.1.3 Pre-emptive Therapy for Avoidance of CMV Disease	2777
3.2 Herpes Simplex Virus	2778
3.3 Varicella-Zoster Virus	2780
3.4 Epstein-Barr Virus	2780
3.4.1 Summary	2783
4. Hepatitis Viruses	2783
4.1 Hepatitis A Virus	2783
4.2 Hepatitis B Virus	2784
4.3 Hepatitis C Virus	2784
5. Community Respiratory Viruses	2785
6. Conclusion	2786

Abstract

Viral pathogens have emerged as the most important microbial agents having deleterious effects on solid organ transplant (SOT) recipients. Antiviral chemoprophylaxis involves the administration of medications to abort transmission of, avoid reactivation of, or prevent progression to disease from, active viral infection.

Cytomegalovirus (CMV) is the major microbial pathogen having a negative effect on SOT recipients. CMV causes infectious disease syndromes, augments iatrogenic immunosuppression and is commonly associated with opportunistic superinfection. CMV has also been implicated in the pathogenesis of rejection. Chemoprophylactic regimens for CMV have included oral aciclovir (acyclovir) at medium and high doses, intravenous and oral ganciclovir, and the prodrugs valaciclovir (valacyclovir) and valganciclovir. CMV prophylactic strategies should be stratified, with the highest-risk patients receiving the most 'potent' prophylactic regimens.

Herpes simplex virus (HSV) reactivation in SOT recipients is more frequent, may become more invasive, takes longer to heal, and has greater potential for dissemination to visceral organs than it does in the immunocompetent host.

Prophylactic regimens for CMV are also effective chemoprophylaxis against HSV; in the absence of CMV prophylaxis, aciclovir, valaciclovir or famciclovir should be used as HSV prophylaxis in seropositive recipients.

Primary varicella-zoster virus (VZV) after SOT is rare and most commonly seen in the paediatric transplant population because of VZV epidemiology. Zoster occurs in 5–15% of patients, usually after the sixth post-transplant month. Prophylactic regimens for zoster are neither practical nor cost effective after SOT because of the late onset of disease and low proportion of affected individuals. All SOT recipients should receive VZV immune globulin after contact with either varicella or zoster.

Epstein-Barr virus has its most significant effect in SOT as the precipitating factor in the development of post-transplant lymphoproliferative disorders. Antiviral agents that could be effective are the same as those used for CMV, but indications for and effectiveness of prophylaxis are poorly established.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are important pathogens in the SOT population as indications for transplantation. So-called 'prophylaxis' for recurrent HBV and HCV after liver transplantation is controversial, suppressive rather than preventive, and potentially lifelong.

Influenza infection after SOT is acquired by person-to-person contact. During epidemic periods of influenza, transplant populations experience a relatively high frequency of infection, and influenza may affect immunosuppressed SOT recipients more adversely than immunocompetent individuals. Antiviral medications for prevention of influenza are administered as post-exposure prophylaxis to SOT recipients, in addition to yearly vaccine, in circumstances such as influenza epidemics and nosocomial outbreaks, and after exposure to a symptomatic individual during 'flu season'.

Organ transplantation has become an accepted form of treatment for end-stage kidney, liver, heart, pancreas and lung disease, and appears promising for some types of severe intestinal dysfunction. With improvements in surgical techniques, immunosuppression and peri-transplant management, survival after organ transplantation has become the rule rather than the exception; however, infection and rejection remain the principal causes of morbidity and mortality in the solid organ transplant (SOT) population. Opportunistic microbial pathogens adversely affect both allograft and patient survival, and viral pathogens have emerged as the most important microbial agents having deleterious effects on SOT recipients.

Three 'groups' of viruses merit particular attention in SOT. The first, and arguably the most important, is the herpesvirus group, which includes

cytomegalovirus (CMV), herpes simplex viruses (HSV) type 1 and type 2, Epstein-Barr virus (EBV), varicella-zoster virus (VZV), and the emerging pathogens human herpes viruses (HHV) 6, 7 and 8. The second group comprises the hepatitis viruses, especially hepatitis B (HBV) and hepatitis C (HCV) viruses. The final group of viruses is more heterogeneous and consists of the viral pathogens that cause community-acquired respiratory tract infections; this group includes influenza, parainfluenza, respiratory syncytial virus and adenovirus. Other viruses not included above that have greater effect on SOT recipients than on the general (immunocompetent) population include the papilloma viruses, the papova viruses (JC and BK) and parvovirus B19.

In this review of viral prophylaxis in SOT, we describe the different modalities that have been considered for prevention of viral infection, review the

Table 1. Modalities for prevention of viral infection

Modality	CMV	HSV	EBV	VZV	Influenza	Other
Avoidance	+	–	–	(Avoid exposure)	(Avoid exposure)	
matching	Not practical		In limited use (EBV R–)			HCV+ (limited use)
blood	Screened, filtered, leucocyte depleted		–			Discarded if HIV+, HBsAg+, HCV+
Vaccine	–	–	–	+ Pre-transplant	+ Yearly	HAV, HBV, pre-/ post-transplant
Passive immunisation	CMVlg	–	–	VZVlg	–	HBVlg, RSVlg, IVlg for HAV
Immune modulation	– ^a	–	– ^b	–	–	IFN for HBV, HCV
Antivirals	GCV, ACV	ACV,	?GCV, ?ACV	–	M2 inhibitors	3TC, FAMV for HBV
	valACV, valGCV	valACV, FAMV			NA inhibitors	IFN + ribavirin for HCV

a IFN not used because of higher incidence of rejection.

b Adoptive T-cell transfer in study.

3TC = lamivudine; **ACV** = aciclovir (acyclovir); **CMV** = cytomegalovirus; **EBV** = Epstein-Barr virus; **FAMV** = famciclovir; **GCV** = ganciclovir; **HAV** = hepatitis A virus; **HBsAg** = hepatitis B surface antigen; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HIV** = human immunodeficiency virus; **HSV** = herpes simplex virus; **IFN** = interferon; **lg** = immunoglobulin; **IV** = intravenous; **NA** = neuraminidase; **R–** = recipient seronegative; **RSV** = respiratory syncytial virus; **valACV** = valaciclovir (valacyclovir); **valGCV** = valganciclovir; **VZV** = varicella-zoster virus; + indicates in use; – indicates not available; ? indicates uncontrolled trials and anecdotal evidence.

principles and definitions of prophylaxis, and discuss the viruses for which potential prophylactic regimens exist. We review the current English language literature regarding viral prophylaxis in organ transplantation and conclude with a discussion of our preferences regarding antiviral regimens.

1. Prevention of Viral Infection

Unlike the immunocompetent population, who primarily acquire their viral infections in the community, SOT patients experience the majority of their significant viral exposures during the peri-transplant period and as a direct consequence of having an organ transplanted. The various methods of prevention of viral infection for SOT recipients can be separated into five categories: avoidance, active immunisation, passive immunisation, immunomodulation and chemoprophylaxis (table I).

Avoidance as a method of prevention of viral infection in SOT is applicable only for viruses that are transmitted by blood products or by a latently infected donor organ. Organ donors are routinely screened for evidence of infection with HIV, HBV, HCV, EBV and CMV, and transplantation of organs

from HIV-infected donors is contraindicated. Use of organs from HCV-positive donors is controversial and is commonly restricted to older candidates who are urgently in need of SOT; long-term outcomes in these patients are unknown as yet. Active infection with HBV (hepatitis B surface antigen-positive; HBsAg+) is also a contraindication to organ donation, but transplantation with hepatitis B core antibody-positive (HBcAb+/HBsAg–) organs is controversial: liver allografts from these donors have been demonstrated to transmit HBV infection^[1] but the risk for transmission by extrahepatic organs is thought to be low. The European Best Practice Guidelines for Renal Transplantation suggest testing the donor for human T-cell lymphotropic virus 1 (HTLV-1) infection as well.^[2] HIV-, HBV- and HCV-infected blood products are not used, and CMV seronegative, leucocyte-depleted or microfiltered blood is used commonly for CMV seronegative recipients.

Transplantation of organs from CMV and EBV seropositive donors (D+) into seronegative recipients (R–) is effectively unavoidable because of the prevalence of latent infection in the adult population and the current paucity of available organs. Progress-

sively more effective prophylactic methods may soon obviate the need for consideration of such drastic measures as exclusion from transplantation based on lack of previous exposure to virus.

Active immunisation by administration of vaccines is an attractive, cost-effective method of prevention of viral infection in general, but vaccines are not currently available for the majority of the SOT-related viral pathogens. Despite the availability of vaccines for prevention of hepatitis A virus (HAV), HBV, VZV and influenza, post-transplant vaccine administration, especially with live vaccine preparations, is controversial. The optimal timing for vaccination is before SOT takes place, but this is not always convenient and may not confer lasting protection. Vaccine immunogenicity is attenuated in chronic disease in general and this is especially true in the presence of iatrogenic immunosuppressive agents. With live vaccines, there is the theoretical risk of enhanced virulence of attenuated virus in the presence of immunosuppression, and VZV vaccine, which is a live attenuated virus preparation, is generally contraindicated after SOT. Killed and component vaccines confer no theoretical risk of infection, but are poorly immunogenic at routine dosages after SOT. Vaccine-provoked allograft injury or rejection is also a concern. Most evidence suggests that the influenza vaccine is 'safe' and annual vaccination is recommended after the first post-transplant year. HBV vaccine is probably 'safe' after SOT, and VZV vaccine has been safely administered in a small study to paediatric renal transplant recipients^[3] and may be recommended in the future.

Passive immunisation is provided transiently with administration of immunoglobulin (Ig) preparations. Virus-specific hyperimmune and unselected Ig are used in prophylactic regimens and for adjunctive treatment of severe infectious disease. They are prepared from the serum of large pools of donors and are filtered to eliminate the risk of serum-transmitted infection. Hyperimmune globulins are used as prophylactic agents against CMV infection,^[4] after primary VZV exposure^[5] and after HBV^[6,7] exposure.

Immunomodulation is still largely experimental. Adoptive T-cell transfer^[8] and recombinant interferon administration^[9,10] are two methods under investigation for a variety of diseases.

Chemoprophylaxis, which is the focus of this review, involves administration of antiviral medications to abort transmission of, avoid reactivation of, or prevent progression to disease from, active viral infection.

2. Antiviral Prophylaxis

For an antiviral prophylactic strategy to have a favourable risk/benefit ratio, several conditions must be present. First, the virus in question must have adverse effects on such a significant proportion of the population at risk, or such dire consequences in a smaller proportion of that population, that the risks and cost of administration of the prophylactic agent are justified.^[11] Secondly, the virus must have clearly associated risk factors for pathogenicity. Finally, the risk period(s) for pathogenicity must be well defined.

The antiviral agent to be used in a prophylactic regimen should be able to be safely administered, with a broad therapeutic range to minimise the need for drug concentration monitoring, have minimal and well defined interactions with other transplant-related medications, and have minimal and easily reversible adverse effects.^[11,12] The prophylactic agent should also be easy for the patient to take; preferably in an orally bioavailable form but if intravenous administration is necessary, the dose administration interval should be infrequent.^[13] The agent should be virucidal or effective in the absence of complete killing, and preferably should cover other SOT-associated pathogens.^[14] The regimen should be cost effective, and administration should prevent both direct and indirect consequences of viral infection.

Currently, several different methods of 'prophylaxis' are in use. To minimise confusion, 'prophylaxis' is defined as administration to prevent active viral replication, and 'therapy' is defined as administration once active viral replication has been dem-

onstrated. The methods of prophylaxis are as follows.

- Prophylaxis: administration of a regimen to an entire population (or to the highest-risk portion of the population), beginning at, shortly before or shortly after transplantation and continuing throughout the defined highest-risk period.^[11-13]
- Pre-emptive targeted prophylaxis: administration of a regimen during the event of an intervention that is known to provoke viral replication and disease in the majority of patients.
- Post-exposure prophylaxis: administration of a regimen to a susceptible individual, shortly after high-risk exposure to an active source of infection, to prevent or attenuate the clinical manifestations of disease.
- Pre-emptive therapy: administration of a regimen beginning once there is laboratory evidence of active infection (viral replication), but before clinical symptoms or signs of disease have occurred, to prevent progression to disease.

The relative merits of prophylaxis versus pre-emptive therapy are often debated. Prophylaxis is advantageous in that it obviates the need for intensive monitoring for laboratory evidence of viral

infection but it involves administration of an antiviral medication to individuals who may never actually be at risk for virus-related consequences. Cost is an issue, since patients take these medications long term. Concern that prolonged exposure to antiviral agents will encourage drug resistance has also been raised. Pre-emptive therapy is advantageous in that antiviral agents are administered only to those at laboratory-confirmed risk of viral disease, but it necessitates frequent monitoring, a high degree of patient compliance, reliable laboratory staff and assays, and rapid reporting of and acting upon positive results. Another disadvantage is the potential for adverse effects of subclinical infection.

With this background, we discuss the viruses that meet the conditions outlined earlier as candidates for antiviral prophylaxis.

3. Herpesviruses

The epidemiology of herpesviruses is summarised in table II. Viral pathogens cause 25–30% of all post-SOT infection and the herpesviruses cause the majority of them.^[15] Herpesviruses are large, enveloped, DNA-containing viruses that produce lifelong latent infection.^[16] Viral latency is of

Table II. Epidemiology of selected viruses in solid organ transplantation

Feature	CMV	HSV	EBV	VZV	Influenza
Adult seroprevalence (%)	40–100	Type 1: 50–70 Type 2: 20–50	>90	>90	na
Transmission					
reactivation	++	+++	+	+++	–
organs	+++	Rare (case reports)	+++	– (one case report)	–
blood	+	–	+	–	–
community	Rare	Rare	Rare	++	+++
Site of latency	?Lymphoid, endothelial tissue	Nerve ganglia	B cells	Dorsal root ganglia	na
Independent risk factors	D+/R– > R+ ALA	R+ Immunosuppression	D+/R– > R+ ALA CMV disease	R+ Immunosuppression Exposure	na
High-risk period	Months 1–4	First month	First year	After sixth month	Epidemics
Indirect effects	Immunosuppression (superinfection) acute/chronic rejection	–	PTLD	–	?Rejection, OB

ALA = antilymphocyte antibody preparation; **CMV** = cytomegalovirus; **D+** = donor seropositive; **EBV** = Epstein-Barr virus; **HSV** = herpes simplex virus; **na** = not applicable; **OB** = obliterative bronchiolitis; **PTLD** = post-transplant lymphoproliferative disorder; **R–** = recipient seronegative; **R+** = recipient seropositive; **VZV** = varicella-zoster virus; – indicates not known to occur; + indicates occurs; ++ indicates important; +++ indicates most important.

Table III. Incidence of cytomegalovirus (CMV) disease in solid organ transplantation

Study	Comparators	CMV disease incidence [% (no.)]	Comments
Smith et al. ^[23]	Natural history, kidney	13 (27/209)	No induction immunosuppression
	D+/R-	50 (14/28)	No difference in 4-year graft survival among serogroups
	R+	7.1 (9/127)	CSA + AZA
	D-/R-	7.7 (2/26)	
Sagedal et al. ^[24]	Natural history, kidney	23 (111/477)	No induction immunosuppression
	D+/R-	54 (43/79)	Risk factors for CMV disease: D+/R-, rejection
	R+	19 (68/358)	CSA + AZA
	D-/R-	0 (0/40)	
Stratta ^[25]	Natural history, liver	35 (73/211)	Not all serologies available
	D+/R-	79 (11/14)	High incidence of CMV disease in D-/R-
	R+	41 (50/121)	CSA + corticosteroids
	D-/R-	22 (4/18)	
Grossi et al. ^[26]	Natural history, heart	17 (51/294)	Symptomatic infection in 51/157 viraemic patients (33%)
	D+/R-	91 (20/22)	Prospective monitoring study (pp65Ag+), treatment if symptomatic only
	R+	12 (33/267)	CSA + AZA
	D-/R-	0 (0/5)	
Smyth et al. ^[27]	Natural history, lung/heart	35 (23/65)	Heart/lung recipients; only reported CMV pneumonitis
	D+/R-	55 (6/11)	Protective seromatching (D-/R-) after the 17th patient
	R+	47 (15/32)	CSA + AZA
	D-/R-	4.5 (1/22)	

AZA = azathioprine; **CSA** = ciclosporin (cyclosporine); **D-** = donor seronegative; **D+** = donor seropositive; **R-** = recipient seronegative; **R+** = recipient seropositive.

concern in SOT because latently infected donor organs can transmit infection and cause severe primary disease. This is especially important if the cellular arm of the immune system, which is the primary target for transplant immunosuppression, is intimately involved in the containment of and recovery from the acute infection.

Latency, and its relationship to primary infection in SOT, is especially relevant for CMV and EBV infection. These infections have been acquired by the majority of adults before coming to transplantation as either donor or recipient. High-risk, serodiscordant transplants (D+/R-) are likely to occur, especially in paediatric SOT, and to cause serious consequences for patients whose cellular immune systems are maximally suppressed during the time of the primary infection.

Viral latency is of less importance with HSV, because allograft transmission of primary HSV infection is extremely rare,^[17,18] and with VZV, because primary infection is community-acquired and, although potentially devastating, a rare occurrence after SOT.

3.1 Cytomegalovirus (CMV)

CMV is the major microbial pathogen having a negative effect on SOT recipients (table III). CMV is a ubiquitous beta herpesvirus, which, along with the other herpesviruses, is capable of latency. The prevalence of CMV seropositivity increases with age,^[19] reaching nearly 100% in populations in developing nations;^[20] in the US, 40–70% of adults have been exposed,^[16] depending on the socioeconomic milieu. In the community, CMV is acquired primarily by intimate contact with virus-containing secretions of all types; transmissible virus can be found in urine, saliva, breast milk, vaginal and cervical secretions, and semen.^[20] CMV can also be acquired *in utero* and perinatally. There is no seasonality to CMV infection^[21] and the majority of primary infections in the healthy host are asymptomatic. Clinically apparent infection can present as a mononucleosis-like syndrome and, more rarely, as hepatitis, gastrointestinal ulcerations or pneumonia.^[20] The exact site of latency for CMV has yet to be fully elucidated but the CMV genome has been found in monocytes/macrophages, neutrophils, lym-

phocytes and endothelial cells; the virus is thought to remain latent in a primitive haematopoietic cell population, possibly stem cells.^[22]

In the SOT population, activation of CMV infection is directly related to the transplant process. CMV is acquired as a primary infection or a secondary superinfection from a latently infected donor organ or, much less commonly, from blood products.^[25] Latent CMV infection is reactivated and/or upregulated by immunosuppressive medications.^[28] CMV is thought to have both direct and indirect effects on transplant recipients.^[29,30] Directly, it causes infectious disease syndromes, with manifestations ranging from subclinical viral replication to disseminated fatal disease, and CMV can affect virtually any organ system.^[25] There is a tendency towards tropism for the transplanted organ; CMV hepatitis is common after liver transplantation, pneumonitis is a frequent complication of lung and heart-lung transplantation,^[31] and enteritis occurs after intestinal transplantation.^[32]

Indirect effects of CMV infection include augmentation of immunosuppression^[33] and CMV is commonly associated with superinfection with fungal opportunists.^[34,35] CMV has also been implicated in the pathogenesis of acute rejection^[36,37] and associated with chronic rejection syndromes^[29] such as transplant-related coronary artery disease after heart transplantation^[38] and bronchiolitis obliterans after lung transplantation.^[39,40] Different types of SOT carry different risks for CMV-associated consequences. The reasons behind the hierarchy of risk are not completely understood but this phenomenon is probably related to two important factors: the relative amount of immunosuppression initially required for successful allograft function, and the relative amounts of lymphoid and endothelial tissue (CMV load) contained in the transplanted organ.^[14] Intestine, lung and pancreas transplantation confer the highest risk for direct and indirect CMV-related problems, liver and heart transplantation confer moderate risk, and kidney allografting confers the lowest risk.^[35] It should be noted that in the case of a multi-organ transplant procedure, the risk of CMV disease is related to that of the highest-risk organ.

Independent risk factors for CMV infection include D+/R- serogroupings and use of antilymphocyte antibody (antilymphocyte globulin; ALA) preparations (both monoclonal and polyclonal) for additional immunosuppression.^[12,25] ALA preparations reactivate CMV from the latent state and, while use of these preparations for induction significantly increases the risk of CMV-related complications, use of ALA for steroid-resistant rejection therapy increases the risk for CMV disease to >60%.^[41] Other risk factors for CMV disease include emergent transplantation (e.g. fulminant hepatic failure),^[42] use of cadaveric allografts, retransplantation (especially for acute rejection)^[25] and occurrence of acute rejection.^[43] In the absence of prophylaxis, the highest-risk period is between the first and fourth months after SOT, or during late episodes of rejection. Even CMV antibody-negative recipients from CMV antibody-negative donors are at risk of acute CMV infection from blood transfusion or exposure to ill healthcare workers and visitors, and some of these patients receive prophylaxis, although this practice is uncommon and may not be cost effective.

3.1.1 Prophylactic Regimens

Prophylactic regimens for CMV that have been studied have included oral aciclovir (acyclovir) at medium (MD, 2–2.5 g/day) or high (HD, 3.2 g/day) dosages, intravenous and oral ganciclovir, and more recently the prodrugs valaciclovir (valacyclovir) and valganciclovir. These agents have been used alone, sequentially, and in combination with both hyperimmune and unselected Ig.

Aciclovir and Valaciclovir

Aciclovir is an acyclic guanosine analogue, which, after activation via triphosphorylation by virus and host cell enzymes, acts to inhibit viral DNA polymerase and block viral DNA synthesis.^[44] The antiviral spectrum of aciclovir includes herpesviruses, with the most potent activity against HSV and VZV, and limited (*in vitro*) activity against EBV and CMV.^[45]

Valaciclovir is the L-valyl ester of aciclovir, which is hydrolysed in the intestinal wall and liver to L-valine and aciclovir;^[46] the major advantage of valaciclovir (vs aciclovir) is oral bioavailability.

Valaciclovir is >50% orally bioavailable, while oral aciclovir bioavailability ranges from 15% to 21%.^[45]

The major toxicity of both agents is neurotoxicity, which is usually minor, and dosage of both drugs must be adjusted for renal insufficiency.^[45]

Ganciclovir and Valganciclovir

Ganciclovir is another acyclic guanosine analogue which, like aciclovir, inhibits viral DNA synthesis after activation by triphosphorylation.^[42] Ganciclovir is also active against the herpesviruses, but has much greater activity against CMV compared with aciclovir (50% inhibitory concentration [IC₅₀] of ganciclovir 0.6–4.9 µmol/L vs aciclovir 10–190 µmol/L).^[42] Oral ganciclovir has very low bioavailability (<10%), which is slightly enhanced when the drug is taken with food.^[45] The major dose-limiting toxicity of ganciclovir is neutropenia; dose-adjustment is necessary for ganciclovir in the setting of renal insufficiency.^[44] Both routine prophylaxis and pre-emptive therapy have resulted in an occasional case of ganciclovir-resistant CMV infection.^[47,48]

The ganciclovir prodrug valganciclovir, which has dramatically improved bioavailability compared with ganciclovir, has recently been licensed for use and its role in transplant prophylaxis has yet to be determined. When studied in liver transplant recipients, once-daily valganciclovir provided systemic exposure of ganciclovir that was superior to standard dosages of oral and equivalent to intravenous ganciclovir.^[49] A recent double-blind study of valganciclovir versus oral ganciclovir in SOT recipients showed valganciclovir to be as clinically effective and as safely used as oral ganciclovir when used for the prevention of CMV disease in D+/R- patients. Patients who received valganciclovir had a lower incidence of and longer time to CMV viraemia, and lower peak CMV viral loads.^[50]

CMV Prophylaxis in Kidney Transplantation

Balfour et al.^[51] compared oral HD aciclovir with placebo in a group of 104 randomised patients (table IV). The incidence of CMV disease was significantly decreased with aciclovir in all patients, in high-risk patients and in those at risk for reactivation disease. HD aciclovir significantly delayed the onset

of CMV disease. There was no difference in patient or graft survival between groups during the 12-month follow-up period.

A randomised, controlled trial compared sequential therapy using intravenous ganciclovir followed by oral HD aciclovir with no treatment and demonstrated a decrease in the overall incidence of symptomatic CMV infection with sequential prophylaxis, but did not find significant differences between groups for incidence of moderate to severe disease, rejection or graft survival at 6 months.^[52]

Two trials compared oral ganciclovir and oral aciclovir in low doses (400 mg/day)^[53] and at high doses (3200 mg/day);^[54] both trials demonstrated significant decreases in rates of CMV disease and significant delay in the onset of CMV disease in the patients receiving oral ganciclovir.

Lowance et al.^[55] studied the efficacy of the prodrug valaciclovir for prophylaxis in patients at risk for CMV infection (donor and/or recipient CMV seropositive) in a randomised, placebo-controlled trial. The valaciclovir cohort had reduced incidence and delayed onset of CMV disease overall, as well as among both high-risk and moderate-risk patients when compared with the placebo cohort. Interestingly, there was a significant reduction in the incidence of biopsy-proven acute rejection episodes in the patients who received valaciclovir compared with those who received placebo.

CMV Prophylaxis in Liver Transplantation

Badley et al.^[56] and Martin et al.^[57] compared oral HD aciclovir alone with sequential intravenous ganciclovir/oral HD aciclovir (table V). In both trials, the addition of ganciclovir provided superior protection against CMV disease and against tissue-invasive CMV disease versus aciclovir alone, but had no significant effect (vs aciclovir) on patient and graft survival at 6^[57] and 12^[56] months after transplantation.

In a study in paediatric liver recipients, comparing 2 weeks of intravenous ganciclovir alone with sequential intravenous ganciclovir/oral HD aciclovir, the authors concluded that addition of oral HD aciclovir did not add to protection against CMV disease.^[58]

Table IV. Cytomegalovirus (CMV) prophylaxis in renal transplantation

Study	ALA [follow-up (mo)]	Regimen (no. pts)	CMV disease [% (no.)]	D+/R- [% (no.)]	R+ [% (no.)]	Comments
Balfour et al. ^[51]	Yes [6]	HD ACV × 3mo (53) Placebo (51)	7.5 (4) 29 (15)	17 (1/6) 100 (7/7)	9.7 (3/31) 28 (8/29)	Randomised, placebo-controlled ACV reduced the rate of CMV disease, mucocutaneous HSV (7% vs 36%) No effect on patient, graft survival ACV increased time to CMV disease
Pouteil-Noble et al. ^[52]	na [6]	IV GCV × 14 days → HD ACV to 3mo (24) Control (26)	25 (6) 54 (14)	ns ns	ns ns	Randomised, controlled No difference in moderate/severe CMV disease No difference in rejection, graft survival
Brennan et al. ^[53]	Yes [4+]	PO GCV × 3mo (19) LD ACV 400 mg/day (23)	21 (4) 61 (14)	ns ns	ns ns	Randomised treatment PO GCV prevents CMV disease, benefits persist after discontinuation PO GCV delays onset of CMV disease
Flechner et al. ^[54]	Yes [6]	PO GCV × 3mo (40) HD ACV × 3mo (39)	5 (2) 23 (9)	0 (0/14) 38 (5/13)	6.7 (1/15) 15 (4/26)	All D+/R- got CMVlg × 8 Randomised treatment One late CMV disease in GCV group ACV only effective in D-; GCV superior for D+
Lowance et al. ^[55]	na [6]	ValACV × 3mo (306) Placebo (310)	5.9 (18) 19 (60)	16 (16/102) 45 (48/106)	1 (2/204) 6 (12/204)	Randomised, placebo-controlled ValACV reduced and delayed CMV disease ValACV reduced HSV lesions ValACV reduced biopsy-proven acute rejection

ACV = aciclovir (acyclovir); **ALA** = antilymphocyte globulin for induction; **D-** = donor seronegative; **D+/R-** = donor seropositive, recipient seronegative; **GCV** = ganciclovir; **HD ACV** = oral aciclovir >3 g/day; **HSV** = herpes simplex virus; **lg** = immunoglobulin; **IV** = intravenous; **LD** = low-dose; **na** = not applicable; **ns** = not stated; **PO GCV** = oral ganciclovir 3 g/day; **R+** = recipient seropositive; **valACV** = valaciclovir (valacyclovir).

King et al.^[59] conducted a trial to compare the efficacy of intravenous Ig (IVIg) plus placebo with that of IVIg plus intravenous ganciclovir for 30 days in high-risk paediatric liver recipients. There were no significant differences in rates of CMV disease, bacteraemia, fungaemia or episodes of rejection between treatment groups. The authors did observe a trend toward later onset of CMV disease in the group that received intravenous ganciclovir and they suggested that a longer course of intravenous ganciclovir might be more effective in this population.

A randomised trial demonstrated the superior efficacy of long-term (100 days) administration of intravenous ganciclovir versus oral HD aciclovir for protection against CMV disease, including among those who had received ALA.^[60] Patient survival

was not significantly different between groups of patients during the 120-day follow-up period.

A placebo-controlled study in liver recipients at risk for CMV infection demonstrated that 14 weeks of oral ganciclovir was effective in lowering the incidence and severity of CMV disease and also delayed the onset of CMV disease, when compared with placebo.^[61] These differences were seen in the high-risk and ALA-treated patients, but oral ganciclovir did not confer survival advantage nor provide protection against rejection compared with placebo during the 12-month follow-up period.

CMV Prophylaxis in Heart Transplantation

Aguado et al.^[62] compared 10 weeks of CMVlg with 14 days of intravenous ganciclovir in 31 CMV seropositive recipients who had received 14 days of muromonab CD3 (OKT3) induction and found a

Table V. Cytomegalovirus (CMV) prophylaxis in liver transplantation

Study	ALA [follow-up (mo)]	Regimen (no. pts)	CMV disease [% (no.)]	D+/R- [% (no.)]	R+ [% (no.)]	Comments
Martin et al. ^[57]	Some [6]	IV GCV × 14 days → HD ACV to 3mo (66)	9.1 (6)	43 (3/7)	3.7 (2/54)	Randomised treatment arms No effect on D+/R- primary infection
		HD ACV (71)	28 (20)	64 (7/11)	22 (12/54)	Decreased invasive CMV disease, recurrence, and delayed onset of infection with GCV/ACV No difference in patient or graft survival
Badley et al. ^[56]	Some [12]	IV GCV × 14 days → HD ACV to 3mo (83)	11 (ns)	25 (ns)	ns	Randomised treatment arms Addition of IV GCV effective in CMV
		HD ACV to 3mo (84)	23 (ns)	58 (ns)	ns	disease prevention, even in D+/R-; reduction in candidiasis No difference in patient/graft survival or rejection
Green et al. ^[58]	No [12+]	IV GCV × 14 days (24)	8.3 (2)	0 (0/5)	20 (2/10)	Paediatric, randomised treatment
		IV GCV × 14 days → HD ACV to 12mo (24)	29 (7)	57 (4/7)	22 (2/9)	Addition of ACV did not add to efficacy of IV GCV No CMV-related deaths in either group
King et al. ^[59]	na [6]	IV GCV × 30 days + IVIg × 16 wks (29)	17 (5)	17 (5/29)	na	Paediatric, randomised, placebo- controlled
		Placebo + IVIg × 16 wks (27)	26 (7)	26 (7/27)	na	No difference in CMV disease, rejection, bacteraemia, fungaemia Trend toward delayed CMV disease with IV GCV
Winston et al. ^[60]	Some [4+]	IV GCV × 100 days (124)	2.4 (3)	10 (1/10)	0 (0/114)	Randomised treatment arms
		HD ACV (126)	11 (14)	9.1 (1/11)	8.4 (9/107)	Long-term IV GCV eliminated CMV disease Two late CMV cases in each group, no HSV or EBV No difference in bacterial/fungal infections, survival or cause of death
Gane et al. ^[61]	Some [12]	PO GCV × 3mo (150)	4.7 (7)	14 (3/21)	3.1 (4/128)	Randomised, placebo-controlled
		Placebo (154)	19 (29)	44 (11/25)	14 (18/128)	PO GCV decreased incidence, severity of CMV disease, delayed onset of CMV disease; even in ALA- treated patients No difference in rejection, survival

ACV = aciclovir (acyclovir); **ALA** = antilymphocyte globulin for induction; **D+/R-** = donor seropositive, recipient seronegative; **EBV** = Epstein-Barr virus; **GCV** = ganciclovir; **HD ACV** = oral aciclovir >3 g/day; **HSV** = herpes simplex virus; **Ig** = immunoglobulin; **IV** = intravenous; **na** = not applicable; **ns** = not stated; **PO GCV** = oral ganciclovir 3 g/day; **R+** = recipient seropositive.

much higher incidence of CMV disease and visceral involvement in the patients who had received CMVig (table VI). There were no differences in rates of opportunistic infection, severe acute rejection or death between groups at 6 months.

In a large randomised study,^[63] enrolment was terminated early when an interim analysis demonstrated a significant difference in CMV disease rate among patients at risk for CMV disease (R+ or D+/

R-) treated with 28 days of intravenous ganciclovir versus placebo. In final analysis, intravenous ganciclovir was effective for CMV prophylaxis but less effective for the D+/R-subgroup than for the R+ subgroup.

Mullen et al.^[64] reported results from a retrospective comparison of sequential prophylaxis with intravenous ganciclovir for 14 days followed by either oral aciclovir or oral ganciclovir. Ganciclovir was

demonstrated to be superior to aciclovir with respect to CMV disease incidence and it also produced a significant delay (to >6 months) in the onset of CMV disease. When subgroup analysis was performed, the D+/R- patients also benefited from ganciclovir versus aciclovir, and the authors noted that the distribution of CMV disease among the ganciclovir recipients was not related to CMV serostatus.

CMV Prophylaxis in Pancreatic Transplantation

We reviewed five retrospective comparative studies of CMV prophylactic regimens in pancreas (\pm kidney) recipients; rates of disease were reported without respect to serological subgroups (table VII).

Elkhammas et al.^[65] compared outcomes for 38 pancreas-kidney recipients given 3 months of oral HD aciclovir and outcomes for a group of 85 historical controls who did not receive antiviral prophylaxis. They did not observe significant differences in CMV disease incidence, patient survival or graft survival for the group who received prophylaxis versus the historical controls.

Eight days of intravenous ganciclovir followed by aciclovir at 1600 mg/day was found to be a more effective prophylactic regimen than 3 months of low-dose (800 mg/day) aciclovir in pancreas \pm kidney recipients.^[66] The authors did not observe differ-

ences in the rates of rejection, graft survival or patient survival between groups at 1 year.

The incidence of CMV disease was reduced, and the onset of CMV disease was delayed, if intravenous ganciclovir during ALA induction was added to 3 months of oral MD aciclovir.^[67]

Somerville et al.^[68] demonstrated that oral ganciclovir was more effective than low-dose (1200 mg/day) aciclovir when given for prophylaxis and during ALA treatment for rejection. The results were striking, with a 9.7% incidence of CMV disease in the ganciclovir group versus 50% incidence in the aciclovir group, but were confounded by the significant differences in immunosuppressive regimens between the groups. In both groups, the average time to CMV disease onset was >6 months.

Stratta et al.^[69] compared four prophylactic regimens. Two groups were prospectively randomised to receive 2 weeks of intravenous ganciclovir followed by oral HD aciclovir, plus either IVIg or CMVIg. The randomised patients were compared with two historical groups: one group of patients had received 2 weeks of intravenous ganciclovir followed by oral MD aciclovir and the other had received oral MD aciclovir plus IVIg. The authors concluded that there were no significant differences between prophylactic regimens with regard to the

Table VI. Cytomegalovirus (CMV) prophylaxis in heart transplantation

Study	ALA [follow-up (mo)]	Regimen (no. pts)	CMV disease [% (no.)]	D+/R- [% (no.)]	R+ [% (no.)]	Comments
Aguado et al. ^[62]	Yes [6]	IV GCV \times 14 days (16) CMVIg \times 6 doses (15)	6 (1) 40 (6)	na na	6 (1/6) 40 (6/15)	Randomised treatment arms CMVIg group had more CMV (and tissue invasion) disease
Merigan et al. ^[63]	Yes [4+]	IV GCV \times 28 days (76) Placebo (73)	16 (12) 42 (31)	37 (7/19) 31 (5/16)	8.9 (5/56) 46 (26/56)	Randomised, placebo-controlled Stopped enrolment early because of interim result Decreased HSV (26% \rightarrow 4%) with GCV D+/R- needed longer prophylactic regimen
Mullen et al. ^[64]	na [6+]	IV GCV \times 14 days \rightarrow PO GCV to 3mo (62) IV GCV \times 14 days \rightarrow ACV 2.4 g/day to 3mo (77)	2 (1) 18 (14)	0 (0/14) 14 (2/14)	2.7 (1/37) 20 (11/54)	Retrospective, comparison GCV much more effective prophylaxis than ACV GCV delayed CMV disease to beyond 6 months

ACV = aciclovir (acyclovir); **ALA** = antilymphocyte globulin for induction; **D+/R-** = donor seropositive, recipient seronegative; **HD ACV** = oral aciclovir >3 g/day; **GCV** = ganciclovir; **HSV** = herpes simplex virus; **Ig** = immunoglobulin; **IV** = intravenous; **na** = not applicable; **PO GCV** = oral ganciclovir 3 g/day; **R+** = recipient seropositive.

Table VII. Cytomegalovirus (CMV) prophylaxis in pancreas transplantation

Study	ALA [follow-up (mo)]	Regimen (no. pts)	CMV disease [% (no.)]	Comments
Elkhammas et al. ^[65]	Yes [ns]	HD ACV to 3mo (38) Historic controls (85)	26 (10) 35 (30)	Retrospective No significant difference in CMV disease, patient or graft survival with ACV
Harland et al. ^[66]	Yes [3+]	IV GCV × 8 days → ACV 1600 mg/day to 3mo (24) ACV 800 mg/day to 3mo (16)	25 (6) 56 (9)	Retrospective GCV/ACV more effective than ACV alone
Kohli et al. ^[67]	Yes [6+]	IV GCV with ALA, ACV 2.4 g/day to 3mo (23) ACV 2.4 g/day to 3mo (23)	17 (4) 74 (17)	Retrospective, ?GCV only during induction IV GCV reduced, delayed CMV disease
Somerville et al. ^[68]	Some [5+]	IV GCV with ALA → PO GCV × 3–6mo (31) IV GCV with ALA → ACV 1.2 g/day × 3–6mo (22)	9.7 (3) 50 (11)	Retrospective, comparison ACV got more induction (95% vs 25%) GCV got more MMF (100% vs 23%) PO GCV was effective targeted CMV prophylaxis
Stratta et al. ^[69]	Yes [6+]	IV GCV × 14 days → HD ACV × 3mo + IVIg (9) IV GCV → HD ACV + CMVlg (9) IV GCV × 14 days → ACV 2 g/day to 3mo (34) ACV 2 g/day to 3mo + IVIg × 6 doses (30)	44 (4) 22 (2) 26 (9) 27 (8)	Part randomised, historical comparisons No differences in CMV disease (incidence timing, severity) No added benefit to Ig

ACV = aciclovir (acyclovir); **ALA** = antilymphocyte globulin for induction; **GCV** = ganciclovir; **HD ACV** = oral aciclovir >3 g/day; **Ig** = immunoglobulin; **IV** = intravenous; **MMF** = mycophenolate mofetil; **ns** = not stated; **PO GCV** = oral ganciclovir 3 g/day.

incidence, timing or severity of CMV disease, and that there was no benefit to the addition of Ig to prophylactic regimens.

CMV Prophylaxis in Lung Transplantation

Studies investigating CMV prophylactic regimens in lung transplant recipients are more difficult to interpret because the numbers of subjects studied are small, and inclusion of untreated or placebo groups for comparison is usually not prudent in these high-risk patients (table VIII).

Definitions of CMV disease among the studies varied considerably, but reported CMV disease incidence in lung recipients at risk for CMV disease was significantly higher than reported incidence in other types of SOT recipients, approaching 60–70% even in the lower-risk patient groups. Long courses (>90 days) of intravenous or oral ganciclovir, with or without additional Ig, provided the most effective protection against CMV disease.^[39,70–74] Shorter courses of intravenous ganciclovir (4–6 weeks), with or without sequential aciclovir, were less effective,^[75–77] and 3 months of oral MD aciclovir was essentially ineffective in the prevention of CMV disease.^[70,77] CMV D–/R– lung recipients did not usually experience CMV disease.^[70]

Intestinal Transplantation

One group in Pittsburgh, PA, USA published their results with 72 (adult and paediatric) intestine transplant recipients.^[78] The overall incidence of CMV disease was 33% but when the 28 D–/R– recipients (who did not experience CMV disease) are excluded, CMV disease incidence was 55% (24 of 44). Recurrences were common (52 episodes in 24 patients), graft enteritis was the most frequent manifestation (43 of 52 total episodes) and enteritis not infrequently presented without viraemia.

Summary

The results of these studies, although based on small sample sizes with different incidences of CMV disease, essentially recapitulate the earlier review of CMV disease in SOT. The incidence of CMV disease occurred in rate hierarchies: by organ, with the highest rates were observed in intestine, lung and pancreas recipients, and the lowest rates were seen in kidney recipients; by serostatus (D+/R– > R+ > D–/R–); and by amount of immunosuppression administered (ALA for rejection > ALA induction > no ALA). Similarly, prophylactic regimens were more effective in the lower-risk organ transplants, in the lower-risk serogroups and in the patients who received less intensive immunosuppres-

sion regimens. Ganciclovir-based prophylactic regimens were more effective than aciclovir-based regimens, long-term prophylaxis was superior to short-term prophylaxis in lung transplant recipients, and results with use of Ig preparations were conflicting.

Universal prophylaxis is widely used and is effective in reducing CMV-related morbidity, but exposes patients who might never be at risk for CMV

disease to medications and has the potential for selection of resistant strains of virus by providing long exposure to relatively low doses of antiviral medications. More selective regimens might be more cost effective, both monetarily and in terms of reduced exposure for lower-risk patients. Even effective regimens, while delaying the onset of CMV infection, have not been definitively shown to benefit patient or graft survival.

Table VIII. Cytomegalovirus (CMV) prophylaxis in lung transplantation

Study	ALA [follow-up (mo)]	Regimen (no. pts)	CMV disease [% (no.)]	D+/R- [% (no.)]	R+ [% (no.)]	Comments
Maurer et al. ^[70]	na [na]	CMVlg to 3mo (14)	na (only pneumonitis recorded)	50 (2/4)	20 (2/10)	Retrospective, CMV pneumonitis incidence
		ACV 2.4 g/day + CMVlg to 3mo (12)	na	100 (2/2)	60 (6/10)	No deaths due to CMV pneumonitis
		IV GCV/CMVlg × 3mo (17)	na	40 (2/5)	41 (5/12)	No prophylaxis, no CMV disease in D-/R- (n = 14) 1-year survival only independent of CMV serostatus in the IV GCV group
Weinberg et al. ^[71]	na [na]	D+/R- IV GCV × 90 days → MD ACV to 6mo + CMVlg × 7 doses (7)	17 (7/41) [all patients]	29 (2)	na	Followed prospectively, observation 4 D-/R-, no prophylaxis, no CMV disease
		R+ IV GCV × 28 days → MD ACV to 6mo + CMVlg once (30)		na	17 (5/30)	If OKT3 for rejection, all got IV GCV × 5 days plus CMVlg once
Gerbase et al. ^[72]	Yes [4+]	IV GCV × 5mo (21)	na	20 (1/5)	na	Observation
Gutierrez et al. ^[73]	Varied [na]	IV GCV × 12wk + CMVlg × 6wk (39)	13 (5)	12 (2/17)	14 (3/22)	Observation Prophylaxis prevented or delayed CMV disease (all at >100 days)
Speich et al. ^[74]	Yes [6+]	IV GCV days 7–90 (5)	0 (0)	ns	ns	Open-label, comparison, historical controls
		IV GCV days 7–21 → PO GCV days 22–90+ (9)	11 (1)	ns	ns	All CMV-at-risk (D+ and/or R+)
		Historical controls (8)	75 (6)	ns	ns	GCV delayed time to CMV disease
Zamora et al. ^[75]	No [na]	IV GCV × 28 days → HD ACV to 6mo + CMVlg × 3 doses (23)	na	na	30 (7)	Retrospective observation; all got CMVlg once with OKT3 for rejection Prophylaxis limited and delayed the onset of CMV disease in CMV R+
Kelly et al. ^[76]	No [6+]	IV GCV × 6wk (21)	38 (8)	50 (3/6)	33 (5/15)	Observation No deaths, mechanical ventilation due to CMV
Duncan et al. ^[77]	Yes [3+]	IV GCV days 5–27 → MD ACV to 80 days (13)	15 (2)	100 (ns)	ns	Observation, historical comparison; CMV-at-risk
		MD ACV days 7–97 (11)	64 (7)	100 (na)	ns	All got IV GCV × 21 days for CMV infection All D+/R- had CMV disease; numbers not given

ACV = aciclovir (acyclovir); **ALA** = antilymphocyte globulin for induction; **D-** = donor seronegative; **D+** = donor seropositive; **GCV** = ganciclovir; **HD ACV** = oral aciclovir >3 g/day; **Ig** = immunoglobulin; **IV** = intravenous; **MD** = medium dose; **na** = not applicable; **ns** = not stated; **OKT3** = muromonab-CD3; **PO GCV** = oral ganciclovir 3 g/day; **R-** = recipient seronegative; **R+** = recipient seropositive.

Table IX. Pre-emptive prophylactic regimens for cytomegalovirus (CMV)

Study	ALA [follow-up (mo)]	Regimen (no. pts)	CMV disease [% (no.)]	D+/R- [% (no.)]	R+ [% (no.)]	Comments
Hibberd et al. ^[79]	Some [6]	IV GCV (64) Controls (49)	ns ns	ns ns	14 (9) 33 (16)	Randomised, controlled Prophylaxis during any ALA administration Pre-emptive IV GCV reduced CMV disease Incidence of CMV disease was higher when ALA was used for rejection than for induction
Conti et al. ^[80]	Yes [12]	IV GCV (22) Controls (18)	9 (2) 56 (10)	na na	9 (2) 56 (10)	Randomised, controlled Prophylaxis during any ALA administration Pre-emptive IV GCV reduced CMV disease
Lumbreras et al. ^[81]	No [6]	IV GCV × 14 days (25) Historical controls (25)	12 (3) 52 (13)	100 (1/1) 100 (2/2)	8.3 (2/24) 48 (11/23)	Retrospective comparison Prophylaxis during OKT3 for rejection
Hopt et al. ^[82]	Yes [12]	IV GCV during ALA + 5 days after (36) Historical controls (34)	14 (5) 38 (13)	ns (4) ns (3)	ns ns	Retrospective, pre-emptive prophylaxis versus none Pre-emptive prophylaxis markedly reduced the incidence of CMV disease

ALA = antilymphocyte globulin for induction; **D+/R-** = donor seropositive, recipient seronegative; **GCV** = ganciclovir; **IV** = intravenous; **na** = not applicable; **ns** = not stated; **OKT3** = muromonab-CD3; **R+** = recipient seropositive.

3.1.2 Pre-emptive Prophylactic Regimens

Pre-emptive prophylaxis (table IX) is generally used in SOT recipients at risk for CMV disease, during administration of ALA preparations for induction or for treatment of steroid-resistant episodes of rejection.

Hibberd et al.^[79] reported the results of a multi-centre, randomised trial that compared the incidence of CMV disease in CMV R+ kidney recipients who had received intravenous ganciclovir during ALA administration (for induction and/or rejection) with the incidence in similar kidney recipients who had not received antiviral medications during ALA administration. The group that received ganciclovir had a lower incidence of CMV disease than the control group but the incidence of tissue invasive disease was similar between groups. The patients who had received ALA for rejection had significantly higher incidence of CMV disease than those who had received only ALA induction therapy.

In a similar study, Conti et al.^[80] randomised a group of CMV R+ kidney recipients to receive intravenous ganciclovir or no specific therapy

during ALA administration. The group who had received ganciclovir experienced significantly less CMV disease than the control group.

Lumbreras et al.^[81] retrospectively compared outcomes in liver transplant recipients at risk for CMV disease who had received intravenous ganciclovir during administration of muromonab-CD3 for treatment of rejection with outcomes in a similar group of historical controls who had not received pre-emptive prophylaxis. A significant decrease in symptomatic CMV disease was demonstrated in the ganciclovir group but all of the D+/R- patients developed CMV disease.

The effect of pre-emptive prophylaxis in kidney-pancreas recipients was retrospectively reported.^[82] Outcomes for 34 patients who did not receive pre-emptive prophylaxis were compared with those for a group of 36 individuals who had received intravenous ganciclovir, during (and for 5 days after) each course of ALA therapy, within the first year after transplantation. The incidence of CMV disease was reduced significantly for the patients who had received ganciclovir, and the authors concluded that

pre-emptive ganciclovir prophylaxis during ALA therapy was very effective in preventing CMV disease after kidney-pancreas transplantation.

Summary

Pre-emptive, or targeted, prophylaxis with intravenous ganciclovir was effective in reducing the incidence of CMV disease among patients who received ALA.

3.1.3 Pre-emptive Therapy for Avoidance of CMV Disease

Singh et al.^[83] conducted a randomised, prospective trial comparing efficacy of CMV prophylaxis with that of pre-emptive therapy (table X). A cohort of 47 liver transplant recipients was monitored for CMV infection with shell vial cultures of buffy coat and urine. Twenty-four patients received oral HD aciclovir prophylaxis for 24 weeks and 23 patients received 7 days of pre-emptive intravenous ganciclovir only if a positive culture result was obtained (six patients received eight courses of pre-emptive therapy). At 24 weeks, 42% of the prophylaxis group had CMV isolated by culture, versus 26% of the pre-emptive therapy group, and CMV disease occurred in 29% of the prophylaxis group versus 4%

of the pre-emptive therapy group. CMV disease occurred without prior positive cultures in four of seven cases in the prophylaxis group and in one of one case in the pre-emptive group. The authors concluded that HD aciclovir was ineffective as CMV prophylaxis for liver recipients and that, although pre-emptive therapy based on shell vial culture appeared to reduce the incidence of CMV disease, the shell vial method of monitoring was inadequate for accurate prediction of the occurrence of CMV disease.

With the advent of sensitive, specific tests such as those for antigenaemia and polymerase chain reaction (PCR)-based assays, some centres have begun to use pre-emptive therapy in lieu of prophylaxis and have reported their results with this method of prevention of CMV disease.

Kusne et al.^[84] prospectively monitored a group of 144 adult liver transplant recipients with pp65 antigen (pp65Ag) assay weekly for 3 months, then monthly for a further 3 months. Pre-emptive therapy with intravenous ganciclovir was initiated only if a positive pp65Ag result was obtained and was continued until the assay results became negative. A total of 45% of the patients never had a positive

Table X. Pre-emptive therapy for cytomegalovirus (CMV)

Study	Follow-up (mo)	Monitoring	Treated if	Treatment	CMV disease [% (no.)]	D+/R- [% (no.)]	R+ [% (no.)]	Comments
Singh et al. ^[83]	6	Shell vial cx Shell vial cx	Cx positive Symptomatic	IV GCV × 7 days 24wk prophylaxis (HD ACV)	4.3 (1/23) 29 (7/24)	100 (2/2) 50 (1/2)	0 (0/20) 23 (5/22)	Liver, randomised: prophylaxis vs pre-emptive therapy CMV disease without prior positive cultures in <i>both</i> groups
Kusne et al. ^[84]	6+	pp65Ag	R-: pp65Ag+ R+: pp65Ag >100 cells/10 000 leukocytes	IV GCV until pp65Ag-	8 (12/144)	21 (5/24) na	na 6.4 (7/110)	Liver, observation D-/R- no disease but 2/10 treated for pp65Ag+
Egan et al. ^[85]	Varied	CMV Ag	CMV antigenaemia in >50/200 000 PMNL	IV GCV × 21 days	37 (7/19)	ns	ns	CMV-at-risk heart ± lung; pre-emptive vs symptomatic treatment
		CMV Ag	Symptomatic	Treatment at clinician's discretion	78 (14/18)	ns	ns	No tissue-invasive disease with pre-emptive vs five cases in controls

Ag = antigen; **cx** = culture; **D+/R-** = donor seropositive, recipient seronegative; **D-** = donor seronegative; **HD ACV** = oral aciclovir >3 g/day; **IV GCV** = intravenous ganciclovir; **na** = not applicable; **ns** = not stated; **PMNL** = peripheral blood polymorphonuclear leukocytes; **R+** = recipient seropositive.

pp65Ag result and did not receive antiviral treatment. The remaining 55% of patients had a positive pp65Ag result and were treated pre-emptively, but 8.3% of the patients experienced CMV disease despite pre-emptive therapy. A total of 21% of the D+/R- recipients (30% of the high-risk patients who had received pre-emptive treatment), 6.4% of the R+ recipients (12% of the moderate-risk patients who had received pre-emptive treatment), and none of the ten D-/R- patients (two had been treated for a positive pp65Ag result) experienced an episode of CMV disease. The estimated cost of the pre-emptive therapy, including monitoring costs, was less than the estimated cost of universal prophylaxis for 144 patients, and the authors concluded that pre-emptive therapy guided by pp65Ag monitoring was a useful and cost-effective strategy for prevention of CMV disease.

Egan et al.^[85] compared CMV-related outcomes for a group of 39 heart, lung and heart-lung recipients at risk for CMV disease who were monitored with CMV antigenaemia testing. Nineteen recipients were included in a treatment study and received intravenous ganciclovir for 21 days (if this result was obtained within 120 days of transplant) for high-level CMV antigenaemia. Outcomes for these patients were compared with those of a group of 18 similar patients who had also been monitored with CMV antigenaemia testing but had been treated at the clinician's discretion, in the absence of knowledge regarding the antigenaemia results. All high-risk (D+/R-) patients received prophylactic CMV Ig. CMV antigenaemia was monitored weekly for 6 weeks, then fortnightly to week 12, then monthly thereafter. A total of 81% of the patients developed positive CMV antigenaemia at any level. Of the patients in the pre-emptive group, 53% developed high-level antigenaemias compared with 50% of the control recipients. Symptomatic CMV infection had developed in 37% of the pre-emptive group versus 78% of the control group at 120 days after transplant. During the same period, five patients developed tissue invasive disease in the control group versus none in the pre-emptive therapy group. CMV duodenitis developed late in one patient in the pre-

emptive group. This patient had developed high-level antigenaemia prior to disease onset but had not been treated because the level was obtained after the 120-day pre-emptive treatment period. The authors acknowledge the limitations of the study (small population, retrospective analysis) and state that long-term follow-up is needed to determine whether pre-emptive therapy will prevent the immunological consequences of subclinical CMV infection.

Summary

Pre-emptive therapy for prevention of CMV disease is an attractive concept, as medications are administered only to patients at documented risk of disease. In theory, this method reduces both total costs of CMV-related care and the risk of emergence of resistance to antiviral medications; however, this method is also associated with some risks that are not present with use of universal prophylactic regimens. CMV replication is associated with additional immunosuppressive effects and with rejection, even when active CMV infection is clinically inapparent. In addition, patient compliance with monitoring protocols, effective laboratory staff and assays, and the ability to respond quickly to evidence of viral replication are paramount to the success of a pre-emptive therapy strategy.

As with prophylactic regimens, the higher-risk patients receiving pre-emptive therapy regimens have higher rates of CMV disease than the lower-risk patients.

3.2 Herpes Simplex Virus

The herpes simplex viruses types 1 and 2 are alpha herpesviruses. Worldwide, more than 90% of adults have antibody to HSV by their fifth decade;^[86] in the US, 50–70% of adults are HSV-1 seropositive and 20–50% of adults have latent HSV-2 infection.^[16] Similar to CMV, HSV seroprevalence varies with age and socioeconomic status.^[16] Transmission occurs by direct contact with the mucosal surfaces and oral and genital secretions of actively infected individuals.^[86] Transmission of HSV also occurs in the absence of clinical symptoms because intermittent asymptomatic viral shedding continues after infection.^[87]

After primary infection, HSV replicates in epidermal and dermal cells, and spreads to local sensory or autonomic nerve endings; latency occurs in the nerve ganglia.^[86] The exact mechanism of reactivation is unknown, but reactivation has been associated with ultraviolet light, stress, fever and immunosuppression.^[86]

Clinical manifestations of HSV infection are varied and depend on the anatomic site and the age and immune status of the host. The major morbidity associated with HSV is a result of the frequency of clinically apparent reactivations.^[86] HSV-1 lesions typically occur above the waist (orolabial) and HSV-2 lesions are more common below the waist (anogenital), but either type can occur in either area depending on the original site of contact with the virus.^[87] Typical reactivations present as clustered vesicles on an erythematous base,^[86] which then ulcerate, crust and heal spontaneously within 5–10 days.^[15]

T cell-mediated immune responses are critical for virus containment^[86] and SOT recipients are at increased risk for severe HSV disease. After SOT the vast majority of HSV infections are reactivations that occur within the first few weeks after transplant. Primary HSV infection can rarely be transmitted by an infected donor organ^[88] and HSV seronegative patients can acquire the disease in the community.

HSV reactivation in SOT commonly presents in similar fashion to reactivation in an immunocom-

petent host, but is more frequent, may become more invasive, takes longer to heal and has greater potential for dissemination to visceral organs.^[15] Local spread can result in ulcerative oesophagitis, tracheobronchitis or pneumonitis.^[31,89] Visceral dissemination is usually via HSV viraemia,^[86] and can involve the liver, lungs, adrenal glands, gastrointestinal tract and skin;^[15] this is rare and has a high associated mortality rate.^[88,90] HSV pneumonia is most common in lung and heart-lung transplant recipients^[15] but can occur in other types of SOT, especially if instrumentation (intubation, bronchoscopy) takes place during an active HSV infection.

Fortunately, HSV encephalitis is rare after SOT.^[31] Mucocutaneous HSV is usually self-limited, even after SOT, and rarely fatal. There is no clear detrimental effect of HSV infection on allograft survival.^[15]

The importance of considering prophylaxis for HSV has diminished in view of the widespread practice of CMV prophylaxis, which is also effective in prevention of HSV reactivation. With the recent advent of pre-emptive therapy regimens, the issue of HSV prophylaxis should again be addressed.

Table XI presents data from HSV prophylactic regimens using low doses (600–800 mg/day) of oral aciclovir for periods of 2–12 weeks after SOT.^[91–95] These trials report reductions in rates of symptomatic HSV infection versus placebo or historical con-

Table XI. Herpes simplex virus (HSV) prophylaxis

Study	Follow-up (mo)	Regimen (no. pts)	HSV disease [% (no.)]	Comment
Seale et al. ^[95]	na	PO ACV 600 mg/day × 30 days (19)	0	Randomised, placebo-controlled
		Placebo (21)	52 (11)	Kidney transplant, all HSV R+
Pettersson et al. ^[94]	na	PO ACV 800 mg/day × 28 days (18)	0	Randomised, placebo-controlled
		Placebo (17)	53 (9)	Kidney transplant, all HSV R+
Jirisiritham et al. ^[91]	6	PO ACV 600 mg/day × 60 days (20)	5 (1)	Randomised, controlled
		PO ACV 600 mg/day × 30 days (20)	10 (2)	Kidney transplant, all HSV R+
		Controls (20)	30 (6)	
Carrier et al. ^[93]	12	PO ACV to discharge (58)	9 (5)	Retrospective comparison
		Historical controls (24)	46 (11)	Heart transplant, ?HSV status (serology not obtained)
Arazi et al. ^[92]	6	PO ACV 600 mg/day × 14 days (45)	16 (7)	Retrospective comparison
		Historical controls (10)	80 (8)	Heart transplant, HSV status variable

na = not applicable; PO ACV = oral aciclovir (acyclovir); R+ = recipient seropositive.

trols from 30–50% to 0–10% in kidney recipients and from 46–80% to 9–16% in heart transplant recipients, with persistence of protective effects after discontinuation of prophylaxis. Similar results are incidentally reported in trials of aciclovir,^[51,60] ganciclovir^[60,63] and valaciclovir^[55] for CMV prophylaxis in various organs.

3.3 Varicella-Zoster Virus

VZV is a member of the alpha subgroup of herpesviruses. VZV causes two distinct clinical syndromes, depending on whether infection is primary or reactivation of latent VZV. The primary syndrome, varicella or chickenpox, is a common, highly contagious childhood illness that affects more than 90% of the population by the age of 15 years.^[96] VZV epidemics occur annually in late winter-early spring and household attack rates for susceptible individuals exceed 70%.^[15] Chickenpox is infectious from approximately 2 days prior to rash onset until all of the lesions have crusted (4–5 days).^[96] Transmission probably occurs via respiratory tract secretions.^[97] Asymptomatic primary infection is extremely rare and severity of disease increases with age at infection.^[97] VZV is latent in the dorsal root ganglion.^[98]

The reactivation syndrome for VZV is herpes zoster (shingles), which occurs in more than 20% of the latently infected population, usually in the elderly years; rarely, second episodes of zoster can occur.^[96] Although less contagious than primary VZV, shingles lesions contain transmissible virus until crusted and transmission of virus, via contact with an individual with zoster, can occur to previously unexposed individuals.

Primary VZV after SOT is rare and most commonly seen in the paediatric transplant population because of VZV epidemiology,^[99] but varicella after SOT is usually more extensive, more severe and longer-lasting, and has a higher mortality rate than varicella in the normal host.^[98] Post-transplant varicella can occasionally present as disseminated disease, which has a very high mortality rate, or as isolated hepatitis.^[31] Previously uninfected SOT recipients should avoid contact with actively VZV-

infected individuals and, if exposure does occur, should receive prompt medical attention and varicella-zoster Ig (VZIg) within 96 hours of exposure.

Recurrent VZV disease occurs in 5–15% of patients after SOT, usually after the sixth post-transplant month.^[31] Zoster after SOT is generally uncomplicated and rarely disseminates,^[100] but lesions can involve two or more adjacent dermatomes, can be more extensive than in immunocompetent hosts, and can be haemorrhagic and/or necrotic.^[98] There are also reported cases of second episodes of (primary) varicella after SOT.^[100]

Prophylactic regimens for reactivated VZV are neither practical nor cost effective after SOT because of the late onset of disease and low proportion of affected individuals.^[98] All SOT recipients should receive prompt medical attention and VZIg (or possibly antiviral medications if previously VZV seropositive) immediately after contact with either varicella or zoster.

3.4 Epstein-Barr Virus

EBV is a gamma herpesvirus that is capable of both lytic (replicative) and latent infection. Unlike other herpesviruses, which primarily affect SOT recipients by causing infectious disease complications, EBV has its most significant impact in SOT as the precipitating factor in the development of post-transplant lymphoproliferative disorders (PTLD) [table XII].

In developed countries more than 90% of adults are EBV seropositive and EBV seroprevalence is even greater in underdeveloped nations.^[101] In the US, 85–95% of adults have been infected with EBV.^[16] In immunocompetent hosts, primary EBV infection has a range of manifestations from asymptomatic infection to (rarely) fatal disseminated disease.^[114] EBV infection is acquired by close personal contact with virus-containing oropharyngeal secretions.^[115,116] The incidence of clinically apparent EBV infection increases with age; most EBV infections in children are asymptomatic,^[117] whereas EBV-associated mononucleosis is most common in populations where primary infection is delayed until late adolescence or early adulthood.^[116] Similar to

Table XII. Incidence of post-transplant lymphoproliferative disorders (PTLD) in solid organ transplantation

Organ	Overall [% (no.)]	Reported (%)	References
Kidney	1.3 (27/2017)	0.2–6.5	101–105
paediatric	12 (10/81) [EBV R– 10/46 (22%) vs EBV R+ 0/35 (0%)]	na	106
Liver	2.2 (8/359)	2.1–2.6	104,107
paediatric	5 (2/40) [protocol for PTLD prophylaxis]	na	108
Heart	2.5 (20/813)	1.9–7.2	101,103,107
Pancreas-kidney	5.4 (6/111)	2.7–11	104,107
Lung ± heart	6.5 (24/372)	1.8–20	101,103,107,109–112
paediatric	14 (2/14)	na	109
Intestine	9.4 (3/32)	na	113
paediatric	32 (13/41) [EBV R– 31% (4/13) vs EBV R+ 32% (9/28)]	na	113

EBV = Epstein-Barr virus; na = not applicable; R+ = recipient seropositive; R– = recipient seronegative.

that of other herpesviruses, EBV seroprevalence is higher with lower socioeconomic status.

After primary EBV infection has taken place, ongoing low-grade replication in oropharyngeal epithelium occurs simultaneously with predominantly latent B cell infection,^[101] and B cells are the main site of viral persistence.^[115,117] EBV causes proliferation and immortalisation of infected B cells which is countered in the immunocompetent host by strong humoral and cell-mediated responses to EBV infection.^[101] Proliferation of EBV-infected B cells is normally limited by removal by EBV-specific cytotoxic T cells and natural killer cells.^[107,118]

In SOT the vast majority of active EBV infections are reactivations, and are usually asymptomatic and probably clinically unimportant; however, EBV-associated PTLD, although relatively infrequent compared with other herpesvirus-associated diseases, is a significant and potentially avoidable problem in the SOT population. PTLD is very likely to be a progression of EBV-associated disease, resulting from an uncontrolled proliferation of EBV-infected B cells^[101] that is initially polyclonal and reversible, which may progress if untreated to a monoclonal, EBV-autonomous malignant lymphoma.^[119] Independent of pre-transplant serology, SOT patients who develop PTLD generate higher measurable EBV viral loads than those who do not develop PTLD.^[102]

Like CMV-associated disease, PTLD occurs more often with primary EBV infection than during reactivation of EBV and there is a similar organ-

associated risk hierarchy:^[115] intestine/lung/pancreas > heart/liver > kidney transplant.^[101] The reasons for the differences in attack rates by organ are probably related to similar predisposing factors for CMV- and EBV-related disease: relative amount of lymphoid tissue (CMV, EBV load) per organ^[120] and relative amount of total immunosuppression necessary for successful allograft function.

Primary EBV infection is the most significant risk factor for the development of PTLD,^[28,90] and recipient EBV seronegativity is actually a relative contraindication to some types of organ transplantation at some centres.^[109] Although EBV-naïve patients constitute a small proportion of SOT recipients, approximately 50% of PTLDs are preceded by primary EBV infection,^[119] and the risk of PTLD in EBV R– is ten times higher than that of previously EBV R+.^[115]

Total amount of immunosuppression is also an important risk factor for PTLD.^[102] PTLD is reported to be occurring more frequently^[101,107] and earlier in the post-SOT course^[103] than previously, and the increase in frequency has been incremental with the incorporation of ciclosporin (cyclosporine),^[110] muromonab-CD3 and finally tacrolimus (FK 506) into immunosuppressive regimens.^[108] One group of authors from Portugal^[102] reported that PTLD occurs twice as frequently in North America as in Europe and speculated that this is related to the greater use of induction regimens containing ALA preparations in the former.

Other risk factors reported to be associated with the development of EBV-associated PTLD include high EBV viral load,^[41,102,120-122] CMV seromismatch (D+/R-),^[101] preceding symptomatic CMV infection,^[13,28] high degree of HLA mismatch between donor and recipient,^[123] and occurrence of retransplantation.^[115] The greatest risk period for PTLD is within the first year after SOT. Monitoring of EBV loads in high-risk patients is a technique which, if standardised, could prove useful in preventing PTLD or in pre-emptively treating it by reducing immunosuppression. Wadowsky et al.^[124] recently reported on correlation of whole-blood EBV DNA loads measured by PCR with peripheral blood lymphocyte DNA loads. They concluded that testing whole blood is an acceptable alternative to the more complicated technique of testing peripheral blood lymphocytes for EBV DNA. In the light of these observations, potential opportunities for prophylactic and/or pre-emptive strategies exist, and we reviewed several studies that seem to support the use of prophylactic strategies for EBV-associated PTLD.

At the Mayo Clinic in Minnesota, Walker et al.^[107] studied the occurrence of PTLD among a group of nonrenal transplant recipients to assess pre- and post-transplant risk factors. A total of 381 SOT recipients were identified: 281 liver, 43 heart, 37 pancreas-kidney and 20 lung transplant recipients. Pre-transplant risk factors assessed included EBV recipient serology as well as CMV serology for both donor and recipient. Post-transplant maintenance regimens included ciclosporin, azathioprine and corticosteroids; routine use of ALA for induction was not consistent. Categorisation of ALA use was stratified: none, ALA induction only, muromonab-CD3 induction only, muromonab-CD3 for rejection only, or muromonab-CD3 for rejection after ALA induction. All patients received oral aciclovir 600 mg/day for 1–2 months after SOT, and CMV D+/R- heart and lung recipients received either intravenous ganciclovir for 14 weeks after SOT or sequential prophylaxis with intravenous ganciclovir for 14 days followed by oral HD aciclovir for an additional 12 weeks. Fourteen cases of PTLD were identified.

There were three cases among 361 EBV R+ patients and nine among 18 EBV R- patients; the original EBV serologies were incomplete for two of the cases. The risk of PTLD in the presence of the various risk factors was calculated. In the absence of other risk factors, the incidence of PTLD was 24 times higher for patients who were EBV R- than those who were EBV R+. Administration of muromonab-CD3 for rejection and CMV D+/R- serostatus each further amplified the risk 5- to 6-fold, and all three risk factors together (EBV R-, muromonab-CD3 for rejection, CMV D+/R-) acted synergistically to increase the risk of PTLD by a factor of 592. The authors concluded that two important risk factors that together increased PTLD risk by more than 100-fold (EBV R-, CMV R-) could be identified before the occurrence of SOT. EBV and CMV seronegativity, along with muromonab-CD3 administration for rejection, were independent risk factors for PTLD, and the three factors when present in the same individual acted synergistically to markedly increase the risk of PTLD. They also indicated that routine ALA induction was not found to significantly increase the risk of PTLD.

Levine et al.^[111] reviewed the records of 109 (primarily adult) lung transplant recipients to evaluate the incidence of and risk factors for development of PTLD. Sixty patients received muromonab-CD3 induction, all of the patients received maintenance immunosuppression consisting of ciclosporin, azathioprine and corticosteroids, and all of the patients received intravenous ganciclovir for 14 days, two doses of CMVig and oral aciclovir (2.4 g/day for 3 months, then 1.2 g/day for life). EBV antibody screening via IgG and IgM was performed monthly (or at clinic visits) after discharge. Two cases of PTLD were identified among the 109 lung transplant recipients (1.8%), both were adults. Five patients were EBV R- prior to transplant; all five seroconverted following transplant, and one of the cases of PTLD was among this group. The other case occurred in a previously EBV seropositive recipient. Both patients had received muromonab-CD3 induction but neither had experienced episodes

of rejection prior to the onset of PTLD. The incidence rate of PTLD in this group of lung transplant recipients was low compared with the usual rates reported in the literature, and the authors postulated that this was due to their use of lifelong aciclovir prophylaxis and the resulting prolonged suppression of EBV replication. They recommended this approach in EBV R⁻ lung transplant recipients.

Darenkov et al.^[125] retrospectively analysed the effect of antiviral prophylaxis on the development of PTLD in a group of 377 kidney, pancreas and liver SOT recipients. They compared 179 consecutive recipients (1990–3) who had not received antiviral prophylaxis with 198 similar SOT recipients (1994–6) who had received antivirals during ALA therapy. Standard immunosuppression consisted of ciclosporin and corticosteroids, and was augmented in some patients with azathioprine and/or ALA induction therapy. Pre-emptive prophylaxis consisted of intravenous ganciclovir for patients at risk for CMV disease and oral HD aciclovir for CMV D⁻/R⁻ patients, and was administered throughout the period of ALA administration and discontinued concomitantly with ALA discontinuation. PTLD developed in 3.9% of the early cohort versus in 0.5% of the later cohort ($p < 0.03$). In the early cohort, PTLD occurred in seven patients, all of whom were EBV R⁺, had received at least one course of muromonab-CD3 for rejection and were diagnosed within 6 months of transplantation (30–123 days). PTLD occurred in one patient in the later cohort, a 15-year-old liver transplant recipient who was EBV R⁻ and CMV R⁺, and who had received a liver from a donor who was both EBV and CMV seropositive. This patient had experienced recurrent episodes of biopsy-proven, refractory rejection that required several courses of ALA and muromonab-CD3. The authors concluded that pre-emptive antiviral prophylaxis during ALA administration was effective in reducing the incidence of PTLD and recommended this approach.

3.4.1 Summary

PTLD adversely affects graft and patient survival after organ transplantation. Risk factors for this disease are EBV D⁺/R⁻, administration of ALA for

rejection therapy and young age at transplantation. PTLD is more common among intestine and lung transplant recipients. The highest risk period for PTLD is within the first year after SOT. Antiviral agents that could be effective are the same as the agents used for CMV prophylaxis. Although some centres are attempting to provide prophylaxis against EBV, there is insufficient evidence to recommend any particular prophylactic regimen. Monitoring methods are not well developed, but have potential for detection of upregulation of EBV replication.

4. Hepatitis Viruses

Despite the ability to cause similar syndromes with clinically apparent infection, the viruses in the hepatitis virus group are genetically and epidemiologically diverse. HBV and HCV are important pathogens in the SOT population, but the diseases produced by these viruses are more important as indications for transplantation than as consequences of receiving a transplanted organ. HAV-related disease is a rare indication for transplantation and the consequences of HAV infection after SOT are debatable. So-called 'prophylaxis' for recurrent HBV and HCV after liver transplantation is controversial, suppressive rather than preventive and potentially lifelong, and full discussion of the regimens is beyond the scope of this review. We include brief overviews of these viruses for the sake of completeness.

4.1 Hepatitis A Virus

HAV is a non-enveloped (RNA-containing) picornavirus that is hyperendemic in developing countries.^[126] Transmission is by the faecal-oral route and clinical severity of HAV disease is related to age at infection. Childhood infection is usually asymptomatic or mild, but >70% of HAV acquired in adulthood is symptomatic.^[127] The majority of severe disease and HAV-related mortality occur in adults who contract the disease beyond the age of 50 years.^[128] Acute liver failure secondary to HAV is uncommon,^[127] chronic carriage does not occur, and development of antibody after infection provides

complete and long-lasting protection against reinfection.^[128] The clinical course of HAV is not thought to be more severe in immunocompromised hosts,^[128] although there is some evidence that HAV disease can be more severe in the setting of chronic liver disease.^[127] Pre- or post-exposure prophylaxis can be provided against HAV with IVIg administration,^[126] if vaccination is inconvenient or will not provide timely protection, and can be given simultaneously with vaccine.

4.2 Hepatitis B Virus

HBV is a DNA-containing hepadnavirus that is transmitted by infected blood and body fluids as well as perinatally;^[129] HBV is endemic in some countries,^[130] and in up to 30% of cases of HBV infection there are no identifiable risk factors.^[129] HBV infection can be asymptomatic, especially if acquired perinatally or in early childhood, but long-term adverse consequences of HBV infection are inversely related to age at acquisition of infection. Perinatal HBV infection carries up to 90% chance of chronic infection but the risk declines to 5–10% if HBV infection is acquired in adolescence or adulthood.^[129]

Chronic HBV infection confers a 25–40% lifetime risk for death due to liver failure or hepatocellular carcinoma, and chronic liver disease due to HBV is among the ten most common indications for liver transplantation in adults.^[131] Recurrence of active HBV liver disease occurs after liver transplantation in more than 90% of cases and is associated with poor outcomes.^[131–133] Administration of HBV Ig (HBIG) dramatically improves outcomes, although breakthroughs do occur.^[133] HBIG is very expensive and the general consensus is that administration must continue indefinitely to maintain effectiveness.^[131,132] The antiviral medications famciclovir and lamivudine are currently being evaluated as adjuncts to and substitutes for HBIG administration; these medications appear to be partially effective, but resistance develops frequently^[134] and outcomes with these agents are not as consistent as with use of HBIG.^[133] Some recent promising data on the use of adefovir dipivoxil in the treatment of HBV^[135,136]

have led to its successful use after liver transplantation to prevent recurrence.^[137] Combination antiviral therapy with two or more agents may ultimately prove to be the most effective approach in order to minimise the development of drug resistance.^[138]

The effect of chronic HBV infection on non-liver SOT is largely unknown. Medium-term outcomes after kidney^[130] and heart^[139] transplantation in the setting of chronic HBV infection are relatively good, and SOT in the setting of chronic HBV infection is generally contraindicated only for non-hepatic organs if cirrhosis or active viral replication (HBV DNA detected in blood by PCR) is present.^[130]

4.3 Hepatitis C Virus

HCV is an enveloped, single-stranded, RNA-containing virus that is related to the Flaviviridae.^[140] Since the development of later-generation serological assays and PCR-based methods of detection, transmission by blood transfusion or organ transplantation is much less common, and injection drug abuse is currently the most frequent mode of acquisition of HCV infection.^[140] HCV infection has also been associated with intranasal cocaine use, tattooing^[140] and body piercing; less than 5% of HCV transmission occurs sexually or intrafamilially, and in up to 40% of community-acquired HCV infections no risk factors can be identified.^[141]

Acute HCV infection is largely asymptomatic,^[140] but chronicity occurs in 85% and chronic liver disease occurs in 20% after infection.^[141] Chronic HCV infection carries an increased risk for development of cirrhosis and hepatocellular carcinoma, and is currently the leading indication for liver transplantation in the US.^[127]

After orthotopic liver transplantation (OLT) for chronic HCV disease, recurrence of HCV is almost universal and usually occurs within 1 month after OLT.^[141,142] The long-term effect of recurrent HCV after liver transplantation is largely unknown, but 5-year outcomes appear comparable to those observed in patients transplanted for non-HCV-related liver disease.^[143] After OLT, serological testing for HCV is unreliable and serum HCV-RNA levels are not

correlated with histological severity of HCV-induced liver damage.^[141]

Similarly, 5-year survival rates for non-hepatic SOT in the setting of HCV infection appear to be comparable to those among non-HCV-infected SOT recipients,^[139] and transplantation of HCV Ab+ organs is considered acceptable under some circumstances.^[141] Non-hepatic transplantation for HCV-infected candidates is strongly contraindicated only if biopsy evidence of significant liver disease is present.^[141]

Treatment for HCV currently consists of administration of 6 months or more of interferon, is successful in only a fraction of patients, and success of therapy depends in part on the genetic type of HCV. Some promising data exist on the use of interferon and ribavirin therapy as prophylaxis of recurrent HCV after transplantation.^[144] Treatment for HCV recurrence after liver transplantation is even less successful and indications for this are controversial;^[141,142] studies regarding the utility of post-transplant treatment of HCV are currently in progress.

5. Community Respiratory Viruses

Community-acquired respiratory viruses include respiratory syncytial virus, adenovirus, parainfluenza virus and influenza virus. Although all of these viruses can affect SOT recipients more severely than immunocompetent patients, prophylactic medications are available only for influenza, and we limit the discussion of these viruses to influenza.

Influenza is an enveloped, RNA-containing orthomyxovirus that occurs seasonally and does not exhibit latency. There are three types of influenza virus:^[145] influenza A is associated with pandemics and can cause significant morbidity (and mortality) in all hosts; influenza B causes severe disease mainly in the elderly; and influenza C causes mild disease and does not occur seasonally. Influenza A and B occur in yearly outbreaks,^[146] in temperate climates, influenza occurs almost exclusively in winter months,^[147] but it occurs year-round in the tropics.^[145] Transmission occurs person-to-person via small-particle aerosols from the respiratory tract of clinically symptomatic individuals.^[145] Influenza in-

fection is controlled by both antibody and cytotoxic T cell responses,^[148] both of which play a role in recovery from and resistance to reinfection. Influenza can progress to pneumonia which is not uncommonly complicated by bacterial superinfection, especially with *Streptococcus pneumoniae* or *Staphylococcus aureus*.^[149] This accounts for a large proportion of the associated lower respiratory tract influenza disease.

Influenza infection after SOT is also acquired by person-to-person contact and, thus, can occur at any timepoint in relation to transplantation.^[147] Antiviral medications for prevention of influenza are administered as post-exposure prophylaxis, rather than in relation to any specific high-risk period or during a high-risk intervention. During epidemic periods of influenza, transplant populations experience a relatively high frequency of infection,^[148] although data are sparse and sometimes conflicting, the more prevalent (and prudent) view is that influenza affects immunosuppressed SOT recipients more adversely^[150,151] than immunocompetent individuals. In addition to morbidity associated with influenza-related infectious syndromes, community-acquired respiratory viruses (including influenza) have been associated with allograft rejection, especially bronchiolitis obliterans after lung transplantation.^[149,152]

Risk factors for severe influenza after SOT are age <1 year, onset within 3 months of SOT and onset during therapy for rejection.^[148] Influenza vaccine is safe and readily available, and therefore recommended yearly after SOT. Poor antibody response to vaccine has been seen in SOT recipients compared with healthy controls;^[153] still, most of the severe cases of influenza reported in SOT recipients have occurred in individuals without prior immunisation.^[148]

Currently two types of anti-influenza medication are available for prophylaxis: the M2 matrix protein inhibitors amantadine and rimantadine, and the newly released neuraminidase inhibitors oseltamivir and zanamivir. Neither class has been tested extensively in immunocompromised patients in general nor in SOT recipients in particular, and interactions with transplant medications are not characterised.^[148]

M2 inhibitors are effective only against influenza A.^[154] Acquisition of resistance to these agents is rapid when they are used for treatment of influenza or for prophylaxis in a household contact of a treated source patient, but the M2 inhibitors have been relatively effective when used for prophylaxis to prevent influenza. The M2 inhibitors are indicated for both prophylaxis and treatment of influenza A.^[151]

The neuraminidase inhibitors are active against both influenza A and B types.^[155] They are better tolerated and have less potential for emergence of resistance than the M2 inhibitors,^[151] but because of the 'newness' of these agents, they have not been widely tested and efficacy in immunocompromised patients has not been assessed.^[155,156]

6. Conclusion

Infection and rejection are the main stumbling blocks faced by all SOT recipients. Immunosuppression is necessary for successful allograft function but predisposes SOT recipients to more severe consequences of exposure to microbial pathogens. Viral pathogens, in particular, are a problem for this population for several reasons. Transplant immunosuppressive medications specifically target the cellular arm of the immune system, which is the arm that causes allograft rejection but is also responsible for most of the effective avoidance of harmful viral effects.

Viral pathogens that are capable of latent and/or chronic infection have the greatest effect on morbidity and mortality after SOT, and it is, therefore, not surprising that herpesviruses cause the majority of viral illness in the transplant population. Viral disease that occurs after SOT is usually directly related to the transplant process itself. Adverse consequences of viral infection generally vary directly with intensity of immunosuppression and inversely with the extent of the host immune system's previous experience with the viral pathogen in question. Reduction of immunosuppression is, therefore, frequently necessary to allow a patient to effectively combat a viral infection. Viral infection can also, in

and of itself, increase the overall state of immunosuppression.

The herpesviruses are a particular problem after SOT for many reasons, including their capacity for latency and reactivation, their high seroprevalence among adult populations, the potentially severe consequences of primary infection under immunosuppression, and our general lack of knowledge regarding the mechanisms of pathology for the indirect effects of these viruses. Regardless of the prophylactic regimens already in use, more information and testing are required in reference to all aspects of viral illness in SOT. The patients at highest risk apparently benefit the least from prophylactic regimens and these patients are also those at highest risk for development of antiviral-resistant virus.

Prevention of active viral infection by antiviral prophylaxis is successful only if the overall risks of administration of the antiviral medication are offset by the overall benefit to the SOT recipient by avoidance of the adverse effects caused by the virus. In order to recommend a prophylactic strategy, risk factors and risk periods for viral illness, indirect effects of viral replication, and cost-effectiveness of a proposed regimen must be taken into consideration.

CMV is the most important microbial pathogen affecting the SOT population and evidence for beneficial effects of CMV prevention is abundant. Despite the lack of studies with definitive, statistically significant increases in survival and the paucity of studies comparing the pre-emptive therapy approach to prophylaxis, clinicians in most centres consider the trends in the literature sufficient to support the use of prophylactic strategies against CMV. These strategies are generally stratified according to serostatus, type of organ transplanted and amount of additional immunosuppression needed for successful allograft function. For high-risk, serodiscordant (CMV D+/R-) transplantation of all organs, a 'universal' prophylactic approach should be used because the majority of these patients will experience CMV disease in the absence of prophylaxis. Among the high-risk patients, the highest-risk organ recipients (intestine, lung, pancreas) should optimally re-

ceive combination regimens with long-term (>90 days) ganciclovir or valganciclovir and CMVIG. High-risk heart and liver recipients should receive long-term ganciclovir or valganciclovir prophylaxis, with or without CMVIG, and high-risk kidney recipients should receive valganciclovir, ganciclovir or valganciclovir for 3 months after transplantation.

Recipients who are at moderate risk by serostatus but have received high-risk organs should also receive long-term antiviral prophylaxis, with or without addition of CMVIG. Previously CMV seropositive heart, liver and kidney recipients could also benefit from long-term ganciclovir or valganciclovir prophylaxis, especially if pre-emptive therapy approaches are not feasible because of a lack of patient or laboratory compliance with surveillance, reporting and rapid treatment of positive results. If patients are accessible, and laboratory and ancillary personnel are reliable, these moderate-risk recipients could be managed with a pre-emptive therapy approach. All recipients at risk for CMV disease should also receive pre-emptive prophylaxis with intravenous ganciclovir during administration of antilymphocyte preparations, especially during ALA therapy for rejection.

Clinical manifestations of HSV occur in previously HSV-infected SOT recipients, most commonly during the first month or two after transplantation, and are likely to be more frequent and severe than those in the immunocompetent host. All CMV prophylactic antiviral regimens also prevent HSV recurrence and no additional measures are needed if CMV prophylaxis is used. If CMV prophylaxis is not used, HSV seropositive recipients should receive 4–8 weeks of aciclovir, valganciclovir or famciclovir to prevent clinically relevant recurrences of HSV. HSV prophylaxis should also be considered during periods of intensified immunosuppression (treatment for episodes of rejection) and during episodes of (non-CMV) severe illness.

EBV prophylaxis has not yet been extensively investigated but should certainly be considered for the patients at high risk for EBV-associated PTLT. Effective antiviral regimens would consist of the same agents as those used for CMV prophylaxis and

risk stratification would be assessed by similar hierarchies. The recipients at highest risk for PTLT are those who receive EBV serodiscordant (EBV D+/R-) transplants, those who receive organs with large amounts of lymphoid tissue (intestine, lung and pancreas), and those who receive organs that require more intense immunosuppressive regimens for successful function (also intestine, lung and pancreas). Patients who receive ALA for treatment of rejection are also at higher risk for EBV-related PTLT, and paediatric SOT recipients should be considered at higher risk than their adult counterparts with respect to all predisposing factors.

Influenza prophylaxis should be administered to SOT recipients, in addition to annual vaccination, in circumstances such as influenza epidemics and nosocomial outbreaks and after exposure to a symptomatic individual during the 'flu season'.

Great strides have been made over a relatively short period, such that organ transplantation is a viable treatment option for end-stage organ disease, but the ongoing organ shortage limits this option, and infection and rejection continue to be the main causes of morbidity and mortality among these patients. More information is certainly required regarding the pathogenicity of EBV and surrogate markers of progression to PTLT, and clinical trials are warranted for utility of prophylactic and pre-emptive strategies for prevention.

Acknowledgements

Dr Snyderman has had consulting relationships with MedImmune, Roche and GlaxoWellcome. Dr Slifkin was supported by a grant from MedImmune while writing this manuscript. Dr Doron was supported by NIH training grant number T32 AI07329.

References

1. Marusawa H, Uemoto S, Hijikata M, et al. Latent hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. *Hepatology* 2000; 31 (2): 488-95
2. EBPG (European Expert Group on Renal Transplantation), European Renal Association, European Society for Organ Transplantation (ESOT). European best practice guidelines for renal transplantation (part 1). *Nephrol Dial Transplant* 2000; 15 Suppl. 7: 1-85
3. Burroughs M, Moscona A. Immunization of pediatric solid organ transplant candidates and recipients. *Clin Infect Dis* 2000; 30 (6): 857-69

4. Snyderman DR, Werner BG, Dougherty NN, et al. Cytomegalovirus immune globulin prophylaxis in liver transplantation: a randomized, double-blind, placebo-controlled trial. The Boston Center for Liver Transplantation CMVIG Study Group. *Ann Intern Med* 1993; 119 (10): 984-91
5. Leads from the MMWR: varicella-zoster immune globulin for the prevention of chickenpox. *JAMA* 1984; 251 (11): 1401, 1405, 1409
6. Cirera I, Mas A, Salmeron JM, et al. Reduced doses of hepatitis B immunoglobulin protect against hepatitis B virus infection recurrence after liver transplantation. *Transplant Proc* 2001; 33 (4): 2551-3
7. Honaker MR, Shokouh-Amiri MH, Vera SR, et al. Evolving experience of hepatitis B virus prophylaxis in liver transplantation. *Transpl Infect Dis* 2002; 4 (3): 137-43
8. Riddell SR, Watanabe KS, Goodrich JM, et al. Restoration of viral immunity in immunodeficient humans by the adoptive transfer of T cell clones. *Science* 1992; 257 (5067): 238-41
9. Cheeseman SH, Rubin RH, Stewart JA, et al. Controlled clinical trial of prophylactic human-leukocyte interferon in renal transplantation: effects on cytomegalovirus and herpes simplex virus infections. *N Engl J Med* 1979; 300 (24): 1345-9
10. Cheeseman SH, Henle W, Rubin RH, et al. Epstein-Barr virus infection in renal transplant recipients: effects of antithymocyte globulin and interferon. *Ann Intern Med* 1980; 93 (1): 39-42
11. Kontoyiannis DP, Rubin RH. Infection in the organ transplant recipient: an overview. *Infect Dis Clin North Am* 1995; 9: 811-22
12. Paya CV. Prevention of cytomegalovirus disease in recipients of solid-organ transplants. *Clin Infect Dis* 2001; 32 (4): 596-603
13. Paya CV. Defining an optimal regimen for cytomegalovirus prophylaxis in organ transplant recipients. *Transplant Proc* 1996; 28 (6 Suppl. 2): 9-11
14. Patel R, Paya C. Cytomegalovirus infection and disease in solid organ transplant recipients. In: Bowden RA, Ljungman P, Paya C, editors. *Transplant infections*. Philadelphia (PA): Lippencott-Raven, 1998: 229-44
15. Gnann JW. Other herpesviruses: herpes simplex virus, varicella-zoster virus, human herpesvirus types 6, 7 and 8. In: Bowden RA, Ljungman P, Paya CV, editors. *Transplant infections*. Philadelphia (PA): Lippencott-Raven, 1998: 265-85
16. Strauss SE. Introduction to *Herpesviridae*. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. Philadelphia (PA): Harcourt Health Sciences, 2000: 1557-64
17. Koneru B, Tzakis AG, DePuydt LE, et al. Transmission of fatal herpes simplex infection through renal transplantation. *Transplantation* 1988; 45 (3): 653-6
18. Dummer JS, Armstrong J, Somers J, et al. Transmission of infection with herpes simplex virus by renal transplantation. *J Infect Dis* 1987; 155 (2): 202-6
19. Riley Jr HD. History of the cytomegalovirus. *South Med J* 1997; 90 (2): 184-90
20. Nankervis GZ, Kumar ML. Diseases produced by the cytomegalovirus. *Med Clin North Am* 1978; 62 (5): 1021-35
21. American Academy of Pediatrics. Cytomegalovirus infection. In: Peter G, editor. 1997 Redbook: report of the Committee on Infectious Diseases. Elk Grove Village (IL): American Academy of Pediatrics, 1997: 187-91
22. Hahn G, Jores R, Mocarski ES. Cytomegalovirus remains latent in a common precursor of dendritic and myeloid cells. *Proc Natl Acad Sci U S A* 1998; 95 (7): 3937-42
23. Smith SR, Butterly DW, Conlon PJ, et al. Incidence of cytomegalovirus disease in renal transplantation without antilymphocyte induction: is prophylaxis necessary? *Transplant Proc* 1998; 30 (5): 2097-9
24. Sagedal S, Nordal KP, Hartmann A, et al. A prospective study of the natural course of cytomegalovirus infection and disease in renal allograft recipients. *Transplantation* 2000; 70 (8): 1166-74
25. Stratta RJ. Clinical patterns and treatment of cytomegalovirus infection after solid-organ transplantation. *Transplant Proc* 1993; 25 Suppl. 4: 15-21
26. Grossi P, Minoli L, Percivalle E. Clinical and virological monitoring of human cytomegalovirus infection in 294 heart transplant recipients. *Transplantation* 1995; 59: 847-51
27. Smyth RL, Scott JP, Borysiewicz LK. Cytomegalovirus infection in heart-lung transplant recipients: risk factors, clinical associations, and response to treatment. *J Infect Dis* 1991; 164: 1045-50
28. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998; 338 (24): 1741-51
29. Legendre C, Thervet E. Cytomegalovirus prophylaxis in solid organ transplant recipients: the issues. *Transplant Proc* 2000; 32 (2): 377-8
30. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. *Clin Infect Dis* 2002; 34 (8): 1094-7
31. Patel R, Paya CV. Infections in solid-organ transplant recipients. *Clin Microbiol Rev* 1997; 10 (1): 86-124
32. Manez R, Kusne S, Green M, et al. Incidence and risk factors associated with the development of cytomegalovirus disease after intestinal transplantation. *Transplantation* 1995; 59: 1010-4
33. Kim WR, Badley AD, Wiesner RH, et al. The economic impact of cytomegalovirus infection after liver transplantation. *Transplantation* 2000; 69 (3): 357-61
34. Kanj SS, Sharara AI, Clavien PA, et al. Cytomegalovirus infection following liver transplantation: review of the literature. *Clin Infect Dis* 1996; 22 (3): 537-49
35. Snyderman DR. Infection in solid organ transplantation. *Transpl Infect Dis* 1999; 1 (1): 21-8
36. Toupance O, Bouedjoro-Camus MC, Carquin J, et al. Cytomegalovirus-related disease and risk of acute rejection in renal transplant recipients: a cohort study with case-control analyses. *Transpl Int* 2000; 13 (6): 413-9
37. Dickenmann MJ, Cathomas G, Steiger J, et al. Cytomegalovirus infection and graft rejection in renal transplantation. *Transplantation* 2001; 71 (6): 764-7
38. Madden BP. Late complications after cardiac transplantation. *Br Heart J* 1994; 72: 89-91
39. Duncan SR, Grgurich WF, Iacono T. A comparison of ganciclovir and acyclovir to prevent cytomegalovirus after lung transplantation. *Am J Respir Crit Care Med* 1994; 150: 146-52
40. Keenan RJ, Lega ME, Dummer JS. Cytomegalovirus serologic status and postoperative infection correlated with the risk of developing chronic rejection after pulmonary infection. *Transplantation* 1991; 51: 433-8
41. Tolkoff-Rubin NE, Rubin RH. Viral infections in organ transplantation. *Transplant Proc* 1998; 30 (5): 2060-3
42. Noble S, Faulds D. Ganciclovir: an update of its use in the prevention of cytomegalovirus infection and disease in transplant recipients. *Drugs* 1998; 56 (1): 115-46

43. Brayman KL, Stephanian E, Matas AJ. Analysis of infectious complications occurring after solid organ transplantation. *Arch Surg* 1992; 127: 38-48
44. Balfour HH. Management of cytomegalovirus disease with antiviral drugs. *Rev Infect Dis* 2004; 12 Suppl. 7: s849-60
45. Hayden FG. Antiviral drugs (other than antiretrovirals). In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. Philadelphia (PA): Harcourt Health Sciences, 2000: 460-91
46. Ommrod D, Scott LJ, Perry CM. Valaciclovir: a review of its long term utility in the management of genital herpes simplex virus and cytomegalovirus infections. *Drugs* 2000; 59 (4): 839-63
47. Limaye AP, Raghu G, Koelle DM, et al. High incidence of ganciclovir-resistant cytomegalovirus infection among lung transplant recipients receiving preemptive therapy. *J Infect Dis* 2002; 185 (1): 20-7
48. Limaye AP, Corey L, Koelle DM, et al. Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. *Lancet* 2000; 356 (9230): 645-9
49. Pescovitz MD, Rabkin J, Merion RM, et al. Valganciclovir results in improved oral absorption of ganciclovir in liver transplant recipients. *Antimicrob Agents Chemother* 2000; 44 (10): 2811-5
50. Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant* 2004; 4 (4): 611-20
51. Balfour HH, Chase BA, Stapleton JT. A randomized placebo-controlled trial of oral acyclovir for the prevention of cytomegalovirus disease in recipients of renal allografts. *N Engl J Med* 1989; 320: 1381-7
52. Pouteil-Noble C, Megas F, Chapuis F, et al. Cytomegalovirus prophylaxis by ganciclovir followed by high-dose acyclovir in renal transplantation: a randomized, controlled trial. *Transplant Proc* 1996; 28 (5): 2811
53. Brennan DC, Garlock KA, Singer GG, et al. Prophylactic oral ganciclovir compared with deferred therapy for control of cytomegalovirus in renal transplant recipients. *Transplantation* 1997; 64 (12): 1843-6
54. Flechner SM, Avery RK, Fisher R, et al. A randomized prospective controlled trial of oral acyclovir versus oral ganciclovir for cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Transplantation* 1998; 66 (12): 1682-8
55. Lowance D, Neumayer HH, Legendre CM, et al. Valaciclovir for the prevention of cytomegalovirus disease after renal transplantation: International Valaciclovir Cytomegalovirus Prophylaxis Transplantation Study Group. *N Engl J Med* 1999; 340 (19): 1462-70
56. Badley AD, Seaberg EC, Porayko MK, et al. Prophylaxis of cytomegalovirus infection in liver transplantation: a randomized trial comparing a combination of ganciclovir and acyclovir to acyclovir. *NIDDK Liver Transplantation Database. Transplantation* 1997; 64 (1): 66-73
57. Martin M, Manez R, Linden P. A prospective randomized trial comparing sequential ganciclovir-high dose acyclovir to high dose acyclovir for prevention of cytomegalovirus disease in adult liver transplant recipients. *Transplantation* 1994; 58: 779-85
58. Green M, Kaufmann M, Wilson J, et al. Comparison of intravenous ganciclovir followed by oral acyclovir with intravenous ganciclovir alone for prevention of cytomegalovirus and Epstein-Barr virus disease after liver transplantation in children. *Clin Infect Dis* 1997; 25 (6): 1344-9
59. King SM, Superina R, Andrews W, et al. Randomized comparison of ganciclovir plus intravenous immune globulin (IVIG) with IVIG alone for prevention of primary cytomegalovirus disease in children receiving liver transplants. *Clin Infect Dis* 1997; 25 (5): 1173-9
60. Winston DJ, Wirin D, Shaked A, et al. Randomised comparison of ganciclovir and high-dose acyclovir for long-term cytomegalovirus prophylaxis in liver transplant recipients. *Lancet* 1995; 346: 69-74
61. Gane E, Saliba F, Valdecasas GJ, et al. Randomised trial of efficacy and safety of oral ganciclovir in the prevention of cytomegalovirus disease in liver-transplant recipients: the Oral Ganciclovir International Transplantation Study Group. *Lancet* 1997; 350 (9093): 1729-33
62. Aguado JM, Gomez-Sanchez MA, Lumberras C. Prospective randomized trial of efficacy of ganciclovir versus that of anti-cytomegalovirus (CMV) immunoglobulin to prevent CMV disease in CMV seropositive heart transplant recipients treated with OKT3. *Antimicrob Agents Chemother* 1995; 39: 1643-5
63. Merigan TC, Renlund DG, Keay S. A controlled trial of ganciclovir to prevent cytomegalovirus disease after heart transplantation. *N Engl J Med* 1992; 326: 1182-6
64. Mullen GM, Silver MA, Malinowska K, et al. Effective oral ganciclovir prophylaxis against cytomegalovirus disease in heart transplant recipients. *Transplant Proc* 1998; 30 (8): 4110-2
65. Elkhammas EA, Henry ML, Tesi RJ, et al. Cytomegalovirus prevention in combined kidney-pancreas transplantation using acyclovir alone. *Transplant Proc* 1994; 65: 747-52
66. Harland RC, Vernon WB, Bunzendahl H, et al. Ganciclovir/acyclovir prophylaxis reduces the incidence of cytomegalovirus infections in pancreas transplant recipients. *Transplant Proc* 1994; 26: 432-3
67. Kohli V, Velosa J, Sterioff S, et al. Prophylaxis for cytomegalovirus in pancreas transplant recipients using intravenous ganciclovir. *Transplant Proc* 1995; 27 (6): 2993
68. Somerville T, Hurst G, Alloway R, et al. Superior efficacy of oral ganciclovir over oral acyclovir for cytomegalovirus prophylaxis in kidney-pancreas and pancreas alone recipients. *Transplant Proc* 1998; 30 (4): 1546-8
69. Stratta RJ, Taylor RG, Bynon JS. Viral prophylaxis in combined pancreas-kidney transplant recipients. *Transplantation* 1994; 57: 506-12
70. Maurer JR, Snell G, DeHoyas A. Outcomes of lung transplantation using three different cytomegalovirus prophylactic regimens. *Transplant Proc* 1993; 25: 1434-5
71. Weinberg A, Hodges TN, Li S, et al. Comparison of PCR, antigenemia assay, and rapid blood culture for detection and prevention of cytomegalovirus disease after lung transplantation. *J Clin Microbiol* 2000; 38 (2): 768-72
72. Gerbase MW, Dubois D, Rothmeier C, et al. Costs and outcomes of prolonged cytomegalovirus prophylaxis to cover the enhanced immunosuppression phase following lung transplantation. *Chest* 1999; 116 (5): 1265-72
73. Gutierrez CA, Chaparro C, Krajden M, et al. Cytomegalovirus viremia in lung transplant recipients receiving ganciclovir and immune globulin. *Chest* 1998; 113 (4): 924-32
74. Speich R, Thurnheer R, Gaspert A, et al. Efficacy and cost effectiveness of oral ganciclovir in the prevention of cytomegalovirus disease after lung transplantation. *Transplantation* 1999; 67 (2): 315-20
75. Zamora MR, Fullerton DA, Campbell DN. Use of cytomegalovirus (CMV) hyperimmune globulin for prevention of

- CMV disease in CMV-seropositive lung transplantation recipients. *Transplant Proc* 1994; 26 (5 Suppl. 1): 49-51
76. Kelly JL, Albert RK, Wood DE, et al. Efficacy of a 6-week prophylactic ganciclovir regimen and the role of serial cytomegalovirus antibody testing in lung transplant recipients. *Transplantation* 1995; 59: 1144-7
 77. Duncan SR, Paradis IL, Dauber JH, et al. Ganciclovir prophylaxis for cytomegalovirus infections in pulmonary allograft recipients. *Am Rev Respir Dis* 1992; 146: 1213-5
 78. Furukawa H, Kusne S, Abu-Elmagd K, et al. Effect of CMV serology on outcome after clinical intestinal transplantation. *Transplant Proc* 1996; 28 (5): 2780-1
 79. Hibberd PL, Tolkoff-Rubin NE, Conti DJ. Preemptive ganciclovir therapy to prevent cytomegalovirus disease in cytomegalovirus antibody-positive renal transplant recipients: a randomized controlled trial. *Ann Intern Med* 1995; 123: 18-26
 80. Conti DJ, Freed BM, Singh TP. Preemptive ganciclovir therapy in cytomegalovirus-seropositive renal transplant recipients. *Arch Surg* 1995; 130: 1217-22
 81. Lumbieras C, Otero JR, Herrero JA. Ganciclovir prophylaxis decreases frequency and severity of cytomegalovirus disease in seropositive liver transplant recipients treated with OKT3 monoclonal antibodies. *Antimicrob Agents Chemother* 1993; 37: 2490-2
 82. Hopt UT, Pfeffer F, Schareck W. Ganciclovir for prophylaxis of CMV disease after pancreas-kidney transplantation. *Transplant Proc* 1994; 26: 434-5
 83. Singh N, Yu VL, Miele L. High-dose acyclovir compared with short-course preemptive ganciclovir therapy to prevent cytomegalovirus disease in liver transplant recipients. *Ann Intern Med* 1994; 120: 375-81
 84. Kusne S, Grossi P, Irish W, et al. Cytomegalovirus PP65 antigenemia monitoring as a guide for preemptive therapy: a cost effective strategy for prevention of cytomegalovirus disease in adult liver transplant recipients. *Transplantation* 1999; 68 (8): 1125-31
 85. Egan JJ, Lomax J, Barber L, et al. Preemptive treatment for the prevention of cytomegalovirus disease: in lung and heart transplant recipients. *Transplantation* 1998; 65 (5): 747-52
 86. Corey L. Herpes simplex virus. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. Philadelphia (PA): Harcourt Health Sciences, 2000: 1564-80
 87. American Academy of Pediatrics. Herpes simplex. In: Peter G, editor. 1997 Redbook: report of the Committee on Infectious Diseases. Elk Grove Village (IL): American Academy of Pediatrics, 1997: 266-76
 88. Goodman JL. Possible transmission of herpes simplex virus by organ transplantation. *Transplantation* 1989; 47: 609-13
 89. Hirsch MS. Herpes group virus infections in the compromised host. In: Rubin RH, Young LS, editors. *Clinical approach to infection in the compromised host*. New York: Plenum Publishing Corporation, 1994: 379-96
 90. Nicholson V, Johnson PC. Infectious complications in solid organ transplant recipients. *Surg Clin North Am* 1994; 74: 1223-45
 91. Jirisiritham S, Sumethkul V, Chiawilp P, et al. Prevention of recurrent herpes infection after renal transplantation by low-dose oral acyclovir. *Transplant Proc* 1994; 26: 2125-6
 92. Arazi HC, Delgado D, Carosella V, et al. Prevention of symptomatic infection by herpesvirus in patients after heart transplantation. *Transplant Proc* 1999; 31 (6): 2530
 93. Carrier M, Pelletier GB, Cartier R. Prevention of herpes simplex virus infection by oral acyclovir after cardiac transplantation. *Can J Surg* 1992; 35: 513-6
 94. Petterson E, Hovi T, Ahonen J, et al. Prophylactic acyclovir after renal transplantation. *Transplantation* 1985; 39: 279-81
 95. Seale L, Jones CJ, Kathpalia S. Prevention of herpesvirus infections in renal allograft recipients by low-dose oral acyclovir. *JAMA* 1985; 254: 3435-8
 96. Whitley RJ. Varicella-zoster virus. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. Philadelphia (PA): Harcourt Health Sciences, 2000: 1580-6
 97. American Academy of Pediatrics. Varicella-zoster infections. In: Peter G, editor. 1997 Redbook: report of the Committee on Infectious Diseases. Elk Grove Village (IL): American Academy of Pediatrics, 1997: 573-85
 98. Griffiths PD. Viral complications after transplantation. *J Antimicrob Chemother* 1995; 36 Suppl. B: 91-106
 99. Ljungman P. Prophylaxis against herpesvirus infections in transplant recipients. *Drugs* 2001; 61 (2): 187-96
 100. Kusne S, Pappo O, Manez R. Varicella-zoster virus hepatitis and a suggested management plan for prevention of VZV infection in adult liver transplant recipients. *Transplantation* 1995; 60: 619-21
 101. Preiksaitis JK, Diaz-Miroma F, Mirzayans F, et al. Quantitative oropharyngeal Epstein-Barr virus shedding in renal and cardiac transplant recipients: relationship to immunosuppressive therapy, serologic responses, and the risk of posttransplant lymphoproliferative disorder. *J Infect Dis* 1992; 166: 986-94
 102. Paiva A, Freitas L, Pratas J, et al. Post-transplant lymphoproliferative disease. *Nephrol Dial Transplant* 1998; 13 (11): 2968-71
 103. Lebond B, Sutton L, Dorent R. Lymphoproliferative disorders after organ transplantation: a report of 24 cases observed in a single center. *J Clin Oncol* 1995; 13: 961-8
 104. Schaaf CG, van der Pijl JW, van Hoek B, et al. Successful outcome with a "quintuple approach" of posttransplant lymphoproliferative disorder. *Transplantation* 2001; 71 (1): 47-52
 105. Birkeland SA, Andersen HK, Hamilton-Dutoit SJ. Preventing acute rejection, Epstein-Barr virus infection, and posttransplant lymphoproliferative disorders after kidney transplantation: use of aciclovir and mycophenolate mofetil in a steroid-free immunosuppressive protocol. *Transplantation* 1999; 67 (9): 1209-14
 106. Ellis D, Jaffe R, Green M, et al. Epstein-Barr virus-related disorders in children undergoing renal transplantation with tacrolimus-based immunosuppression. *Transplantation* 1999; 68 (7): 997-1003
 107. Walker RC, Marshall WF, Strickler JG. Pretransplantation assessment of the risk of lymphoproliferative disorder. *Clin Infect Dis* 1995; 20: 1346-53
 108. McDiarmid SV, Jordan S, Kim GS, et al. Prevention and preemptive therapy of posttransplant lymphoproliferative disease in pediatric liver recipients [published erratum appears in *Transplantation* 1999 Sep 27; 68 (6): 909]. *Transplantation* 1998; 66 (12): 1604-11
 109. Aris RM, Maia DM, Neuringer IP, et al. Post-transplantation lymphoproliferative disorder in the Epstein-Barr virus-naïve lung transplant recipient. *Am J Respir Crit Care Med* 1996; 154 (6 Pt 1): 1712-7
 110. Montone KT, Litzky LA, Wurster A, et al. Analysis of Epstein-Barr virus-associated posttransplantation lymphoproliferative

- disorder after lung transplantation. *Surgery* 1996; 119 (5): 544-51
111. Levine SM, Angel L, Anzueto A, et al. A low incidence of posttransplant lymphoproliferative disorder in 109 lung transplant recipients. *Chest* 1999; 116 (5): 1273-7
 112. Wood BL, Sabath D, Broudy VC, et al. The recipient origin of posttransplant lymphoproliferative disorders in pulmonary transplant patients: a report of three cases. *Cancer* 1996; 78 (10): 2223-8
 113. Reyes J, Green M, Bueno J, et al. Epstein Barr virus associated posttransplant lymphoproliferative disease after intestinal transplantation. *Transplant Proc* 1996; 28 (5): 2768-9
 114. American Academy of Pediatrics. Epstein-Barr virus infections. In: Peter G, editor. 1997 Redbook: report of the Committee on Infectious Diseases. Elk Grove Village (IL): American Academy of Pediatrics, 1997: 199-201
 115. Haque T, Crawford DH. The role of adoptive immunotherapy in the prevention and treatment of lymphoproliferative disease following transplantation. *Br J Haematol* 1999; 106 (2): 309-16
 116. Schooley RT. Epstein-Barr virus (infectious mononucleosis). In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas and Bennett's principles and practice of infectious diseases. Philadelphia (PA): Harcourt Health Sciences, 2000: 1599-13
 117. Birkeland SA, Hamilton-Dutoit SJ, Sandvej K. EBV-induced post-transplant lymphoproliferative disorder (PTLD). *Transplant Proc* 1995; 27: 3467-72
 118. Savage P, Waxman J. Post-transplantation lymphoproliferative disease. *QJM* 1997; 90 (8): 497-503
 119. Haque T, Thomas JA, Parratt R, et al. A prospective study in heart and lung transplant recipients correlating persistent Epstein-Barr virus infection with clinical events. *Transplantation* 1997; 64 (7): 1028-34
 120. Stevens SJ, Verschuren EA, Pronk I, et al. Frequent monitoring of Epstein-Barr virus DNA load in unfractionated whole blood is essential for early detection of posttransplant lymphoproliferative disease in high-risk patients. *Blood* 2001; 97 (5): 1165-71
 121. Lucas KG, Filo F, Heilman DK, et al. Semiquantitative Epstein-Barr virus polymerase chain reaction analysis of peripheral blood from organ transplant patients and risk for the development of lymphoproliferative disease. *Blood* 1998; 92 (10): 3977-8
 122. Green M. Preemptive therapy: Epstein-Barr virus. *Transplant Proc* 1996; 28 (6 Suppl. 2): 5-6
 123. Kuo PC, Dafoe DC, Alfrey EJ. Posttransplant lymphoproliferative disorders and Epstein-Barr virus prophylaxis. *Transplantation* 1995; 59: 135-8
 124. Wadowsky RM, Laus S, Green M, et al. Measurement of Epstein-Barr virus DNA loads in whole blood and plasma by TaqMan PCR and in peripheral blood lymphocytes by competitive PCR. *J Clin Microbiol* 2003; 41 (11): 5245-9
 125. Darenkov IA, Marcarelli MA, Basadonna GP, et al. Reduced incidence of Epstein-Barr virus-associated posttransplant lymphoproliferative disorder using preemptive antiviral therapy. *Transplantation* 1997; 64 (6): 848-52
 126. American Academy of Pediatrics. Hepatitis A. In: Peter G, editor. 1997 Redbook: report of the Committee on Infectious Diseases. Elk Grove Village (IL): American Academy of Pediatrics, 1997: 237-46
 127. Myers RP, Gregor JC, Marotta PJ. The cost-effectiveness of hepatitis A vaccination in patients with chronic hepatitis C. *Hepatology* 2000; 31 (4): 834-9
 128. Feinstone SM, Gust SA. Hepatitis A virus. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas and Bennett's principles and practice of infectious diseases. Philadelphia (PA): Harcourt Health Sciences, 2000: 1920-40
 129. American Academy of Pediatrics. Hepatitis B. In: Peter G, editor. 1997 Redbook: report of the Committee on Infectious Diseases. Elk Grove Village (IL): American Academy of Pediatrics, 1997: 247-60
 130. Huo TI, Yang WC, Wu JC, et al. Kidney transplantation in patients with chronic hepatitis B virus infection: is the prognosis worse? *Dig Dis Sci* 2001; 46 (3): 469-75
 131. Perrillo RP, Wright T, Rakela J, et al. A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B. *Hepatology* 2001; 33 (2): 424-32
 132. Sanchez-Fueyo A, Rimola A, Grande L, et al. Hepatitis B immunoglobulin discontinuation followed by hepatitis B virus vaccination: a new strategy in the prophylaxis of hepatitis B virus recurrence after liver transplantation. *Hepatology* 2000; 31 (2): 496-501
 133. Rayes N, Seehofer D, Hopf U, et al. Comparison of famciclovir and lamivudine in the long-term treatment of hepatitis B infection after liver transplantation. *Transplantation* 2001; 71 (1): 96-101
 134. Seehofer D, Rayes N, Steinmuller T, et al. Occurrence and clinical outcome of lamivudine-resistant hepatitis B infection after liver transplantation. *Liver Transplant* 2001; 7 (11): 976-82
 135. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; 348 (9): 800-7
 136. Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; 348 (9): 808-16
 137. Peters MG, Singer G, Howard T, et al. Fulminant hepatic failure resulting from lamivudine-resistant hepatitis B virus in a renal transplant recipient: durable response after orthotopic liver transplantation on adefovir dipivoxil and hepatitis B immune globulin. *Transplantation* 1999; 68 (12): 1912-4
 138. Terrault NA. Treatment of recurrent hepatitis B infection in liver transplant recipients. *Liver Transplant* 2002; 8 (10 Suppl. 1): S74-81
 139. Lunel F, Cadranet JF, Rosenheim M, et al. Hepatitis virus infections in heart transplant recipients: epidemiology, natural history, characteristics, and impact on survival. *Gastroenterology* 2000; 119 (4): 1064-74
 140. Thomas DL, Lemon SM. Hepatitis C. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas and Bennett's principles and practice of infectious diseases. Philadelphia (PA): Harcourt Health Sciences, 2000: 1736-60
 141. Fishman JA, Rubin RH, Koziel MJ, et al. Hepatitis C virus and organ transplantation. *Transplantation* 1996; 62 (2): 147-54
 142. Szabo G, Katz E, Bonkovsky HL. Management of recurrent hepatitis C after liver transplantation: a concise review. *Am J Gastroenterol* 2000; 95 (9): 2164-70
 143. Feray C, Caccamo L, Alexander GJ, et al. European collaborative study on factors influencing outcome after liver transplantation for hepatitis C: European Concerted Action on Viral Hepatitis (EUROHEP) Group. *Gastroenterology* 1999; 117 (3): 619-25
 144. Mazzaferro V, Regalia E, Pulvirenti A, et al. Prophylaxis against HCV recurrence after liver transplantation: effect of interferon and ribavirin combination. *Transplant Proc* 1997; 29 (1-2): 519-21

145. Treanor JJ. Influenza virus. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell, Douglas and Bennett's principles and practice of infectious diseases*. Philadelphia (PA): Harcourt Health Sciences, 2000: 1823-49
146. Kimball P, Verbeke S, Flattery M, et al. Influenza vaccination does not promote cellular or humoral activation among heart transplant recipients. *Transplantation* 2000; 69 (11): 2449-51
147. Whimbey EE, Englund JA. Community respiratory virus infections in transplant recipients. In: Bowden RA, Ljungman P, Paya CV, editors. *Transplant infections*. Philadelphia (PA): Lippencott-Raven, 1998: 295-308
148. Hayden FG. Prevention and treatment of influenza in immunocompromised patients. *Am J Med* 1997; 102 (3A): 55-60
149. Garantzios S, Howell DN, McAdams HP, et al. Influenza pneumonia in lung transplant recipients: clinical features and association with bronchiolitis obliterans syndrome. *Chest* 2001; 119 (4): 1277-80
150. Sable CA, Hayden FG. Orthomyxoviral and paramyxoviral infections in transplant patients. *Infect Dis Clin North Am* 1995; 9: 987-1003
151. Massad MG, Ramirez AM. Influenza pneumonia in thoracic organ transplant recipients: what can we do to avoid it? *Chest* 2001; 119 (4): 997-9
152. Palmer Jr SM, Henshaw NG, Howell DN, et al. Community respiratory viral infection in adult lung transplant recipients. *Chest* 1998; 113 (4): 944-50
153. Blumberg EA, Albano C, Pruett T, et al. The immunogenicity of influenza virus vaccine in solid organ transplant recipients. *Clin Infect Dis* 1996; 22 (2): 295-302
154. Stephenson I, Nicholson KG. Chemotherapeutic control of influenza. *J Antimicrob Chemother* 1999; 44 (1): 6-10
155. Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. *Lancet* 2000; 355 (9206): 827-35
156. Goodrich J. A comparison of cytomegalovirus and community respiratory viruses in immunocompromised patients. *Am J Med* 1997; 102: 37-41

Correspondence and offprints: Dr *Shira Doron*, 750 Washington St, NEMC #041, Boston, MA 02111, USA.
E-mail: sdoron@tufts-nemc.org