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Chemoprophylaxis of Viral Infection in Immunocompromised Patients

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Abstract—*Viral infections are of increasing importance in the compromised host, particularly herpesvirus infections. Both intravenous and oral acyclovir are effective in preventing reactivation of herpes simplex virus infection; oral regimens are less expensive but compliance may be problematic. Varicella zoster virus reactivation can be suppressed for* 6–12 *months after marrow transplant using oral acyclovir, although infection may occur at the usual rate when prophylaxis is stopped. Intravenous acyclovir given for* 30 *days after marrow transplant reduced cytomegalovirus disease by* 50%. *New agents such as ganciclovir or foscarnet promise better control of cytomegalovirus infection.*

INTRODUCTION

VIRAL INFECTIONS have assumed increasing importance in immunocompromised patients over the last two decades (Table 1). In transplant patients, they are considered by some to be the most important class of infections and are not far behind bacterial and fungal infections in patients undergoing conventional therapy for leukemia or lymphoma. The reasons for this increase in importance are several. Firstly, with improvements in conventional antibiotics, bacterial infections have decreased in importance as a cause of death even in the neutropenic patient. Secondly, diagnostic techniques and the availability of viral diagnostic laboratories have dramatically improved so that rapid diagnosis of viral infections is both now practical and available. This has increased our awareness of the presence of viral infection in our patients. Thirdly, the availability of treatment and chemoprophylaxis, at least for some viral infections, makes the ability to diagnose viral infections of clinical importance for our patients.

Virtually any virus of humans is a potential cause of serious infection in immunocompromised patients (Table 2). Human immunodeficiency virus (HIV) is probably the most recent addition, although universal screening of blood products should make the occurrence of HIV infection rare. In general, RNA viruses do not occur as commonly as DNA virus infections. The major reason is that RNA viruses do not establish latency after primary infection and thus are not present to reactivate during periods of immunosuppression. Some RNA viruses such as HIV 'persist' after initial infection, but this is an exception. RNA virus infections do occur in both community and hospital epidemics and may cause severe disease. Respiratory viruses including influenza A, respiratory syncytial virus and parainfluenza 3 clearly can cause severe pneumonia in immunocomprised patients. But with the exception of influenza A, there is no chemoprophylaxis available for RNA viruses or specifically for respiratory RNA viruses. Amantadine or rimantadine are effective for prophylaxis of influenza A in normal persons, and also somewhat effective for treatment of influenza A pneumonia in normal persons. Whether these agents are effective for chemoprophylaxis in immunocompromised patients is not known.

As mentioned, the major reason that DNA viruses more commonly cause disease in immunocompromised patients is that DNA viruses become latent after initial infection and reactive during subsequent periods of stress, including immunosuppression or cytotoxic chemotherapy. A second hypothetically important reason is that most current chemotherapeutic or immunosuppressive regimens for transplant or for leukemic induction therapy are highly suppressive of cellular immunity, more so than of humoral immunity, and cellular immune mechanisms are accepted as being of primary importance in control of DNA viruses. These regimens also appear very efficient in reactivating some DNA viruses such as herpes simplex virus (HSV) by mechanisms that are not understood. The end result is the DNA virus infections are most common and cause the most severe syndromes in immunocompromised patients.

Among the DNA viruses of special note is the herpesvirus family which now contains six viruses with the recent discovery of human herpes virus type 6 (HHV 6). Although the first four have elicited

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Table 1. Important causes of infection in the immunocompromised host

		1980s	
1960s	1970s	Leukemia	Transplant
1. Bacterial	Bacterial	Bacterial	**Viral**
2. Bacterial	Bacterial	Fungal	Fungal
3. Bacterial	Fungal	Fungal	Bacterial
4. Bacterial	Fungal	**Viral**	Protozoan
5. Bacterial	Protozoan	Protozoan	
6. Fungal	**Viral**		
7. Protozoan			
8. **Viral**			

Table 2. Important viral infections in the immunocompromised host

RNA viruses	DNA viruses
Influenza A and B	Herpes simplex virus 1 and 2
Parainfluenza 1 and 3	Varicella zoster virus
Respiratory syncytial virus	Cytomegalovirus
Enteroviruses	Epstein–Barr virus
Measles	Human herpes virus 6
Rotavirus	Adenoviruses
Hepatitis A	Papovaviruses
Hepatitis non-A non-B	Hepatitis B

much attention in recent years because treatment is available, little is known about Epstein–Barr virus in the immunocompromised host and even less about HHV 6.

HERPES SIMPLEX VIRUS

Multiple studies have illustrated the high incidence of active herpes simplex virus (HSV) infection among immunocompromised patients who have had previous HSV infection, that is those who are already seropositive. An incidence of HSV reactivation of 70–80% has been documented in marrow and renal transplant patients and in patients undergoing induction therapy for leukemia or lymphoma [1, 2]. It is likely that the incidence is equally high among any group of seropositive patients undergoing similar immunosuppressive or cytotoxic therapy. In contrast, true primary infection is unusual, although it will also occur if exposure is adequate.

Some studies conducted among leukemic patients have shown lower rates of reactivation possibly related to less intensive induction therapy [3]. There may also be differences in the severity of HSV infection depending on factors such as the type of antileukemic or immunosuppressive therapy. One comparison of renal transplant and leukemic patients showed an approximately equal incidence of HSV reactivation, about 50%, but a substantial difference in the severity of HSV infection (Table 3) [4]. In this study every leukemic patient with positive cultures for HSV had clinically apparent lesions whereas only about one-third of the patients who had positive cultures after renal transplant had lesions attributed to HSV infection.

Table 3. HSV infection in renal transplant and leukemia patients

	Renal transplant	Leukemia
Total number of patients	47	26
Number with:		
HSV reactivation	22 (0.47)	13 (0.50)
Median time	6–10 days	6–10 days
HSV lesions	7 (0.15)*	13 (0.50)*
Mean number of sites	1.6	1.8

* $P < 0.01$.
Adapted from Greenberg, *J Infect Dis* 1987, **156**, 280–287.

In the past many lesions associated with HSV infection were attributed to other causes, for example the toxicity of cytotoxic chemotherapy. It is extremely difficult to make the diagnosis of mucocutaneous HSV infection by clinical examination alone. Many HSV lesions are intra-oral, not solely external. It has now been emphasized in many studies that oral mucosal disease attributed to cytotoxic chemotherapy, so called 'mucositis', may in fact be due to HSV infection. However, it is identifiable as due to HSV only if viral cultures are performed. This is also true of perineal or vaginal lesions due to HSV infection. Although serologies are not useful in establishing the diagnosis of active HSV infection, especially in immunocompromised patients, they are helpful in identifying patients at risk of virus reactivation during periods of immunosuppression. Viral cultures must be performed when HSV infection is suspected. Cultures for HSV are usually positive within 2–3 days, and immunofluorescence testing for viral antigens of material taken from lesions can be performed within hours. Another important manifestation of HSV infection, especially in patients who have instrumentation of the bronchopulmonary tract or who aspirate oral secretions, is pneumonia due to HSV. HSV pneumonia is usually a localized rather than a diffuse process, although it may be multifocal. It is impossible to distinguish from other forms of aspiration pneumonia. The exception to this is that HSV pneumonia arising from viremia may be appear as a diffuse, interstitial process [5]. This infrequent but severe complication of oral HSV infection must also be diagnosed by culture of material from the lower respiratory tract.

One of the characteristics of HSV infection, either after transplant or after induction therapy for leukemia or lymphoma, is the rapidity of reactivation

after the beginning of treatment. Indeed about 80% of patients who are going to reactive HSV infection do so within the first three weeks after the onset of treatment. This is a situation well suited for chemoprophylaxis. The seminal study of acyclovir prophylaxis for HSV infection was performed by Saral *et al.* [1]. In this study they showed that 10 seropositive marrow transplant recipients receiving intravenous acyclovir were completely protected against HSV reactivation during the period of acyclovir administration whereas reactivation of HSV occurred among seven of 10 patients receiving placebo. More recently they reported virtually identical data among patients undergoing leukemic induction therapy [2]. In both of these studies acyclovir was given at the 'treatment dose' usually recommended for HSV, namely 250 mg/m^2 every 8 h. It has also been shown that the same dose given only twice daily is 90% effective [6]. Many subsequent studies have been performed which show that orally administered acyclovir is similarly effective, although there are the predictable problems with compliance among patients undergoing cytotoxic chemotherapy or transplant conditioning.

There are important differences in the costs of these regimens. Table 4 shows representative costs in our Center for several of the recommended acyclovir regimens. A lower intravenous dose of 75–125 mg/m^2 given every 8–12 h should also be effective, based on the known pharmacology of acyclovir, but these regimens have not been tested in patients and thus cannot yet be recommended. The oral regimens are substantially less expensive, although compliance may be problematic as mentioned above. It is controversial whether all seropositive patients should receive acyclovir prophylaxis, knowing that some of them will not have reactivation of infection or develop severe disease, or whether patients should receive treatment only when infection has been documented [7]. However, based on the lower cost of orally administered acyclovir, it is possible to give oral prophylaxis to 10–15 patients per week for the costing of treating one patient with intravenous acyclovir for serious HSV infection. It thus seems that among patients who can tolerate oral drug, it *is* cost effective to give oral prophylaxis rather than waiting to treat those who develop active HSV disease with intravenous acyclovir.

Table 4. Approximate cost of acyclovir prophylactic regimens given for 1 week

*Intravenous acyclovir**	
250 mg/m^2 every 8 h†	$ 946
250 mg/m^2 every 12 h	631
125 mg/m^2 every 12 h	377
Oral acyclovir	
400 mg given five times daily†	81
800 mg given twice daily	64

* Calculated for ≤ 2.0 m^2 body surface area.
† This is also the recommended treatment regimen for HSV infection.

Do all seropositive patients warrant acyclovir prophylaxis? Prophylaxis should be given to patients who are at high risk of reactivation by virtue of their seropositivity and who are to undergo intensive cytotoxic chemotherapy or immunosuppression. Such patients are at risk of severe clinical disease, especially during the period of neutropenia when the possibility of bacterial superinfection is also present [8]. Prophylaxis should be continued until the period of risk has decreased, which may need to be individualized for different patients. Many centers give acyclovir prophylaxis until the end of the neutropenic period which is usually 3 or 4 weeks after the beginning of antileukemic or other treatment.

VARICELLA ZOSTER VIRUS

Varicella zoster virus (VZV) is the cause of both varicella (chickenpox) as a primary infection and herpes zoster (shingles) as a reactivation infection usually during adulthood. It is well known that either varicella or herpes zoster may be severe infections in immunocompromised patients, causing local complications such as scarring or bacterial superinfection, and visceral manifestations including pneumonia, hepatitis or encephalitis if the virus disseminates. The harbinger of visceral dissemination among patients with dermatomal herpes zoster is cutaneous dissemination. The other major sequela of herpes zoster is post-herpetic neuralgia which is more common in older patients and in the immunocompromised host. Table 5 shows a variety of studies which illustrate both the incidence of herpes zoster and the rate of dissemination in various patient groups. The highest probability of herpes zoster has been observed in patients with Hodgkin's disease and perhaps other lymphomas or those undergoing marrow transplantation, and is somewhat lower after renal transplant. The risk of cutaneous dissemination or severe visceral disease follows that same order.

Varicella zoster virus takes longer to reactive after the beginning of immunosuppression than does HSV. However, most cases of herpes zoster occur within the first 2 years after initial treatment for Hodgkin's disease and within 1 year after marrow transplant. Although the period of prophylaxis therefore must be longer than for HSV, it would appear possible to offer prophylaxis for a finite period of time with the goal of preventing VZV reactivation during the period of highest risk for serious manifestations, i.e. during the period of greatest immunosuppression. It is possible that

Table 5. Incidence of herpes zoster in the immunocompromised host

Study	Patient group	Incidence of herpes zoster	Cutaneous dissemination
Rifkind [12]	Renal transplant	8%	0%
Schimpff [13]	Adult Hodgkin's disease	25%	32%
	Other lymphomas	9	
	Solid tumors	2%	
Feldman [14]	Childhood Hodgkin's disease	22%	50%
	Acute lymphocytic leukemia	10%	
	Other malignancies	5%	
Goodman [15]	Childhood Hodgkin's disease	52%	2%
Reboul [16]	Childhood Hodgkin's disease	33%	23%
Locksley [17]	Marrow transplant	30%*	36%

* Kaplan–Meier probability.

Table 6. Effect of long-term acyclovir prophylaxis for varicella zoster virus infection after marrow transplant

	Time after transplant	
Patient group	0–6 months	6–12 months
Acyclovir	0/20*	4/13 (0.31)
Placebo	5/22 (0.23)	1/13 (0.08)
Significance	<0.05	ns

* Entries represent proportion of patients with varicella zoster virus infection/total number of patients in group at the start of the time period.
From Ljungman P *et al. Bone Marrow Transplantation* 1986, **1**, 185–192.

VZV reactivation would still occur after prophylaxis is ended, but the hypothesis would be that infection during this period would be less severe.

There have been two recent studies showing in small numbers of marrow transplant patients that oral cyclovir will prevent VZV reactivation during the period of drug administration [9]. The first study from Stockholm reported that an oral dose of acyclovir of 400 mg given three times a day for 6 months after marrow transplant completely prevented VZV reactivation compared to a 25% incidence in the placebo recipients (Table 6). After acyclovir was stopped the patients who had previously received acyclovir had reactivation of VZV infection at the usual incidence, and there was no difference in overall incidence at one year. Very similar data were reported from London, although a higher oral acyclovir of 800 mg given four times a day was used for the first 6 months after transplant [10]. As in the first study, the incidence was the same at 1 year in the two groups.

Additional studies should be done to include more patients, and also to further define the post-acyclovir 'rebound' effect if prophylaxis is given for longer periods, for example for 1 year. However, pending such data, these studies do suggest that oral acyclovir at doses as low as 400 mg given three times daily is effective for prevention of VZV reactivation for periods up to 6 months. This or similar regimens might be considered in patients considered at high risk of VZV reactivation, with the understanding that VZV infection may only be delayed until the end of prophylaxis. It is intriguing to consider whether the live varicella vaccine might be effective in restoring virus-specific immunity at that time.

CYTOMEGALOVIRUS

Cytomegalovirus (CMV) infection also has a range of manifestations from asymptomatic excretion to severe disseminated infection including pneumonia. Although CMV is probably best known for causing severe disease among marrow and other allograft (e.g. liver) recipients, recent studies suggest that it may also be a substantial problem among other patients such as those undergoing leukemic induction therapy (personal communication, J. Wade). In contrast to HSV and VZV, acyclovir does not have good activity against CMV. The reason is that acyclovir must be phosphorylated (activated) by viral thymidine kinase before it is an effective and selective inhibitor of viral DNA polymerase. In contrast to HSV and VZV, CMV does not specify a thymidine kinase. Nevertheless, some patient strains of CMV are inhibited by the higher concentrations of acyclovir which may be achieved by intravenous administration.

Despite the poor efficacy of acyclovir in the treatment of established CMV infection, a study of the prophylactic benefit of high-dose intravenous acyclovir was conducted in two marrow transplant centers [11]. In this controlled, but not randomized, study, intravenous acyclovir was given to CMV- and HSV-seropositive patients undergoing allogeneic marrow transplantation for hematologic malignancy at the dose of 500 mg/m^2 every 8 h from 5 days before to 30 days after transplant. Patients who were CMV-seropositive but HSV-seronegative served as the control group. Patients who received acyclovir had a statistically significant 22-day delay in time to first positive culture and a lower overall probability of excretion in the first 100 days after transplant (Table 7). More importantly, the probability of CMV disease, including pneumonia and gastroenteritis, was significantly reduced. Finally, survival within the first 100 days

*Table 7. Effect of acyclovir prophylaxis on reactivation of cytomegalovirus infection and on cytomegalovirus disease after allogeneic marrow transplantation**

Parameter	Patient group		
	Acyclovir	Control	*P*-value†
CMV excretion from			
Oropharynx	0.44‡	0.77	0.0001
Urine	0.50	0.59	0.007
Blood	0.39	0.48	0.10
Any site	0.70	0.87	0.0001
CMV disease syndromes:			
Pneumonia	0.21	0.40	0.04
Pneumonia or enteritis	0.25	0.49	0.008
Survival	0.71	0.46	0.002

* All patients CMV-seropositive before transplantation.
† Probability testing by log-rank test.
‡ Data are expressed as Kaplan–Meier probability ≤ 100 days after transplant.

was significantly better among acyclovir recipients (71%) than control patients (46%). When these data were subjected to multivariate analysis, the use of acyclovir was shown to be associated with the protective benefit.

The only apparent explanation for these observations is that small amounts of acyclovir were phosphorylated either in uninfected or infected cells, and that this amount was sufficient to delay CMV reactivation until a later period after transplant when the likelihood of severe manifestations associated with CMV infection was less. However, at best, acyclovir prophylaxis was only 50% effective and further improvement is needed.

There are newer agents with better activity against cytomegalovirus, including the nucleoside-analog ganciclovir and phosphonoformate (foscarnet). Initial studies indicate that ganciclovir may cause marrow suppression in as many as 25–50% of treated patients. Foscarnet is not marrow suppressive, but has been associated with transient nephrotoxicity in about 30% of patients who have received the drug in initial treatment studies. Despite these concerns, both agents show promise for both the prophylaxis and treatment of CMV infection.

DISCUSSION

Agents which promise efficacy for both the prevention and treatment of virus infections continue to enter clinical testing. The major addition has been acyclovir, which is highly effective for treatment and prevention of HSV and VZV infection, and appears to be partially effective for prevention of CMV infection. Other agents are on the horizon. As in other areas of medicine, prevention should be more effective than treatment especially among severely immunocompromised patients. Although the potential costs of both prophylaxis and treatment can no longer be ignored, it is now possible to design prophylactic regimens of orally administered acyclovir that are effective for the prevention of HSV, and probably VZV, infection and which may ultimately be less expensive than in-hospital therapy for these same infections. Prophylactic use of these regimens should benefit our patients accordingly.

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