Preface

The major goal of *Opportunistic Infections: Treatment and Prophylaxis* is to guide clinicians who provide care for patients suffering from an underlying immunodeficiency that may significantly weaken their immune defenses and will complicate the effective treatment of opportunistic infections. In spite of a wealth of isolated data, no single text exists in which all the essential information about various infectious opportunistic infections. Although I make no claim to completeness, it is my hope that the present book will fulfill that need. To achieve this goal, I have endeavored to integrate both results from large-scale clinical trials and trials involving small numbers of patients, as well as reports of single cases—mindful that such an approach has its limitations.

Opportunistic Infections: Treatment and Prophylaxis is organized into four major parts: bacterial, viral, parasitic, and fungal diseases affecting the immunocompromised population. Each part surveys individual infections caused not only by well-known etiologic agents, but also by new and emerging species often taxonomically closely related to a major disease-producing microorganism and until recently not considered to be human pathogens (*Candida* spp. and nontuberculous mycobacteria, for example). For the sake of uniformity, within each part, the species have been arranged according to their taxonomic characteristics.

As the title of the book suggests, the array of diseases included has been broadened to encompass not only opportunistic infections exclusively associated with immunocompromised patients, but also infections commonly benign and self-resolving while affecting immunocompetent hosts, but becoming fulminant or disseminated, and very often life-threatening, in immunosuppressed individuals.

In contrast to normal hosts, where many infectious diseases are usually self-limited, in immunocompromised patients, such infections have the potential of becoming serious illnesses characterized by high morbidity and mortality rates. There are also the opportunistic infections that occur almost exclusively in immunocompromised hosts. Usually widely distributed in the environment, opportunistic pathogens rarely cause serious illness in normal hosts. In this context, it is important to note that prompt and correct diagnosis of a disseminated infection may become crucial as a result of overt differences in the susceptibility to anti-infectious drugs of sometimes closely related opportunistic pathogens. For example, while both *Pseudallescheria boydii* and *Scedosporium prolificans* have been recognized as causes of opportunistic hyalohyphomycoses in immunocompromised patients, diagnosis of disseminated disease caused by *S. prolificans* has been difficult to attain, since its spectrum and symptoms strongly resemble those of pseudallescheriasis and pulmonary aspergillosis. However, early positive identification of *S. prolificans* may prove to be essential because of its extreme drug tolerance and the related poor prognosis of disseminated disease caused by this fungal pathogen.

The information contained in *Opportunistic Infections: Treatment and Prophylaxis* includes—in addition to well-planned, large-scale clinical trials—reports of individual cases or treatment of small numbers of patients. When comparing large-scale clinical trials with therapies of individual cases, a multicenter clinical therapy involving large patient cohorts is unquestionably by far the better means of evaluating the therapeutic efficacy of a drug. A large-scale clinical trial provides the necessary information, clinical experience, as well as the perspective and direction needed for future research. On the other hand, clinical data involving limited numbers of patients or individuals, when well documented, may become useful in evaluating the therapeutic efficacy of a drug that might otherwise go unnoticed by those involved in drug research and development or in clinical practice. However, even with its benefits, such information, because of its limited scope, should be viewed with caution when evaluating the therapeutic efficacy and/or adverse toxicity of a therapeutic modality. Inevitably, in such cases, individual authors will differ and will include their specific (sometimes divergent or controversial) interpretations. It should also be emphasized that in some cases of rare or emerging infections, just the small number of patients and/or their distant geographic distribution would preclude any large-scale clinical trials, thereby leaving reports on treatment of individual cases as the only available data. In addition, there are also those unique cases of immunocompromised patients where an underlying condition may profoundly influence and/or even predicate the treatment of infection.

We trust that in its entirety, the information contained in *Opportunistic Infections: Treatment and Prophylaxis* represents a balanced and accurate account of the current status of opportunistic infections, and will serve as a useful resource for both clinicians and established investigators, as well as for new researchers in the field of drug development and treatment. It will also be especially helpful to those health care practitioners who do not have easy access to medical libraries and journals. We hope, too, that this book will facilitate further understanding of those areas of drug development and treatment that are still not well understood. Our aim is to encourage both scientists and clinicians to explore new avenues in their search for novel, safer, and more effective therapeutic modalities against infectious diseases in immunocompromised patients.

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Varicella-Zoster Virus (Herpes Zoster) Infections

1. INTRODUCTION

Varicella-zoster virus is one of six herpesviruses isolated from humans. The core of a typical herpesvirus contains a linear, double-stranded DNA, whereas the viral capsid is icosadeltahedral and contains 162 capsomeres with a hole running down the long axis *(1)*.

The varicella-zoster virus (VZV) is associated with two distinct clinical syndromes: varicella (chickenpox) and herpes zoster (shingles). Whereas varicella is a ubiquitous and highly contagious primary infection affecting the general population (especially in childhood), herpes zoster is less common endemic clinical condition that usually occurs in older and/or immunocompromised individuals.

AIDS patients with $CD4^+$ counts of 500 cells/mm^3 or less, or organ-transplant recipients (especially bone-marrow allograft recipients) are at significant risk of VZV infections. Furthermore, patients who have received prior repeated acyclovir treatment have the highest risk of harboring acyclovir-resistant strains *(2,3)*.

Herpes zoster usually is manifested with a painful vesicular eruption customary limited to a single dermatome, although cases of generalized eruptions have also been observed. It does not associate to exogenous exposure but appears to be secondary to reactivation of VZV that remained latent after an earlier attack of varicella *(4)*.

In general, the pathogenesis and mechanism of reactivation of herpes zoster are not well-understood. Predisposing factors associated with the appearance of herpes zoster are generally linked to compromised immune defenses *(5)* and include Hodgkin's disease and other lymphomas, immunosuppressive therapy, trauma to the spinal cord and adjacent structures, and heavy-metal poisoning *(5–8)*. In some instances, the host immune response is still viable enough to halt cutaneous lesions, but not the necrosis and inflammatory response in the ganglion. Such cases, known as zoster sine herpete, are characterized with radicular pain without associated skin lesions *(7,9,10)*.

The disease tends to be more severe in patients with malignancies, those with immune deficiencies, or receiving immunosuppressive therapy. Cutaneous dissemination, which occurs in up to 50% of immunocompromised patients, usually does not affect the morbidity and mortality in this population. However, patients with visceral disease (particularly pneumonitis) have increased mortality rate *(4)*.

The most common complication of herpes zoster is the postherpetic neuralgia that occurs in nearly 50% of patients 60 yr and older; it has been rarely observed in patients under 40 yr. Other complications, especially in immunocompromised hosts include chronic zoster *(11)*, and persistent CNS infection *(12,13)*.

De La Blanchardiere et al. *(14)* conducted a multicenter retrospective study to evaluate the clinical features and prognostic significance of VZV-associated neurological complications. Results of the study showed that encephalitis, myelitis, radiculitis, and meningitis were the most predominant neurological manifestations.

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Dolin et al. *(15)* found linkage between increased severity of herpes zoster and compromised status of the cell-mediated response. The presence of VZV-induced lymphocyte blastogenesis and interferon production correlated well with the ability to contain VZV reactivation.

In immunosuppressed patients, varicella infections are common with 50% of patients developing infection after bone-marrow transplantation *(16)*, over 20% following cardiac transplantation *(17)*, and up to 25% of patients receiving chemotherapy for Hodgkin's disease *(18)*. In fact, patients with Hodgkin's disease have been reported to have an increased risk for disseminated herpes zoster virus infection *(19–21)*. Chemotherapeutic regimens consisting of chlorambucil, vinblastin, procarbazine, and prednisone have been associated with increased incidence of herpes zoster infections in patients treated for Hodgkin's disease *(22)*; procarbazine has been suspected to be the cause behind it *(23)*. On several occasions in cancer patients, disseminated herpes zoster infections had been diagnosed concomitant with bacterial and/or fungal infections *(24)*. Varicella infections have also been reported in AIDS-related syndromes *(25)*, especially in Africa *(26)*, but it appears to be less common in patients with established AIDS in spite of their severely immunocompromised state *(27)*.

2. STUDIES ON THERAPEUTICS

2.1. Acyclovir

Acyclovir, a cyclic analog of 2-deoxyguanosine, was introduced into clinic as antiviral drug in 1977 *(28)*. It has highly selective mode of action against both VZV and herpes simplex *(29–32)* resulting in the inhibition of herpesvirus replication at concentrations 300- to 3,000-fold lower than those needed to inhibit mammalian cell functions *(33)*.

A note of caution should be applied when acyclovir is administered orally or even intravenously at lower dosages, because acyclovir-resistant mutant strains of VZV can be readily selected in the presence of the drug *(34)*.

In general, acyclovir is well tolerated in a wide variety of disease states, population types, and age groups *(29)*. However, there have been several reports of acyclovir-associated neurotoxicity *(35)* (confusion, hallucinations, seizures, and coma) in bone-marrow transplant recipients *(36)* and patients with chronic renal failure *(59)*. In the latter case, however, when the dosage regimens of acyclovir had been reduced according to the degree of renal failure, the neurotoxicity was reversed *(38–40)*.

Acute neurotoxicity in patients receiving intravenous acyclovir, although infrequently, has been well-documented *(35)*, especially in patients with renal failure *(37)*. Acute nephrotoxicity has also been observed in patients given oral acyclovir therapy *(41,42,64)*. Davenport et al. *(43)* and Beales et al. *(44)* treated oral acyclovir-induced neurotoxicity in patients with herpes zoster and end-stage renal failure (undergoing continuous ambulatory peritoneal dialysis) with hemodialysis, which by removing the drug *(45)*, effectively reduced the plasma concentrations of acyclovir. It would also seem advisable to recommend dose modification in those patients with end-stage renal failure, by either reducing the dose, increasing the dose intervals, or both *(44)*. A modified acyclovir regimen for intravenous route of admnistration has also been described *(46)*.

However, based on their clinical experience with patients undergoing dialysis, MacDiarmaid-Gordon et al. *(47)* reported that acyclovir-induced neurotoxicity can occur in spite of dose reduction and within the time-course of a standard course of treatment.

Since there is a wide overlap of serum concentrations in patients with and without neurologic side effects, the relation between CNS effects and acyclovir serum concentrations remains unclear *(35,39,48–52)*. Symptoms of neurotoxicity usually appear 24–72 h after acyclovir peak concentrations. Therefore, single drug level measurements may be of little diagnostic value *(52)*.

2.2. Famciclovir

A similar to valaciclovir approach has been taken in the development of famciclovir (famvir), the diacetyl ester of 6-deoxypenciclovir and a prodrug of penciclovir *(53)*. Famciclovir is absorbed in the

upper intestine and rapidly metabolized in the intestinal wall and liver to penciclovir by deacetylation and oxidation *(54)*; the bioavailability of penciclovir is about 77% *(55)*. Similar to valaciclovir, famciclovir also reduced the duration of postherpetic neuralgia *(56)*. The primary elimination pathway appeared to be renal excretion of unchanged penciclovir.

In a multicenter, double-blind, controlled trial, 1-wk treatment with oral famciclovir (either 500 mg or 750 mg, t.i.d.) was compared to placebo *(57,58)*. The time to full crusting of zoster lesions was 5 d with the drug and 7 d with placebo. Furthermore, the duration of postherpetic neuralgia was 61 d in patients receiving 750 mg of famciclovir, 63 d in those taking 500 mg, and 119 d in the placebo-receiving group. In another controlled trial, oral famciclovir (administred at doses of either 250, 500, or 750 mg, t.i.d.) was compared to acyclovir (800 mg, 5 times daily) in 545 patients with herpes zoster; the time of crusting, loss of acute pain, and duration of postherpetic neuralgia were similar in all groups. Although there were no significant differences among the three famciclovir dosing regimens, the primary advantage of famciclovir over acyclovir appeared to be its more convenient dosing schedule *(57,59)*.

The recommended dosage of famciclovir for treatment of acute herpes zoster is 500 mg, 3 times daily (every 8 h) for 1 wk. Famciclovir therapy should be initiated within 72 h after the onset of rash *(57)*.

Side effects with famciclovir (given at doses ranging from 125 mg to 2.25 g) during clinical trials occured no more frequently than with the placebo and include headache (9.3% of treated patients), nausea (4.5%), diarrhea (2.4%), and to a lesser extent fatigue, dizziness, abdominal pain, and dyspepsia. When studied for toxicity on testicular functions in male patients with recurrent genital herpes, famciclovir has shown no adverse side effects *(57,60)*. The safety of famciclovir therapy during pregnancy or breast feeding has not yet been established *(57)*.

Aside from fewer doses of medication per day than acyclovir, there appears to be little clinical advantage of famciclovir over acyclovir.

2.3. Sorivudine

The efficacy of sorivudine (BV-araU), a nucleoside antiviral drug has been compared with acyclovir in a double-blind/double-dummy study for the treatment of dermatormal herpes zoster in 170 HIV-infected patients *(61)*. Forty mg of sorivudine were given orally once daily for 10 d, whereas oral acyclovir was administered at 800 mg, 5 times daily for 10 d. Although both drugs were well-tolerated, sorivudine was deemed superior to acyclovir in accelerating the cutaneous healing with the added advantage of once-daily dosing.

3. TREATMENT OF VARICELLA-ZOSTER INFECTIONS

Acyclovir has been the standard therapy for VZV infections for more than a decade. However, it has a relatively short half-life and poor bioavailability necessitating the administration of high doses five times daily in order to maintain adequate plasma concentrations above the IC_{50} for VZV. Nevertheless, its systemic administration has been effective in reducing the severity of acute attack of herpes zoster *(62,63)*. In immunocompromised hosts, infections owing to acyclovir-resistant VZV strains have attained some urgency creating the need for alternative antiviral therapies *(64,65)*. In general, antiviral medications have been most effective when started within 72 h after the onset of rash. The addition of an orally administerd corticosteroid can provide modest benefits in reducing the pain of herpes zoster and the incidence of postherpetic neuralgia. Also, tricyclic antidepressants or anticonvulsants, often administered in low dosages may help in controlling neuropathic pain *(66)*.

In addition to acyclovir, famciclovir and valaciclovir have been used in treating VZV infections *(66)*. Foscarnet has been recommended for treatment of varicella zoster infections in severely immunocompromised patients (such as those with AIDS or bone-marrow transplant recipients) when acyclovir-resistant VZV strains were present *(2,67,68)*. The low incidence of myelosuppression associated with foscarnet allows for the drug to be used in combination with bone marrow-toxic

Table 1
Antiviral Therapy for Varicella-Zoster Infections

Infection	Drug/route of administration	Dose	VZV Duration
Immunocompromised patients	Acyclovir/i.v. divided every 8 h (1500 mg/m^2 daily divided every 8 h for children <12 yr old)	30 mg/kg daily	5–7 d
	Vidarabine/i.v. infused over 12 h	10 mg/kg daily	5–7 d
	Foscarnet/i.v. divided every 8 h	40 mg/kg daily	5–7 d
Immunocompetent patients	Acyclovir/p.o. q.i.d. for children; 800 mg per dose, q.i.d. for adolescents; 800 mg per dose, 5 times daily for adults	20 mg/kg per dose	5 d

antiretroviral therapies, such as zidovudine. To minimize adverse effects, patients should receive adequate hydration prior to and during foscarnet therapy *(69)*. Nevertheless, patients should be monitored frequently for renal toxicity, electrolyte abnormalities, and alterations in the calcium/phosphorus metabolism during therapy. Chronic maintenance therapy has not been recommended in this situation *(2)*.

In retrospect, the currently available clinical data have estabiliched that both acyclovir and vidarabine favorably alter the clinical course of herpes zoster in immunocompromised patients. However, the fact that it is perhaps less toxic and easier to administer have made intravenous acyclovir the drug of choice for treatment of herpes zoster in immunocompromised patients *(64)* (Table 1).

Studies by Sempere et al. *(70)* showned that long-term acyclovir prophylaxis delayed but did not prevent VZV infections after autologous blood stem-cell transplantation in patients with acute leukemia.

3.1. Herpes Zoster in Organ-Transplant Recipients

Varicella zoster infections in immunocompromised patients, such as bone-marrow transplant (BMT) recipients can be severe and frequently associated with widespread dissemination reaching mortality rate as high as 50% *(71–73)*.

Reactivation of VZV infections, which has been documented after allogeneic BMT in 30–40% of patients *(74)*, most commonly presents as zoster. Therefore, the prophylactic use of acyclovir in this population has been recommended *(75,76)*.

When compared to vidarabine, acyclovir proved superior in the treatment of BMT recipients *(71,77,78)*.

It has been postulated that when used in organ transplant recipients receiving immunosuppressive cyclosporine A therapy, acyclovir may adversely interact with cyclosporin A by increasing its nephrotoxicity *(71,79–82)*. However, based on several cases of renal-transplant recipients with herpes zoster, Hayes et al. *(83)* found that acyclovir therapy did not interefere with the concomitant cyclosporin A medication. These results seem to contradict two earlier reports, one by Johnson et al. *(84)*, who suggested a slight improvement in renal functions of renal-allograft recipients while being treated with cyclosporin A and intravenous acyclovir, and by Shepp et al. *(71)* who observed a deterioration in the renal functions of BMT patients on cyclosporin A therapy following treatment with intravenous acyclovir.

3.2. Herpes Zoster in HIV-Infected Patients

VZV infections are among the most frequent viral opportunistic infections in HIV-infected patients *(85)*. The incidence of herpes zoster among HIV-infected patients is nearly seven times higher as compared to the general population *(86)*.

Snoeck et al. *(87)* described a case of an AIDS patients who developed meningoradiculoneuritis while receiving prophylactically oral acyclovir (400 mg, b.i.d.) for 8 mo following recurrent multidermatomal zoster. A thymidine kinase (TK)-deficient, acyclovir-resistant VZV strain has been isolated from the cerebrospinal fluid (CSF). Upon initiation of foscarnet therapy, the virus became undetectable and the CSF was cleared from mononuclear cells (pleiocytosis) and protein overload (proteinorachia).

3.3. Management of Drug-Resistant Varicella-Zoster Virus Infections

Acyclovir, which is inactive as nucleoside, exerts its antiviral activity after phosphorylation to the nucleotide acyclovir triphosphate *(88)*. The monophosphorylation of the drug is carried out by a virally encoded enzyme, the TK. Viral TK is induced in cells infected with VZV. The acyclovir monophosphate is further phosphorylated to its triphosphate nucleotide form by host-cell enzymes. Decreased or absent induction of virus-encoded TK is one mechanism by which VZV become resistant to acyclovir *(3,89)*. One other potential mode to acquire resistance is alterations in substrate specificity of either viral TK or viral DNA polymerase *(2)*. Acyclovir-resistant VZV infection have been reported exclusively in HIV-seropositive patients, usually in the setting of advanced immunosuppression and previous exposure to acyclovir *(3,90–93)*. One acyclovir-resistant isolate was obtained from a bone marrow transplant recipient who had received the drug intravenously *(89)*.

Intravenous foscarnet has been evaluated as an alternative therapy for acyclovir-resistant VZV at dosage regimens of 60 mg/kg twice-daily or 40 mg/kg (t.i.d.) for 10 d or until the lesion is completely healed *(2)*. At daily doses of 120 mg/kg, i.v. for 10 d, foscarnet produced complete healing in 4 of 5 AIDS patients with TK-deficient VZV strains; the remaining patient developed resistance to foscarnet *(67)*. Smith et al. *(68)* described a patient with chronic hyperkeratoic VZV lesions and acyclovir resistance who responded well to a 3-wk course of foscarnet (120 mg/kg). Adverse effects included nausea, vomiting, bloating, as well as hypokalemia and hyperphosphatemia.

3.4. Varicella-Zoster Virus Pneumonitis

It was not until 1942 that VZV-associated pneumonitis was recognized as a separate clinical entity with potentially lethal outcome in even otherwise healthy adults *(94)*. Currently, VZV-induced pneumonitis is considered to be one of the most serious complications of disseminated VZV infection, especially in immunocompromised individuals *(95)*. Bone-marrow transplant *(73,96,97)*, renal *(98,99)* and liver *(100)* transplant recipients, children with cancer *(101–103)*, and HIV-positive patients *(104)* are at the highest risk of developing VZV pneumonitis.

Corticosteroid therapy administered to patients with underlying disease, such as renal or collagen-vascular disorders, has also been associated with an increased risk of VZV pneumonitis *(95)*. In addition, several reports have indicated that conventional "low-dose" corticosteroid therapy (<2.0 mg/kg daily, or 5.0–20 mg daily) *(105)*, topical nasal corticosteroids for chronic sinusitis *(106)*, and short-course corticosteroid therapy for acute asthma attack when administered during the incubation period of varicella *(107)* may predispose to disseminated varicella infections.

3.5. Herpes-Zoster Ophthalmicus

Herpes-zoster ophthalmicus (HZO) affects the first division of the trigeminal nerve and is associated with a high rate of ocular involvement often leading to serious morbidity *(108–113)*. In the majority of HZO cases, the eye complications appear shortly after the rash and are assumed to be the result by the presence of replicating VZV *(110,114–117)*. The nature of HZO complications are

inflammatory and include conjunctivitis, episcleritis, keratitis, and anterior uveitis. Whereas conjunctivitis and episcleritis tend to be transient and self-limiting, the other inflammatory lesions can become chronic or recurrent *(109)*.

Intravenous acyclovir and vidarabine are the mainstay of therapy in patients with VZV retinitis *(118)*. The recommended dose of acyclovir is 1.5 g/m^2 every 8 h for 7 d; intravenous courses of acyclovir are frequently followed by 1–2-wk courses of oral acyclovir as the retinitis regresses. The recommended dose for vidarabine is 10 mg/kg daily in a 12-h infusion for 5 d, both in normal and immunocompromised patients *(118)*.

Recent attention has been centered on the use of acyclovir as both in prophylaxis and disease management *(108,109)*. Current evidence favors the use of topical acyclovir alone in the treatment of established ocular complications *(119)*. There have also been recommendations for topical use of steroids but the precise relationship between antiviral therapy and steroids is still unclear *(120,121)*, and the use of topical steroids should be considered only for most severe cases *(119)*.

When administered orally, acyclovir (800 mg 5 times daily) has only limited therapeutic benefits because it is only partially absorbed, and its plasma levels remaining virtually unchanged at doses over 800 mg *(120)*. In addition, these plasma levels have been only slightly higher than the mean effective dose (ED_{50}) for most strains of VZV *(123,124)*. However, the aqueous humoral levels have been significantly higher if acyclovir had been administered topically to the eye *(108,125)*.

In two studies on the prophylactic use of acyclovir, the beneficial effects have been observed only when the treatment was initiated within 72 h of the onset of rash *(126,127)*. However, the results were conflicting, because in one study the effect was noticed early *(126)*, whereas in the other it occured late *(127)*. To study the possibility of whether ocular treatment with acyclovir provides better efficacy than oral administration, Neoh et al. *(108)* used a multicenter, open, randomized trial to compare the ocular prophylactic effects of topical and oral acyclovir. The patients received prophylactic treatment within 72 h of the onset of rash consisting of either topical acyclovir ointment or 800 mg of oral acyclovir, both 5 times daily for 1 wk; a follow-up examination was carried out 12 mo after completion of treatment. The results have shown that in spite of its better penetration, topical acyclovir apparently did not offer prophylactic value in the management of early HZO *(108)*.

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