

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 icosahedral 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/mm³ 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.

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 administration has also been described (46).

However, based on their clinical experience with patients undergoing dialysis, MacDiarmid-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 (administered 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 occurred 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 dermatomal 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 administered 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 established 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) showed 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 interfere 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 hyperkeratotic 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/m² 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 (ED₅₀) 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 occurred 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).

REFERENCES

1. Roizman, B. Herpesviridae: a brief introduction, in *Fields Virology*, 2nd ed., Fields, B. N., Knipe, D. M., Chanock, R. M., et al. Eds., Raven Press, New York, 1787, 1990.
2. Balfour, H. H., Benson, C., Braun, J., et al. Management of acyclovir-resistant herpes simplex and varicella-zoster virus infection. *J. Acquir. Immune Defic. Syndr.*, 7, 254, 1994.
3. Jacobson, M. A., Berger, T. G., Fikrig, S., et al. Acyclovir-resistant varicella-zoster virus infection after chronic oral acyclovir therapy in patients with the acquired immunodeficiency syndrome (AIDS). *Ann. Intern. Med.*, 112, 187, 1990.
4. Gelb, L. D., Varicella-zoster virus, in *Fields Virology*, 2nd ed., Fields, B. N., Knipe, D. M., Chanock, R. M., et al. Eds. Raven Press, New York, 2011, 1990.
5. Hope-Simpson, R. E. Infectiousness of communicable diseases in the household (measles, chickenpox, and mumps). *Lancet*, 2, 549, 1952.
6. Head, H. and Campbell, A. W. The pathology of herpes zoster and its bearing on sensory localization. *Brain*, 23, 353, 1900.
7. Juel-Jensen, B. W. and MacCallum, F. O. *Herpes simplex, Varicella and Zoster*. J. B. Lippincott, Philadelphia, 1972.
8. Schimpff, S., Serpick, A., Stoler, B., et al. Varicella-zoster infection in patients with cancer. *Ann. Intern. Med.*, 76, 241, 1972.
9. Easton, H. G. Zoster sine herpete causing trigeminal neuralgia. *Lancet*, 2, 1065, 1970.
10. Luby, J. P., Ramirez-Ronda, C., Rinner, S., Hull, A., and Vergne-Marini, P. A longitudinal study of varicella zoster infections in renal transplant recipients. *J. Infect. Dis.*, 135, 659, 1977.
11. Gallagher, J. G. and Merigan, T. C. Prolonged herpes-zoster infection associated with immunosuppressive therapy. *Ann. Intern. Med.*, 91, 842, 1977.
12. Horten, B., Price, R. W., and Jimenez, D. Multifocal varicella-zoster virus leukoencephalitis temporarily remote from herpes zoster. *Ann. Neurol.*, 9, 251.
13. Ryder, J. W., Croen, K., Kleinschmidt-DeMasters, B. K., Ostrove, J. M., Straus, S. E., and Cohn, D. L. Progressive encephalitis three months after resolution of cutaneous zoster in a patient with AIDS. *Ann. Neurol.*, 19, 182, 1986.
14. De La Blanchardiere, A., Rozenberg, F., Caumes, E., et al. Neurological complications of varicella-zoster infection in adults with human immunodeficiency virus infection. *Scand. J. Infect. Dis.*, 32, 263–269, 2000.

15. Dolin, R., Reichman, R. C., Masur, M. H., and Whitley, R. J. Herpes zoster-varicella infection in immunocompromised patients. *Ann. Intern. Med.*, 89, 375, 1978.
16. Atkinson, K., Meyers, J. D., Storb, R., Prentice, R. L., and Thomas, E. D. Varicella-zoster virus after marrow transplantation for aplastic anaemia or leukaemia. *Transplantation*, 29, 47, 1980.
17. Rand, K. H., Rasmussen, L. E., Pollard, R. B., Arvin, A., and Merigan, T. C. Cellular immunity and herpes virus infections in cardiac-transplant patient. *N. Engl. J. Med.*, 296, 1372, 1976.
18. Guinee, V. F., Guido, J. J., Pfalzgraf, K. A., et al. The incidence of herpes zoster in patients with Hodgkin's disease: an analysis of prognostic factors. *Cancer*, 56, 642, 1985.
19. Correale, J., Monteverde, D. A., Bueri, J. A., and Reich, E. G. Peripheral nervous system and spinal cord involvement in lymphoma. *Acta Neurol. Scand.*, 83, 45, 1991.
20. Rusthoven, J. J., Ahlgren, P., Elhakim, T., et al. Varicella zoster infection in adult cancer patients: a population study. *Arch. Intern. Med.*, 148, 1561, 1988.
21. Sokal, J. E. and Firat, D. Varicella-zoster infection in Hodgkin's disease. *Am. J. Med.* 39, 452, 1965.
22. Norum, J., Bremnes, R. M., and Wist, E. The CHVPP regimen, a risk factor for herpes zoster virus infection in patients treated for Hodgkin's disease. *Eur. J. Haematol.*, 53, 51, 1994.
23. Feld, R., Evans, W. K., and DeBoer, G. Herpes zoster in patients with carcinoma of the lung. *Am. J. Med.*, 73, 795, 1982.
24. Maiche, A. G., Kajanti, M. J., and Pirhonen, S. Simultaneous disseminated herpes zoster and bacterial infection in cancer patients. *Acta Oncol.*, 31, 681, 1992.
25. Gottlieb, M. S., Wolfe, P. R., Fahey, J. L., et al. The syndrome of persistent generalized lymphadenopathy: experience with 101 patients, in *AIDS-Associated Syndromes*, Gupta, S., Ed. Plenum Press, New York, 85, 1984.
26. Colebunders, R., Francis, H., Izaley, L., et al. Evaluation of a clinical case-definition of acquired immunodeficiency syndrome in Africa. *Lancet*, 1, 492, 1987.
27. Mandal, B. K. Herpes zoster and the immunocompromised. *J. Infect.*, 14, 1, 1987.
28. King, D. H. History, pharmacokinetics, and pharmacology of acyclovir. *J. Am. Acad. Dermatol.*, 18, 176, 1988.
29. Hopefl, A. W. The clinical use of intravenous acyclovir. *Drug Intell. Clin. Pharmacy*, 17, 623, 1983.
30. Whitley, R. J. and Gnann, J. W. Acyclovir: a decade later. *N. Engl. J. Med.*, 327, 782, 1992.
31. Elion, G. B., Furman, P. A., Fyfe, J. A., de Miranda, P., Beauchamp, L., and Schaeffer, H. J. Selectivity of action of an antitherpetic agent, 9-(2-hydroxyethoxymethyl)guanine. *Proc. Natl. Acad. Sci. USA*, 74, 5716, 1977.
32. Schaeffer, H. J., Beauchamp, L., de Miranda, P., Elion, G. B., Bauer, D. J., and Collins, P. 9-(2-Hydroxyethoxymethyl)guanine activity against viruses of the herpes group. *Nature*, 272, 583-585, 1978.
33. Bridgen, D. and Whiteman, P. The mechanism of action, pharmacokinetics and toxicity of acyclovir - a review. *J. Infect. Dis.*, 6(Suppl.1), 3, 1983.
34. Biron, K. K., Fyfe, J. A., Noblin, J. E., and Elion, G. B. Selection and preliminary characterization of acyclovir-resistant mutants of varicella-zoster virus. *Am. J. Med.*, 73(Suppl. A), 383-386, 1982.
35. Wade, J. C. and Meyers, J. D. Neurologic symptoms associated with parenteral acyclovir treatment after marrow transplantation. *Ann. Intern. Med.*, 98, 921, 1983.
36. Keeney, R. E., Kirk, M. S., and Bridgen, D. Acyclovir tolerance in humans. *Am. J. Med.*, 73(Suppl.), 176, 1982.
37. Tomson, C. R. V., Goodship, T. H. J., and Rodger, R. S. C. Psychiatric side-effects of acyclovir in patients with chronic renal failure. *Lancet*, 2, 385, 1985.
38. Wellcome Medical Division. Zovirax in ABPI Data sheet compendium 1991-1992, Datafarm Publishers, London, 1748, 1991.
39. Bataille, P., Devos, P., Noel, J. L., Dautrevaux, C., and Lokiec, F. Psychiatric side-effects with acyclovir. *Lancet*, 2, 724, 1985.
40. Rubin, R. Overdose with acyclovir in a CAPD patient. *Perit. Dial. Bull.*, 7, 42, 1987.
41. Swan, S. K. and Bennett, W. M. Oral acyclovir and neurotoxicity. *Ann. Intern. Med.*, 111, 188, 1989.
42. Krigel, R. L. Reversible neurotoxicity due to acyclovir in a patient with chronic lymphatic leukaemia. *J. Infect. Dis.*, 154, 189.
43. Davenport, A., Goel, S., and Mackenzie, J. C. Neurotoxicity of acyclovir in patients with end-stage renal failure treated with continuous ambulatory peritoneal dialysis. *Am. J. Kidney Dis.*, 20, 647, 1992.
44. Beales, P., Almond, M. K., and Kwan, J. T. C. Acyclovir neurotoxicity following oral therapy: prevention and treatment in patients on haemodialysis. *Nephron*, 66, 362, 1994.
45. Blum, M. R., Liao, S. H. T., and de Miranda, P. Overview of acyclovir pharmacokinetic desposition in adults and children. *Am. J. Med.*, 73(Suppl. 1A), 186, 1982.
46. Laskin, O. L., Longstreth, J. A., Whelton, A., et al. Effect of renal failure on the pharmacokinetics of acyclovir. *Am. J. Med.* 73(Suppl. 1A), 197, 1982.
47. MacDiarmid-Gordon, A. R., O'Connor, M., Beaman, M., and Ackrill, P. Neurotoxicity associated with oral acyclovir in patients undergoing dialysis. *Nephron*, 62, 280, 1992.
48. Spiegel, D. M. and Lau, K. Acute renal failure and coma secondary to acyclovir therapy. *J. Am. Med. Assoc.*, 255, 1882, 1986.
49. Johnson, R., Douglas, J., Corey, L., and Krasney, H. Adverse effects with acyclovir and meperidine. *Ann. Intern. Med.*, 103, 962, 1985.
50. Gill, M. J. and Burgess, E. Neurotoxicity of acyclovir in end stage disease. *J. Antimicrob. Chemother.*, 25, 300, 1990.

51. Feldman, S., Rodman, J., and Gregory, B. Excessive serum concentrations of acyclovir and neurotoxicity. *J. Infect. Dis.* 157, 385, 1988.
52. Haefeli, W. E., Schoenenberger, R. A. Z., Weiss, P., and Ritz, R. F. Acyclovir-induced neurotoxicity: concentration-side effect relationship in acyclovir overdose. *Am. J. Med.*, 94, 212, 1993.
53. Gnann, J. W. New antivirals with activity against varicella-zoster virus. *Ann. Neurol.*, 34, S69, 1994.
54. Vere Hodge, R. A. Famciclovir and penciclovir: the mode of action of famciclovir including its conversion to penciclovir. *Antiviral Chem. Chemother.*, 42, 67, 1993.
55. Pue, M. A. and Benet, L. Z. Pharmacokinetics of famciclovir in man. *Antiviral Chem. Chemother.*, 4(Suppl. 1), 47, 1993.
56. Abramowitz, M. Famciclovir for herpes zoster. *Med. Lett. Drugs Ther.*, 36, 97, 1994.
57. Saltzman, R., Jurewicz, R., and Boon, R. Safety of famciclovir in patients with herpes zoster and genital herpes. *Antimicrob. Agents Chemother.*, 38, 2454, 1994.
58. Tying, S., Nahlik, J., Cunningham, A., and the Collaborative Famciclovir Herpes Zoster Clinical Study Group. Efficacy and safety of famciclovir in the treatment of patients with herpes zoster. *Proc. 33rd Intersci. Conf. Antimicrob. Agents Chemother.*, American Society for Microbiology, Washington, DC, abstract 1540, 1993.
59. Gheeraert, P., and the Famciclovir Herpes Zoster Virus Clinical Study Group. Efficacy and safety of famciclovir in the treatment of uncomplicated herpes zoster. *Proc. 32nd Intersci. Conf. Antimicrob. Agents Chemother.*, American Society for Microbiology, Washington, DC, abstract 1108, 1992.
60. Sacks, S. L., Bishop, A. M., Fox, R., and Lee, G. C. Y. A double-blind, placebo-controlled trial of the effect of chronically administered oral famciclovir on sperm production in men with recurrent genital herpes infection. *Antiviral Res.*, 23(Suppl. 1), 72, 1994.
61. Gnann, J., Crumpacker, C., Lalezari, J., et al. Sorivudine versus acyclovir for treatment of dermatomal herpes zoster in human immunodeficiency virus-infected patients: results from a randomized, controlled clinical trial. *Antimicrob. Agents Chemother.*, 42, 1139–1145, 1998.
62. Huff, J. C., Bean, B., Balfour, H. H. Jr., et al. Therapy of herpes zoster with oral acyclovir. *Am. J. Med.*, 85(Suppl. 2A), 84, 1988.
63. Wood, M. J., Ogan, P. H., McKendrick, M. W., Care, C. D., McGill, J. I., and Webb, E. M. Efficacy of oral acyclovir treatment of acute herpes zoster. *Am. J. Med.*, 85(Suppl. 2A), 79, 1988.
64. Gnann, J. W. and Whitley, R. J. Natural history and treatment of varicella-zoster in high-risk populations. *J. Hosp. Infect.*, 18(Suppl.), 317, 1991.
65. Balfour, H. H. Jr. Current management of varicella zoster virus infections. *J. Med. Virol.*, Suppl. 1, 74, 1993.
66. Stankus, S. J., Dlugopolski, M., and Packer, D. Management of herpes zoster (shingles) and postherpetic neuralgia. *Am. Fam. Physician*, 61, 2437–2444, 2447–2448, 2000.
67. Safrin, S., Berger, T. G., Gilson, I., et al. Foscarnet therapy in five patients with AIDS and acyclovir-resistant varicella-zoster virus infection. *Ann. Intern. Med.*, 115, 19, 1991.
68. Smith, K. J., Kahlter, D. C., Davis, C., James, W. D., Skelton, H. G., and Angritt, P. Acyclovir-resistant varicella zoster responsive to foscarnet. *Arch. Dermatol.*, 127, 1069, 1991.
69. Deray, G., Martinez, F., Katlama, C., et al. Foscarnet nephrotoxicity: mechanism, incidence and prevention. *Am. J. Nephrol.*, 9, 316, 1989.
70. Sempere, A., Sanz, G. F., Senent, L., et al. Long-term acyclovir prophylaxis for prevention of varicella zoster virus infection after autologous blood stem cell transplantation in patients with acute leukemia. *Bone Marrow Transplant.*, 10, 495, 1992.
71. Shepp, D. H., Dandliker, P. S., and Meyers, J. D. Treatment of varicella-zoster virus infection in severely immunocompromised patients: a randomized comparison of acyclovir and vidarabine. *N. Engl. J. Med.*, 314, 208, 1986.
72. Paryani, S. G. and Azuin, A. M. Intrauterine infection with varicella-zoster virus after maternal varicella. *N. Engl. J. Med.*, 314, 1542, 1986.
73. Locksley, R. M., Flournoy, N., Sullivan, K. M., and Mayers, J. D. Infection with varicella-zoster virus after marrow transplantation. *J. Infect. Dis.*, 152, 1172, 1985.
74. Bustamantem, C. I. and Wade, J. C. Herpes zoster virus infection in the immunocompromised cancer patient. *J. Clin. Oncol.*, 9, 1903, 1991.
75. Selby, P. J., Jameson, B., and Watson, J. G. Parenteral acyclovir: therapy for herpes virus infection in man. *Lancet*, 2, 1267, 1979.
76. Gluckman, E., Devergie, A., and Melo, R. Prophylaxis of herpes infections after bone marrow transplantation by oral acyclovir. *Lancet*, 2, 706, 1983.
77. Wingard, J. R. Viral infections in leukemia and bone marrow transplant patients. *Leuk. Lymphoma*, 11(Suppl. 2), 115, 1993.
78. Feldman, S. Varicella zoster infections in bone marrow transplants. *Recent Results Cancer Res.*, 132, 177, 1993.
79. Ben, B., Buren, C. T., and Balfour, H. H. Jr. Acyclovir therapy for acute herpes zoster. *Lancet*, 2, 118, 1982.
80. Bridgen, D., Rosling, A. E., and Woods, N. C. Renal function after acyclovir intravenous injection. *Am. J. Med.*, 73(Suppl. 1A), 182, 1982.
81. Stoffel, M., Squifflet, J. P., Pirson, Y., Lamy, M., and Alexandre, G. P. J. Effectiveness of oral acyclovir prophylaxis in renal transplant recipients. *Transplant. Proc.*, 19, 2190, 1987.
82. Meyers, J. D., Wade, J. C., Shepp, D. H., and Newton, B. Acyclovir treatment of varicella-zoster virus infection in the

- compromised host. *Transplantation*, 37, 571, 1984.
83. Hayes, K., Shakuntala, V., Pingle, A., Dhawan, I. K., and Masri, M. A. Safe use of acyclovir (zovirax) in renal transplant patients on cyclosporine A therapy: case reports. *Transplant. Proc.*, 24, 1926, 1992.
84. Johnson, P. C., Kumor, K., Welsh, M. S., Woo, J., and Kahan, B. D. Effects of coadministration of cyclosporine and acyclovir on renal function of renal allograft recipients. *Transplantation*, 44, 329, 1987.
85. Glesby, M. J., Moore, R. D., Chaisson, R. E., and the Zidovudine Epidemiology Study Group. Herpes zoster in patients with advanced human immunodeficiency virus infection treated with zidovudine. *J. Infect. Dis.*, 168, 1264, 1993.
86. Friedman-Kien, A. E., Lafleur, F. L., Gendler, E., et al. Herpes zoster: a possible early sign for development of acquired immunodeficiency syndrome in high-risk individuals. *J. Am. Acad. Dermatol.*, 14, 1023, 1986.
87. Snoeck, R., Gérard, M., Sadot-Delvaux, C., et al. Meningoradiculoneuritis due to acyclovir-resistant varicella zoster in an acquired immune deficiency syndrome patient. *J. Med. Virol.*, 42, 338, 1994.
88. Balfour, H. H. Jr. Acyclovir, in *The Antimicrobial Agents Annual/3*, Peterson, P. K. and Verhoef, J., Eds., Elsevier Science, New York, 345, 1988.
89. Collins, P. Viral sensitivity following the introduction of acyclovir. *Am. J. Med.*, 85, 129, 1988.
90. Janier, M., Hillion, M., Baccard, M., et al. Chronic varicella zoster infection in acquired immunodeficiency syndrome. *J. Am. Acad. Dermatol.*, 18, 584, 1988.
91. Pahwa, S., Biron, K., Lim, W., et al. Continuous varicella-zoster infection associated with acyclovir resistance in a child with AIDS. *J. Am. Med. Assoc.*, 260, 2879, 1988.
92. Linneman, C. C., Biron, K. K., Hoppenjans, W. G., and Solinger, A. M. Emergence of acyclovir-resistant varicella zoster virus in an AIDS patient on prolonged acyclovir therapy. *AIDS*, 4, 577, 1990.
93. Hoppenjans, W. B., Bibler, M. R., Ormer, R. L., and Solinger, A. M. Prolonged cutaneous herpes zoster in acquired immunodeficiency syndrome. *Arch. Intern. Med.*, 126, 1048, 1990.
94. Waring, J. J., Neuburger, K., and Geever, E. F. Severe forms of chickenpox in adults. *Arch. Intern. Med.*, 69, 384, 1942.
95. Feldman, S., Varicella-zoster virus pneumonitis. *Chest*, 106(Suppl.), 22S, 1994.
96. Schuchter, L. M., Wingard, J. R., Piantadosi, S., et al. Herpes zoster infection after autologous bone marrow transplantation. *Blood*, 74, 1424, 1989.
97. Wacker, P., Hartmann, O., Benhamou, E., Salloum, E., and Lemerle, J. Varicella-zoster virus infections after autologous bone marrow transplantation in children. *Bone Marrow Transplant.*, 4, 191, 1989.
98. Feldhoff, C. M., Balfour, H. H. Jr., Simmons, R. L., Najarian, J. S., and Maurer, S. M. Varicella in children with renal transplants. *J. Pediatr.*, 98, 25, 1981.
99. Lynfield, R., Herrin, J. T., and Rubin, R. H. Varicella in pediatric renal transplant recipients. *Pediatrics*, 90, 216, 1992.
100. McGregor, R. S., Zitelli, B. J., Urbach, A. H., Malatack, J. J., and Gartner, J. C. Jr. Varicella in pediatric orthotopic liver transplant recipients. *Pediatrics*, 83, 256, 1989.
101. Feldman, S., Hughes, W. T., and Daniel, C. B. Varicella in children with cancer: 77 cases. *Pediatrics*, 56, 388, 1975.
102. Feldman, S. and Lott, L. Varicella in children with cancer: impact of antiviral therapy and prophylaxis. *Pediatrics*, 80, 465, 1987.
103. Feldman, S., Hughes, W. T., and Kim, H. Y. Herpes zoster in children with cancer. *Am. J. Dis. Child.*, 126, 178, 1973.
104. Jura, E., Chadwick, E. G., Josephs, S. H., et al. Varicella-zoster virus infections in children infected with human immunodeficiency virus. *Pediatr. Infect. Dis. J.*, 8, 586, 1989.
105. Dowell, S. F. and Bresee, J. S. Severe varicella associated with steroid use. *Pediatrics*, 92, 223, 1993.
106. Abzug, M. J. and Cotton, M. F. Severe chickenpox after intranasal use of corticosteroids. *J. Pediatr.*, 123, 577, 1993.
107. Kasper, W. J. and Howe, P. M. Fatal varicella after a single course of corticosteroids. *Pediatr. Infect. Dis. J.*, 9, 729, 1990.
108. Neoh, C., Harding, S. P., Saunders, D., et al. Comparison of topical and oral acyclovir in early herpes zoster ophthalmicus. *Eye*, 8, 688, 1994.
109. Aylward, G. W., Claoué, C. M. P., Marsh, R. J., and Yasseem, N. Influence of oral acyclovir on ocular complications of herpes zoster ophthalmicus. *Eye*, 8, 70, 1994.
110. Womack, L. W. and Leisegang, T. J. Complications of herpes zoster ophthalmicus. *Arch. Ophthalmol.*, 101, 42, 1983.
111. Karbassi, M., Raizman, M. B., and Schuman, J. S. Herpes zoster ophthalmicus. *Surv. Ophthalmol.*, 36, 395, 1992.
112. Harding, S. P., Lipton, J. R., and Wells, J. C. D. Natural history of herpes zoster ophthalmicus: predictors of postherpetic neuralgia and ocular involvement. *Br. J. Ophthalmol.*, 71, 353, 1987.
113. Mader, T. H. and Stulting, R. D. Viral keratitis. *Incet. Dis. Clin. North Am.*, 6, 831, 1992.
114. Harding, S. P., Lipton, J. R., and Wells, J. C. D. Natural history of herpes zoster ophthalmicus, predictors of postherpetic neuralgia and ocular involvement. *Br. J. Ophthalmol.*, 71, 353, 1986.
115. Scheie, H. G. Herpes zoster ophthalmicus. *Trans. Ophthalmol. Soc. U.K.*, 90, 899, 1970.
116. Leisegang, T. J. Corneal complications from herpes zoster ophthalmicus. *Ophthalmology*, 92, 316, 1985.
117. Marsh, R. J. and Cooper, M. Ophthalmic herpes zoster. *Eye*, 7, 350, 1993.
118. Yoser, S. L., Forster, D. J., and Rao, N. A. Systemic viral infections and their retinal and choroidal manifestations. *Surv. Ophthalmol.*, 37, 313, 1993.
119. Harding, S. P. Management of ophthalmic zoster. *J. Med. Virol. Suppl.*, 1, 97, 1993.
120. McGill, J. and Chapman, C. A. A comparison of topical acyclovir with steroids in the treatment of herpes zoster keratouveitis. *Br. J. Ophthalmol.*, 67, 746, 1983.

121. Marsh, R. J. and Cooper, M. Double-masked trial of topical acyclovir and steroids in the treatment of herpes zoster ocular inflammations. *Br. J. Ophthalmol.*, 75, 542, 1991.
122. Bridgen, D., Foule, A., and Rosling, A. Acyclovir, a new antiherpetic drug: early experience in man with systemically administered drug, in *Developments in Antiviral Therapy*, Collier, L. H. and Oxford, J., Eds. Academic Press, London, 53, 1980.
123. Biron, K. K. and Elion, G. B. In vitro susceptibility of varicella zoster virus to acyclovir. *Antimicrob. Agents Chemother.*, 18, 443, 1980.
124. Crumpacker, C. S., Schnipper, L. E., Zaia, J. A., and Levin, H. J. Growth inhibition by acycloguanosine of herpesvirus isolated from human infections. *Antimicrob. Agents Chemother.*, 15, 642, 1979.
125. Poirier, R. H., Kingham, J. D., de Miranda, P., and Annel, M. Intraocular antiviral penetration. *Arch. Ophthalmol.*, 100, 1964, 1982.
126. Cobo, L. M., Foulks, G. N., Leisegang, T., et al. Oral acyclovir in the treatment of acute herpes zoster ophthalmicus. *Ophthalmology*, 93, 763, 1986.
127. Harding, S. P. and Porter, S. M. Oral acyclovir in herpes zoster ophthalmicus. *Curr. Eye Res.*, 10, 177, 1991.



<http://www.springer.com/978-1-58829-009-0>

Opportunistic Infections

Treatment and Prophylaxis

Georgiev, V.S.

2003, XX, 545 p., Hardcover

ISBN: 978-1-58829-009-0

A product of Humana Press