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Treatment of Herpes Zoster and Postherpetic Neuralgia

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Each year members of a different medical faculty prepare articles for "Practical Therapeutics." This is the first in a series from the University of Arizona College of Medicine, Tucson. Guest editors of the series are Barry Weiss, M.D. and Evan Kligman, M.D.

Herpes zoster results from reactivation of latent varicella-zoster virus. It is most common in elderly patients and immunosuppressed patients, especially those with human immunodeficiency virus (HIV) infection. Zoster is often the earliest indicator of HIV infection. The acute course of herpes zoster is generally benign, but systemic complications may be fatal. Postherpetic neuralgia is the major chronic complication and is a difficult management problem. High-dose acyclovir (800 mg orally five times daily) has recently been approved for treatment of herpes zoster and, if started early, decreases the duration and severity of symptoms. In the prevention of postherpetic neuralgia, acyclovir does not appear to be effective, and the efficacy of steroids is questionable. The best therapy currently available for postherpetic neuralgia is amitriptyline, topical capsaicin and transcutaneous electrical stimulation.

Herpes zoster results from reactivation of varicella-zoster virus that has been dormant in the dorsal root ganglia. The connection between varicella (chickenpox) and zoster was first suggested in 1892 by a Viennese physician, Janos Von Bokay, after observing several cases of varicella in persons exposed to zoster through household contact.[1] In 1984, restriction endonuclease digestion analysis of virus isolated from a patient who first had chickenpox and then had zoster demonstrated identical varicella-zoster virus DNA in both illnesses, thus confirming the etiologic role of varicella-zoster virus in both varicella and herpes zoster.[2]

Herpes zoster generally presents as a painful, unilateral vesicular eruption within a single dermatome. In young, immunocompetent patients, the course of zoster is usually benign. However, in elderly patients, acute neuritis and postherpetic neuralgia may develop, and can be debilitating. Immunocompromised persons are at risk for more serious disease and increased morbidity.

Treatment of acute zoster has been problematic. Acyclovir (Zovirax), given orally at high doses, now appears effective in limiting the duration of the acute infection if therapy is initiated early in the course. The problem of postherpetic neuralgia has received much attention, and a wide variety of therapies have been used for this condition. No one treatment is uniformly successful, but some offer significant benefits.

Epidemiology

Zoster occurs at some time in 10 to 20 percent of the population.[3] An equal proportion of men and women are affected, and there is no racial predilection. Zoster has no seasonal variation or relation to epidemics of chickenpox.[4] It is important to remember that persons with zoster are contagious to persons not immune to chickenpox. Also, a previous history of zoster does not rule out recurrence of zoster, although recurrence is rare.[5]

Eighty percent of all cases of herpes zoster occur in persons 20 years of age or older. While persons in all age groups may be affected, the incidence clearly increases with age. Herpes zoster occurs at a constant rate of two to three cases per 1,000 persons between the ages of 20 and 50 years; the rate increases to five cases per 1,000 persons between the ages of 50 and 80 years and increases again to 10 cases per 1,000 persons over age 80.[3] The reason for the increased incidence zoster with increasing

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age remains unclear. The most common theory is that age-related impairment of cell-mediated immunity is responsible.[6]

Zoster is clearly associated with immune suppression. For example, bone marrow and other transplant recipients have high rates of zoster, particularly in the first two to six months after transplantation. In addition, persons with malignancies, especially lymphoreticular malignancies, have an increased frequency of zoster; in one two-year study,[7] zoster was found in 25 percent of persons with Hodgkin's disease. However, the longstanding notion that patients with zoster are likely to have an underlying malignancy does not appear to be true. Recent studies have conclusively disproved this belief.[8]

Zoster frequently occurs in patients infected with the human immunodeficiency virus (HIV).[9] In fact, zoster is often the first clinical manifestation of the disease.[10] The exact frequency of zoster in HIV infection is not known; however, in one series of 48 consecutive patients presenting with zoster, 70 percent had HIV infection.[11] Thus, the occurrence of zoster—particularly in persons under age 50 (in whom the frequency of zoster is otherwise low)—warrants consideration of HIV risk factors and possibly HIV antibody testing.

FIGURE 1. The classic dermatomal vesicular rash of herpes zoster.

Patients with zoster may transmit varicella-zoster virus (as chickenpox) to persons at high risk (neonates, nonimmune persons, pregnant women and immunocompromised patients). High-risk persons should be kept away from patients with active zoster.

Clinical Manifestations

The clinical features of zoster have been divided into three phases: the prodromal phase, the acute phase and the chronic phase.[12] Not every patient passes through each phase, and some patients may have unusual or atypical presentations.

PRODROMAL PHASE

Before the development of overt skin lesions, sensations described as burning, tingling, itching, boring, prickly or knife-like occur. These sensory changes appear to result from degeneration of cutaneous nerve fibrils from viral activity. Sensory changes in involved dermatomes precede the development of the rash of zoster by hours to days.

ACUTE PHASE

The rash of zoster is typically erythematous and maculopapular and evolves rapidly to grouped vesicles (*Figure 1*). The emergence of the rash may be accompanied by constitutional symptoms of fatigue, malaise, headache and low-grade fever. Generally, the vesicles become pustular and/or hemorrhagic by the third to the fourth day. Collapse of the vesicles, with drying and crust formation, occurs in about seven to 10 days. Resolution usually occurs in 14 to 21 days, with the crusts falling off, often leaving residual hyperpigmented or hypopigmented scarring.

CHRONIC PHASE

In younger patients, the pain associated with acute zoster generally subsides

TABLE 1

Complications of Herpes Zoster

Meningoencephalitis
Cerebrovasculopathy
Cranial nerve syndromes
Trigeminal (ophthalmic) branch (herpes zoster ophthalmicus)
Facial and auditory nerves (Ramsay Hunt syndrome)
Peripheral motor weakness
Transverse myelitis
Visceral involvement
Pneumonitis
Hepatitis
Pericarditis/myocarditis
Pancreatitis
Esophagitis
Enterocolitis
Cystitis
Synovitis
Cutaneous dissemination
Superinfection of skin lesions

as the rash resolves. Patients over 40 to 50 years of age, however, are at increased risk of developing postherpetic neuralgia. The overall incidence of this chronic pain syndrome is only about 15 percent. However, the percentage of affected persons increases dramatically with age; over 50 percent of those over age 60 will have pain lasting more than one month after the rash has healed.[13]

COMPLICATIONS

While zoster usually follows the typical course, immunocompetent or immunocompromised patients sometimes have unusual presentations or complications. Some of the complications are listed in *Table 1*.

In some patients, the prodromal symptoms are not followed by a rash. This is known as zoster sine herpete, or "zoster without the rash." The frequency of this syndrome is unknown because the diagnosis rests on serologic testing, which may not be performed unless zoster is a diagnostic consideration.[5]

Diagnosis

The diagnosis of zoster is clear when prodromal symptoms have occurred and the typical dermatomal vesicular rash is present. However, differentiating zoster from herpes simplex virus, coxsackievirus, contact dermatitis and superficial pyoderma is sometimes difficult.

Useful diagnostic procedures include viral culture, the Tzanck smear and monoclonal antibody tests. When available, viral culture is the most useful diagnostic test.

The Tzanck smear is prepared with scrapings from the base of a fresh vesicle. When positive, the smear reveals multinucleated giant cells, inclusion bodies and "balloon degeneration" of epithelial cells. Positive results confirm herpes virus etiology but do not distinguish between herpes simplex and herpes zoster. Viral cultures, direct immunofluorescence tests or assessment of acute and convalescent titers may be required to distinguish between herpes simplex virus and varicella-zoster virus. A negative Tzanck smear does not rule out herpes zoster, and many physicians are not skilled in performing this office diagnostic test.

Treatment

The treatment goals in patients with zoster are to minimize discomfort, shorten the duration of symptoms, prevent dissemination or other complications, and prevent or minimize postherpetic neuralgia. The treatment of acute zoster may be divided into three areas of focus: local care, management of acute pain and antiviral drug therapy.

LOCAL CARE

The two goals in management of zoster skin lesions are relief of itching and reduction of bacterial colonization of damaged

skin. Wet dressings or compresses, applied for 30 to 60 minutes four to six times daily, are soothing and help remove exudates or crusts. Either tap water or 5 percent aluminum acetate (Burow's solution) can be used for the dressings. Lotions such as calamine may be applied after the compresses are removed. Care should be taken not to apply so much lotion that the residual powder cakes and becomes difficult to remove.

Ulcerated lesions that become secondarily infected may require antibiotic creams or ointments. It has been reported that silver sulfadiazine (Flint SSD, Silvadene), used four times daily, has antiviral activity in addition to antibacterial activity and may shorten the course of zoster.[14] Topical steroids should not be used.

ACUTE PAIN

The acute pain of zoster can be reduced by good local care. Mild to moderately strong analgesics such as acetaminophen, codeine and nonsteroidal anti-inflammatory agents are generally effective in providing relief from the pain of acute zoster.

ANTIVIRAL DRUGS

Antiviral agents currently available for use against varicella-zoster virus include cytarabine (Cytosar-U), idoxuridine (Herplex, Stoxil), vidarabine (Vira-A) and acyclovir. The primary action of these drugs is inhibition of viral DNA synthesis, either by acting as antimetabolites (cytarabine and idoxuridine) or by inhibiting DNA polymerase (vidarabine and acyclovir).[12]

Each of these drugs must be phosphorylated within cells. Acyclovir may, therefore, have an advantage over other drugs because it has a much higher rate of phosphorylation in herpes virus-infected cells, due to the activity of a herpes-specific thymidine kinase.[15] Vidarabine and acyclovir are both approved by the U.S. Food and Drug Administration for the treatment of zoster; however, most clinicians consider acyclovir the drug of choice because of its relatively low toxicity.

ACYCLOVIR

Acyclovir is available for both oral and intravenous administration. The concentration of acyclovir that inhibits viral replication in culture by 50 percent (ID_{50}) is about 5.05 μg per mL. This concentration is achieved with intravenous or oral administration. Intravenous acyclovir, given in a dosage of 5 mg per kg every eight hours, results in plasma concentrations of 3 to 43 μg per mL. Oral acyclovir, given in a dosage of 800 mg every four hours, achieves plasma levels of 4 to 8 μg per mL.[16]

When given intravenously, acyclovir is effective for the treatment of zoster in immunocompromised or immunocompetent persons and in those with local or systemic disease.[1,6,12] At a dosage of 5 mg per kg every eight hours for seven to 10 days, the drug is generally well tolerated. Transient nephropathy has been reported and is thought to be due to deposition of acyclovir crystals in the lower nephrons.[17] To avoid this complication, intravenous acyclovir should be administered over one hour, the patient should be kept well hy-

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drated and the dose should be reduced if renal disease is present. Other reported side effects include venous inflammation or thrombophlebitis, central nervous system toxicity (including headaches, lethargy and delirium), gastrointestinal toxicity (such as nausea, vomiting and diarrhea) and skin rash.

Oral acyclovir is also effective for zoster. The FDA has recently approved oral acyclovir for this indication at a dosage of 800 mg every four hours (five times daily) for seven to 10 days. Oral acyclovir at this dosage is generally well tolerated. The manufacturer lists malaise, nausea and headache as the most common adverse reactions and recommends dosage reduction in cases of renal impairment.

In two double-blind, placebo-controlled trials,[18,19] oral acyclovir was found to significantly reduce the duration of viral shedding, the duration of lesions and the severity of acute pain. The effect on chronic pain was less clear. Another recent study[20] found oral acyclovir to be as effective as intravenous acyclovir for the treatment and prevention of zoster dissemination in bone marrow transplant recipients.

CANDIDATES FOR TREATMENT

Before acyclovir is used, several factors must be considered. The first is the patient's clinical condition. The importance of administering acyclovir is greatest if the patient is predisposed to herpes zoster because of a concurrent condition (i.e., immunosuppression due to drugs, malignancy, HIV infection or other causes). Early initiation of acyclovir therapy is essential in immunocompromised patients to avert potentially life-threatening complications.

A second consideration is timing. If it is to be effective, acyclovir must be started as early as possible in the course of the disease. Late treatment is less likely to be useful and may be unwarranted.

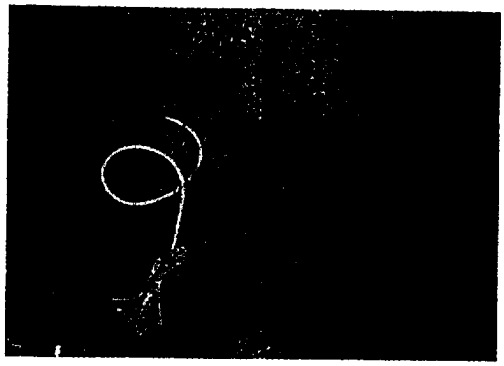

FIGURE 2. Disseminated herpes zoster.

A third consideration is cost. Acyclovir is expensive. (The cost for 10 days of oral therapy is about $150.) In some patients, particularly young, immunocompetent persons, the cost of the drug must be weighed against the risk of zoster, which is usually benign in this population.

Experience with oral acyclovir is limited and thus the indications for treatment await complete clarification. Immunosuppressed patients may be expected to benefit from early high-dose oral or even intravenous treatment. Complications such as disseminated zoster (*Figure 2*) or neurologic problems also warrant aggressive treatment, generally with intravenous acyclovir. In the remaining group of patients (immunocompetent persons with uncomplicated zoster), use of oral acyclovir is safe and effective and, in the absence of evidence to the contrary, will likely become the standard of care.

Postherpetic Neuralgia

Postherpetic neuralgia is the most common and perhaps the most problematic complication of zoster. It is usually defined as pain persisting for at least one month after the zoster rash has healed.[21]

EPIDEMIOLOGY

Between 9 and 14 percent of patients with zoster have postherpetic neuralgia.[22] The complication occurs more frequently with increasing age. In one large, 25-year British study of a general practice population, postherpetic neuralgia developed in only 4 percent of persons between 30 and 50 years of age, compared with 34 percent of those over 80 years of age.[23] Postherpetic neuralgia also tends to resolve over time. In 50 percent of persons, posther-

petic neuralgia resolves in three months; in 78 percent it resolves by one year, and in 98 percent it resolves by five years.

CLINICAL FEATURES

After the acute rash of zoster has healed, the skin is usually scarred and is either hyperpigmented or hypopigmented. In cases of postherpetic neuralgia, the scar is often hyposensitive to pinprick but hypersensitive to light touch.[24]

The pain of postherpetic neuralgia occurs in two patterns. Pain may be paroxysmal and lancinating, or it may be steady, with burning or aching. The pain is frequently aggravated by light touch, and patients often take measures to prevent clothing or bed sheets from coming into contact with the affected area.

PREVENTIVE TREATMENT

A large number of drugs have been used in an effort to prevent postherpetic neuralgia. These include corticosteroids, amantadine (Symmetrel), levodopa (Dopar, Larodopa), vidarabine, alpha interferon and acyclovir.

Corticosteroids have long been recommended and used by clinicians in the prevention of postherpetic neuralgia. Unfortunately, evidence on the effectiveness of corticosteroids is inconclusive. Two recent reviews of studies providing evidence supporting the effectiveness of corticosteroids found serious methodologic problems. Both reviews concluded that the question of effectiveness remained unanswered.[25,26]

If corticosteroids are used, it is recommended that they be given only to patients over 50 years of age, since they are at highest risk. Corticosteroids should be started as early as possible and administered at a dose equivalent to 40 to 60 mg of prednisone daily over a three-week period. Steroids should not be used in immunocompromised patients.[4]

TABLE 2

Agents and Procedures Used in Treatment of Postherpetic Neuralgia

Oral narcotic and nonnarcotic analgesics
Antidepressants
Amitriptyline (Elavil, Endep)
Anticonvulsants
Carbamazepine (Tegretol)
Valproic acid (Depakene)
Neuroleptics
Chlorprothixene (Taractan)
Fluphenazine (Permitil, Prolixin)
Thioridazine (Mellaril)
Perphenazine (Trilafon)
Local anesthetics
Ethyl chloride
Topical lidocaine (Xylocaine)
Aspirin dissolved in chloroform
Capsaicin cream (Zostrix)
Subcutaneous anesthetics
Vibration
Ultrasound
Transcutaneous electrical stimulation (TENS)
Acupuncture
Sympathetic nerve block
Dorsal column stimulation

The effect of acyclovir on postherpetic neuralgia is unclear. Two studies found that pain was significantly reduced in the second and third month after zoster if acyclovir had been given during the acute phase. After three months, however, pain did not differ significantly between acyclovir-treated and placebo groups.[18,27]

PAIN MANAGEMENT

The large number of therapies used for postherpetic neuralgia are testament to the difficulty of managing the condition. *Table 2* lists some of the agents and procedures used.

The effectiveness of the various treatment modalities is difficult to assess because of deficiencies in the design of studies evaluating them.[21] No one therapy is uniformly effective. The best treatments available for postherpetic neuralgia may be capsaicin cream (Zostrix), transcutaneous nerve stimulation (TENS) and low-dose amitriptyline (Elavil, Endep).[21,22]

Capsaicin. Capsaicin (trans-8-methyl-*N*-vanillyl-6-noneramide) is a natu-

rally occurring irritant compound found in the fruit of several members of the nightshade plant family. Two recent studies found capsaicin effective in decreasing postherpetic neuralgia.[28,29] One of these studies was double-blinded and placebo-controlled and showed that after four weeks of treatment, 77 percent of patients had a reduction in pain.[28]

Capsaicin is thought to act by depleting substance P from cell bodies and nerve terminals. Substance P is believed to be the primary chemomediator of painful impulses from the periphery to the central nervous system.[12] Interestingly, capsaicin blocks pain without affecting light touch or vibratory sensations. Capsaicin, available as a 0.025 percent cream, should be applied three to five times daily to affected skin. Local burning, stinging or redness of the skin is common, but generally self-limited. Results are usually achieved by day 14. The optimum duration of treatment is unknown.[28]

Transcutaneous Electrical Stimulation. TENS is believed to reduce pain by activating large low-threshold nerve fibers, thereby counteracting increased discharges from small unmyelinated fibers. One study showed pain reduction in about 30 percent of patients treated with TENS.[27] TENS treatments are usually carried out three or four times daily for 30 to 60 minutes. One to two weeks of therapy may be needed to assess response.

Amitriptyline. Amitriptyline was first recognized as effective in relieving postherpetic neuralgia in 1965, when it was used for the treatment of depression in patients with the pain syndrome.[30] Tricyclic antidepressants (including amitriptyline) are believed to function as analgesics through their ability to block reuptake of serotonin and norepinephrine. Importantly, the analgesic effect of amitriptyline seems to be independent of the antidepressant effect and can be achieved at lower doses.[31] Because of the side effects of amitriptyline, it is recommended that a low dosage be given, particularly in elderly patients; it should be started in doses of 10 to 25 mg per day and then increased slowly in 10-mg increments.[31,32]

Final Comment

The safety and efficacy of high-dose acyclovir (800 mg orally five times daily) in decreasing the duration and severity of zoster represents a major breakthrough in clinical management. The earliest possible use of acyclovir will result in the best possible outcome, particularly in the elderly and in the immunosuppressed, groups that are at greatest risk of complications.

Postherpetic neuralgia will continue to be a problem, since acyclovir does not appear to be effective in prevention. No therapy is uniformly successful for this syndrome. Topical capsaicin, TENS and amitriptyline appear to provide the best results.

Finally, the common occurrence of zoster in HIV-infected persons, the concurrent increased risk of complications in these patients and the availability of therapy for HIV infection warrant a careful investigation of HIV risk factors and, perhaps, HIV antibody testing in persons with zoster, particularly those less than 50 years of age.

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