Topics in Primary Care Medicine

Management of Herpes Simplex and Varicella-Zoster Virus Infections

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Herpes simplex virus and varicella-zoster virus are common infections and are seen frequently in clinical practice. Infection with these viruses results in cutaneous lesions that may be diagnosed clinically, but widely available laboratory testing is useful for confirmation. Asymptomatic herpes simplex virus shedding, or "subclinical reactivation," likely occurs in all persons infected with herpes simplex virus and results in the transmission of virus despite the absence of signs or symptoms that suggest active infection. Oral and intravenous acyclovir are effective in treating initial and recurrent herpes simplex and varicella-zoster virus infections. The daily administration of oral acyclovir as suppressive therapy is effective in patients with frequently recurring genital infection with herpes simplex virus by reducing the number of symptomatic recurrences and the frequency of asymptomatic virus shedding. Two new antiviral agents, famciclovir and valacyclovir hydrochloride, have been approved for the short-term treatment of recurrent genital herpes simplex virus and recurrent zoster in nonimmunocompromised hosts. Famciclovir and valacyclovir demonstrate superior pharmacokinetics compared with acyclovir and allow for less frequent daily dosing with higher achievable serum drug concentrations. The attenuated live varicella virus vaccine is now available in the United States and prevents primary varicella-zoster virus infection in susceptible children and adults.

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The human herpesviruses comprise at least eight distinct DNA viruses, including herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella-zoster virus (VZV), cytomegalovirus, Epstein-Barr virus, and three recently described viruses designated human herpesvirus types 6, 7, and 8. All herpesviruses produce latent infection, allowing for virus reactivation and recurrent clinical illness throughout the life of the infected host.

Infections with HSV and VZV are common and are seen frequently in clinical practice. It has been estimated that there are more than 500,000 new cases of genital HSV and more than 3 million cases of primary VZV infection (chickenpox) per year in the United States. Recurrent infections with HSV and with VZV (zoster) are common, with the latter occurring with increased frequency with advancing age. Specific antiviral therapy is effective for all of these infections, and primary care physicians should be familiar with the clinical presentations, diagnostic tests, and therapeutic options available for patients with first-episode and recurrent HSV and VZV infections.

Herpes Simplex Virus

The herpes simplex viruses types 1 and 2 infect mucous membranes and cutaneous surfaces and cause latent infection in sensory nerve ganglia that corresponds to the site of initial inoculation. The initial infection may be asymptomatic or result in painful vesicles filled with highly infectious clear fluid.[1–3] When present, vesicles unroof within several days to form moist, shallow ulcers. If left untreated, the ulcers dry, crust, and heal by reepithelialization over two to three weeks.

Recurrent HSV infection occurs with varying frequency in infected persons.[4] Recurrent herpes is usually milder in severity than symptomatic initial infection, and patients typically have fewer lesions and faster healing during recurrences. Asymptomatic virus shedding, or "subclinical reactivation," occurs with greater frequency than previously recognized. Persons infected with HSV who have no signs or symptoms of active HSV infection have cultures positive for virus between 1% and 7% of the days tested. These episodes of asymptomatic shedding may result in the transmission of virus to sexual partners, and patients should be counseled appropriately about this risk.[5–7]

Diagnosis of Herpes Simplex Virus

Although the diagnosis of HSV infection is often suspected on clinical grounds, laboratory testing is usually indicated for confirmation. Virus cultures of fresh vesicular fluid and the direct observation of infected cells scraped from ulcerative lesions by direct fluorescent antibody (DFA) stain are the most useful and reliable diagnostic tests available. Cultures are most likely to be positive for the virus when the lesions are still moist, whereas the DFA

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
DFA = direct fluorescent antibody
FDA = Food and Drug Administration
HIV = human immunodeficiency virus
HSV-1, -2 = herpes simplex virus types 1 and 2
VZV = varicella-zoster virus

stain may still be positive in lesions that are dry and healing. Serologic testing is unreliable, as most commercially available assays do not reliably differentiate HSV-1 from HSV-2 antibody.[8] The Western blot is an accurate serologic test for differentiating previous infection with HSV-1 from HSV-2, but this assay is not widely available.[9] The detection of HSV DNA by polymerase chain reaction technique is useful in the diagnosis of HSV encephalitis (discussed later), but has no role in the diagnosis of mucocutaneous HSV infection.

Treatment of Herpes Simplex Virus Infections

Although newer antiviral drugs have recently become available, acyclovir remains the treatment of choice for most HSV infections. Numerous studies have shown that oral acyclovir is safe and effective in the management of patients with first-episode or recurrent genital HSV infection. Acyclovir treatment in these patients results in a faster healing of lesions, a shortened duration of virus shedding, and a faster resolution of symptoms.[10-18] Patients with first-episode genital herpes should be treated with acyclovir, 200 mg five times a day for ten days.[11,12] Patients with recurrent genital herpes can receive acyclovir at dosages of 200 mg five times a day, 400 mg three times a day, or 800 mg twice a day. Treatment should be continued until all lesions have crusted, which is usually about five days.[12,13] Patient-initiated treatment of recurrent genital herpes, allowing well-motivated persons to begin acyclovir therapy during the prodromal symptoms that may precede visible external lesions, results in maximal therapeutic benefit of the antiviral therapy.[13] Although still prescribed by some clinicians, topical acyclovir has little efficacy and no role in the management of patients with HSV infection.

Patients with frequently recurring genital herpes, often defined as more than six outbreaks per year, or those with exceptionally severe HSV recurrences, can be managed with long-term suppressive acyclovir therapy. The daily administration of acyclovir, 200 mg three times a day or 400 mg twice a day, reduces the number of symptomatic recurrences and the frequency of asymptomatic virus shedding.[14-16] Studies to determine whether long-term suppressive therapy decreases the risk of HSV transmission to sexual partners are not available. Suppressive acyclovir therapy has been approved by the Food and Drug Administration (FDA) for as long as 12 months, although studies have shown continued clinical benefit and no cumulative toxicity with therapy extended over five years.[16,17]

Most studies evaluating oral acyclovir have examined its effects on genital herpes, but acyclovir is also effective for the treatment of HSV infection at any anatomic site. Patients with orolabial HSV can be treated with oral acyclovir in a regimen similar to that used for genital herpes.[17,18] Patients at temporary risk for recurrent orolabial herpes (such as from sun exposure during skiing or sailing trips) can receive prophylactic oral acyclovir, 400 mg twice a day, during the period of risk.[18]

Famciclovir and Valacyclovir Hydrochloride

Two newer oral antiviral regimens, famciclovir, 250 mg twice a day, and valacyclovir hydrochloride, 500 mg twice a day, have been approved by the FDA for the treatment of patients with recurrent genital herpes. Valacyclovir hydrochloride, 1 gm twice a day, has also been approved for patients with first episode genital herpes. Both of these oral drugs have superior bioavailability compared with acyclovir. Famciclovir is well absorbed from the gastrointestinal tract and is converted in vivo into the active metabolite, penciclovir. Penciclovir undergoes phosphorylation through mechanisms similar to that of acyclovir. Valacyclovir is also well absorbed following oral administration and is converted in vivo directly into acyclovir. Because of the improved bioavailability, both oral famciclovir and valacyclovir produce higher serum antiviral activity than that achieved with oral acyclovir.[19,20,21] Clinical studies have shown that famciclovir and valacyclovir are superior to placebo in patients with recurrent genital herpes, but studies have not shown these drugs to be superior to the standard regimen of oral acyclovir. As of this writing, famciclovir and valacyclovir have not been approved as long-term suppressive therapy in patients with frequently recurrent genital HSV. Valacyclovir should not be prescribed in patients with advanced human immunodeficiency virus (HIV) disease, bone marrow transplant recipients, or kidney transplant recipients because of the observation of thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome in these patients receiving high doses during clinical trials (data on file, Glaxo Wellcome, Inc).

Herpes Simplex Virus Encephalitis

The clinical diagnosis of HSV encephalitis can be difficult because of the nonspecific presentation of the illness.[22,23] Diagnosis has required brain biopsy with the demonstration of virus in brain tissue, but recent studies have shown that the detection of HSV DNA from cerebrospinal fluid by polymerase chain reaction is a reliable, rapid, and noninvasive method of diagnosis.[24]Because early treatment of HSV encephalitis is essential for survival and full recovery, all patients suspected to have this infection should be treated promptly with intravenous acyclovir, 10 mg per kg of body weight, every eight hours (with dosage reduction for renal failure) pending the results of diagnostic studies.[25,26] The therapy should be given for at least ten days.

Immunocompromised Host With Herpes Simplex Virus Infection

Immunocompromised patients, including patients with the acquired immunodeficiency syndrome (AIDS), are at risk for severe mucocutaneous HSV infections. These

lesions in an immunocompromised person may appear atypical and can be progressive, severe, and disabling. Especially severe recurrent or chronic, nonhealing HSV lesions in a patient not known to be immunocompromised should warrant clinical evaluation and HIV testing. Aggressive treatment with oral or intravenous acyclovir is indicated for these patients, as most patients will respond and their conditions improve with therapy. Acyclovir resistance may occur in an immunocompromised host, however, and should be suspected in patients who fail to respond clinically to acyclovir therapy and have cultures persistently positive for virus.[27,28] Most strains of acyclovir-resistant HSV are thymidine kinase deficient, and patients with these strains of HSV should be treated with intravenous foscarnet, 40 mg per kg every eight hours, until all lesions have healed.[28] Treatment with foscarnet can result in nephrotoxicity and electrolyte imbalance, and dosage adjustment is required in patients with renal impairment. Foscarnet-resistant HSV has also been described, but appears to be infrequent.[29]

Herpes simplex virus esophagitis occurs occasionally in immunocompromised hosts and results in pain and difficult swallowing. Oral ulcerative lesions may not be present in patients with HSV esophagitis, and diagnosis usually requires upper endoscopy and obtaining specimens of esophageal ulcers for culture. Treatment with intravenous acyclovir, 5 to 10 mg per kg three times a day, is usually indicated as initial therapy. Treatment with oral acyclovir, 400 mg five times a day, can be substituted once the patient can tolerate oral medications and should be continued for 10 to 14 days.

Herpes simplex virus proctitis also occurs in immunocompromised hosts and is seen frequently in patients with AIDS. Patients typically have severe perianal and rectal pain, and ulcerative lesions may be visible externally at the gluteal cleft and perianal region. Flexible sigmoidoscopy may reveal diffuse mucosal ulcerations with inflammation and friability. Treatment with high-dose oral acyclovir (400 to 800 mg 4 times a day) or intravenous acyclovir (5 to 10 mg per kg every 8 hours) is indicated in these patients and should be continued until all lesions have healed. Foscarnet may be required in refractory cases due to the development of acyclovir-resistant infection.

Future Prospects

Clinical trials evaluating recombinant HSV glycoprotein vaccines are currently in progress. Phase I and II trials have shown that HSV vaccination produces detectable immune responses that are comparable to those seen following natural HSV infection.[30] Efficacy data to determine whether vaccination lowers the risk of acquiring HSV infection in susceptible persons following virus exposure and studies to determine whether persons with latent HSV have fewer symptomatic recurrences following vaccination are not yet available.

Varicella-Zoster Virus

Varicella-zoster virus, the agent responsible for both chickenpox and shingles, is a common infection, with more than 3 million new primary cases occurring each year in the United States. The high contagiousness of the virus results in a household attack rate in susceptible hosts of more than 90%. Primary infection results in the classic chickenpox rash, with lesions in all stages of development (macules, papules, vesicles, ulcers, and crusts) present simultaneously.[31]

Children with chickenpox usually have a self-limited illness, whereas adults are at higher risk for severe illness with complications, including visceral dissemination and pneumonia. Pneumonia due to VZV occurs more frequently in pregnant women and immunocompromised persons than in other adults with chickenpox. Patients may have shortness of breath and nonproductive cough during evolution of the skin rash, and chest x-ray film reveals diffuse infiltrates. Patients with VZV pneumonia may progress to hypoxemia, respiratory distress, and ventilatory failure.[32]

Recurrent Varicella-Zoster Virus Infection

Recurrent VZV infection may develop many years after the primary infection and results in a classic skin rash referred to as shingles or zoster. The incidence of zoster increases with advancing age and with immunosuppression, possibly due to the waning of host-specific immunity to VZV antigens that is required for maintaining virus latency.[31]

With the reactivation of latent VZV from dorsal nerve root ganglia, virus travels peripherally along sensory nerves to the corresponding cutaneous or mucosal surfaces. Pain may precede the appearance of visible skin lesions and may delay the diagnosis. Skin lesions begin as erythematous papules and progress to vesicles that may become confluent and bullous. The skin rash is usually confined to a single or contiguous dermatomes corresponding to innervation of the reactivated ganglion. Zoster skin lesions ulcerate, dry, and heal by crusting and epithelialization and may leave residual cutaneous scars.[31]

Postherpetic Neuralgia

Postherpetic neuralgia, described as pain that persists despite complete healing of the skin rash, is a common and disabling complication of zoster.[31] The incidence, severity, and duration of postherpetic neuralgia increases with the age of the patient. Its pathogenesis is poorly understood and may be due to inflammation, hemorrhage, and nerve damage occurring during virus reactivation.[33] Patients with ophthalmic zoster and those with severe pain during the zoster rash are at higher risk for postherpetic neuralgia to develop. The pain of postherpetic neuralgia is often described as burning, lancinating, stabbing, or aching, and affected patients often report paresthesia or dysesthesia.[33,34]

Diagnosis of Varicella-Zoster Virus Infection

The diagnosis of VZV infection is often made on the clinical appearance of the rash, but laboratory testing may be required if the rash is atypical. Direct fluorescent antibody staining of cells scraped from cutaneous or mucous membrane lesions is the most useful diagnostic test to confirm chickenpox or zoster. Virus culture is less

useful for the diagnosis of VZV infection than it is for HSV because VZV grows slowly and unreliably in tissue culture. Serologic testing is useful to confirm past infection with VZV, but is not helpful in diagnosing a patient with suspected chickenpox or zoster.[31]

Treatment of Varicella-Zoster Virus Infections

Although chickenpox and zoster are often self-limiting illnesses, antiviral therapy is effective in shortening the duration of the illness and limiting long-term sequelae. Until recently, acyclovir had been the undisputed antiviral agent of choice for VZV infections.[35-37] More recently, however, famciclovir and valacyclovir have been shown to be effective for certain VZV infections. These newer agents allow for less frequent dosing and higher serum antiviral drug activity than acyclovir because of superior bioavailability and longer serum half-life.[19,20]

Treatment of Chickenpox

Oral acyclovir is effective in the treatment of chickenpox in both children and adults. A dosage of 800 mg, five times a day for seven days, in adults[35] and 20-mg-per-kg suspension, four times a day for five days, in children[36] reduces the total number of lesions, the duration of fever, and the duration of illness compared with placebo. Treatment should be started within 24 hours of the onset of the skin rash for efficacy. Clinical studies, however, have not shown a reduced incidence of visceral dissemination or VZV pneumonia in patients receiving acyclovir.

Management of Patients With Zoster

Antiviral therapy is beneficial in patients with zoster. Several studies have shown that patients treated with acyclovir, 800 mg orally five times a day[37]; famciclovir, 500 mg three times a day[19]; or valacyclovir, 1 gram three times a day,[20] for seven days (with treatment begun within 3 days of the onset of rash) have a shorter duration of acute illness, acute pain, and both postherpetic neuralgia and total zoster-associated pain than placebo recipients. Antiviral treatment appears to be most beneficial for elderly patients, as this group is most at risk for the development of postherpetic neuralgia.

Acyclovir therapy has been evaluated in several trials, and studies have suggested a beneficial effect of acyclovir on pain. Most trials have shown a reduction in the duration and severity of the acute pain associated with zoster, and a recent pooled analysis revealed an overall reduction in the risk of postherpetic neuralgia.[37,38]

A recent study of famciclovir therapy for patients with zoster defined postherpetic neuralgia as pain that persisted after the healing of skin lesions and concluded that famciclovir-treated patients in whom postherpetic neuralgia developed had a shorter duration of total pain than placebo-treated patients. This trial did not show a reduction in the overall incidence of postherpetic neuralgia with famciclovir treatment.[19]

A recent trial comparing the use of valacyclovir with acyclovir found that valacyclovir was more effective in shortening the duration of total zoster-associated pain than standard acyclovir, and fewer valacyclovir-treated patients still had pain at six months.[20]

Based on available data, it appears that each of the above regimens are superior to placebo and that valacyclovir or famciclovir may be preferable to oral acyclovir for the treatment of zoster in nonimmunocompromised persons. The superior efficacy of valacyclovir or famciclovir over acyclovir may be due to improved bioavailability, less frequent dosing, and higher tissue antiviral activity.[19,20] Comparative trials of valacyclovir and famciclovir are not yet available. Both famciclovir and valacyclovir require dosage reduction in patients with mild renal dysfunction. As mentioned earlier, valacyclovir should not be prescribed in patients with advanced HIV disease, bone marrow transplant, or kidney transplant because of the occurrence during clinical trials of thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome in these patients receiving high dosages (data on file, Glaxo Wellcome, Inc).

Treatment of patients with zoster with corticosteroids to prevent postherpetic neuralgia remains controversial. Initial reports had suggested that administering steroids reduced the incidence of the neuralgia, but other studies have not confirmed this.[38,39] Recent studies, however, conclude that administering corticosteroids in combination with an effective antiviral agent reduces acute pain and improves the quality of life in patients aged 50 or older, but has no effect on the presence of postherpetic neuralgia six months later.[39,40] In view of the possible risk of steroid-induced immunosuppression and resultant virus dissemination, patients with zoster should not be treated with steroids alone to prevent postherpetic neuralgia, but possibly with a combination of tapering steroids and an effective antiviral regimen.

The management of patients with postherpetic neuralgia can be challenging because the pain may be difficult to control or eradicate. Treatment must be tailored to each patient because although some patients respond well to analgesics or narcotics, others require additional therapies. Aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs have limited activity in patients with severe postherpetic neuralgia. Topical anesthetics, topical capsaicin cream, and oral tricyclic antidepressants offer the best initial choices for patients with neuralgia.[38,39] A regimen of topical capsaicin cream 0.025% (Zostrix) applied four times a day and oral desipramine hydrochloride, 25 mg at bedtime, can be prescribed initially and may be effective, although patients should be cautioned that capsaicin causes a local burning sensation initially.[41]

Varicella-Zoster Virus Vaccine

A vaccine to reduce the risk of VZV infection has been approved by the FDA for nonimmunocompromised persons.[42,43] The vaccine induces VZV-specific immune responses and is effective in preventing varicella following exposure. Because the vaccine is an attenuated live virus, latent infection occurs following vaccination, and vaccine recipients are at risk of zoster developing from the vaccine strain. The duration of protection afforded remains under investigation, and vaccinated persons may require addi-

tional booster doses later in life. The vaccine is administered as a 0.5-ml subcutaneous dose to children aged 1 through 12 years who have not had chickenpox. Persons older than 12 years who have not had chickenpox should receive two 0.5-ml subcutaneous doses one to two months apart. Patients with an uncertain history of previous VZV infection should be screened serologically to determine whether immunity is present before vaccination.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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