

Herpes Zoster: A Clinical Review

**Birinder S. Singh, M.D.,
Stephen J. Scholand, M.D.**

INTRODUCTION

Varicella zoster virus (VZV) is a ubiquitous human virus that belongs to the subfamily alpha-herpesvirinae.¹ It contains the smallest genome of the herpesviruses. It is an icosahedral shaped, enveloped virus that measures approximately 200 nanometers in diameter. The virus has more than 30 structural proteins as well as glycoproteins.² Varicella zoster causes two distinct syndromes. The initial infection first presents as varicella or ‘chickenpox’, which is a contagious and usually self-limiting illness. It occurs in epidemics amongst susceptible children.³ On resolution of the primary infection, the virus migrates from sensory nerve endings to reside in the

dorsal root ganglion.⁴ When cell mediated immunity declines (Table 1) below a crucial level, reactivation of this virus results in herpes zoster (HZ) or ‘shingles.’

The words “herpes zoster” are derived from the Greek *herpein*, meaning “to spread or creep” and *zoster*, meaning “girdle or zone.” ‘Shingles’, another word of Greek origin, means “girdle”, a reference to the dermatomal distribution characteristic of this disease.²

This migration and eventual colonization along this neural route explains the distribution of rash along a sensory nerve dermatome.⁴ *In utero* infection leading to childhood zoster is another possible, albeit rare, mechanism for acquiring herpes zoster. This has been reported in children as young as four months.⁴

Table 1. Risk factors for varicella-zoster virus reactivation.

Prior VZV exposure (chickenpox, vaccine)
Age >50 years
Immunocompromised state
HIV/AIDS
Bone-marrow or organ transplantation
Cancer (most frequently, Hodgkins and non-Hodgkins lymphoma, leukemia, oat cell carcinoma of lung)
Chronic steroid therapy for chronic diseases such as rheumatoid arthritis, or systemic lupus erythematosus
Psychologic stress
Trauma

Table derived from Arvin, 1996¹

St. Mary’s Hospital, Division of Infectious Diseases, Waterbury, Connecticut, USA.

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Reprint request: Birinder S. Singh, M.D., St. Mary’s Hospital, Division of Infectious Diseases, Waterbury, Connecticut, USA.

Epidemiology

The incidence of herpes zoster is 1.2 to 3.4 cases per 1,000 person-years in studies of immunocompetent individuals in the community, but it increases to 3.9-11.8 cases per 1,000 person-years among those greater than 65 years of age.⁵ The incidence of zoster in children younger than 14 years is only 1.1 per 1,000 person-years. In comparison to these world-wide incidence rates, the rate of varicella zoster in Thailand was 0.26 per 1,000 persons. This was reported by a study performed in 2008 in which 53.6% of the population was older than 45 years of age.⁶ There is evidence to suggest that the epidemiology of VZV infection varies according to climate. In Northern latitudes, a higher incidence of VZV infection suggests that transmission of this virus is favored by a temperate climate.⁷ Viral transmission in tropical and subtropical climates is less well described. Seroprevalence of VZV in these areas suggest greater complications from disease may result.⁸ Rates of zoster in individuals who are immunocompromised or those receiving immunosuppressive drugs are increased. The highest incidence has been reported in human immunodeficiency virus (HIV-1) positive individuals; 29.4 cases per 1,000 persons-years.⁴

Pathophysiology

Primary infection with VZV results in the disease of 'chickenpox' or varicella. This initial infection involves dissemination of virus throughout the blood stream to the skin via mononuclear cells, producing the typical generalized rash.⁹ Once the primary varicella infection resolves, the residual provirus segments (viral fragments) migrate from sensory nerve endings through sensory fibers in the cranial or dorsal root ganglia.⁴ Here, the viral particles are protected from high levels of circulating antibody following the primary infection.⁴ VZV has evolved two main mechanisms to evade

detection by the immune system. First, the virus remains latent in the sensory ganglion thus limiting its expression of viral proteins.⁹ Although it does not multiply, VZV retains the ability to revert to an infectious state at any time.⁴ The virus usually remains latent for an extended period without producing any signs or symptoms of infectivity.² Immunohistochemical staining of autopsy specimens shows that certain VZV proteins are confined to the cytoplasm during latency and appear in the nucleus (the site of viral capsid assembly) only after reactivation. In human dorsal root ganglia implanted into SCID-hu mice, viral proteins were found distributed between the nucleus and nerve fibers during latency, thereby preventing assembly into complete virions.¹⁰ The second mechanism to evade the immune system involves down regulating expression of MHC class I antigens on the surface of infected cells. Infection of fibroblasts with VZV causes a reduced level of MHC class I molecules on the surface of infected cells. This was demonstrated in a study whereby infection of human fibroblasts with wild-type or recombinant-derived strain Oka VZV resulted in down regulation of surface expression of MHC I heavy chains.¹¹ Thus, by reducing surface expression of its proteins and limiting presentation of vital peptides to cytotoxic T cells, virus-infected cells may escape destruction by the immune system.⁹ Herpes zoster results from reactivation of latent virus due to a decrease in cell mediated immunity (see Table 1). During VZV reactivation in neuronal cells, the viral proteins relocate from the cytoplasm to the nucleus in a process involving proteasome degradation, implicating this pathway in the regulation of VZV reactivation.¹⁰

Clinical Manifestations

The most prominent feature of herpes zoster is a vesicular rash of unilateral distribution, usually limited to 1 to 3 adjacent dermatomes.⁴ The initial

symptom of herpes zoster is intense pain in the involved dermatome. This pain can be intermittent or continuous and can be throbbing, sharp, stabbing, shooting or burning in quality. During this pre-eruptive stage (before the rash appears), prolonged pain can be misdiagnosed as pleurisy, myocardial infarction, duodenal ulcer, cholecystitis, appendicitis, thrombophlebitis, biliary or renal colic.² In 80% of the patients affected by herpes zoster, the skin manifestations are preceded by a prodromal stage lasting approximately three to five days. Patients during this prodrome often complain of fatigue, mild fevers and abnormal skin sensations including dysesthesia, tingling or itching.¹² Herpes zoster virus has a predilection for ophthalmic (V1) and midthoracic to upper lumbar (T3-L2) dermatomes, corresponding to anatomic areas most severely affected by primary varicella (i.e. face and trunk).²

Rash

The appearance of unilateral dermatomal rash associated with abnormal sensation frequently leads to a clinical diagnosis of herpes zoster. The rash generally appears proximally and spreads distally along the involved dermatome. The first lesions appear as erythematous papules which transform into vesicles usually in 12-24 hours. These vesicles become pustules in approximately three days and form scabs/crusts about 7-10 days later.⁴ The duration of the rash until disappearance of the crusts in immunocompetent children and young adults is usually 2-3 weeks. In comparison, the duration of this rash and pain is more severe and prolonged in elderly and immunocompromised patients.¹² Viral dissemination is very uncommon in immunocompetent patients (1-2%), whereas, it is much more common in immunocompromised individuals (up to 40%).

VZV viremia is defined as: more than 20 vesicles outside the primary and immediately adjacent dermatomes.¹³ Cutaneous dissemination is preceded by visceral (lungs, liver, brain) involvement in about 10% of high risk individuals. At times, a few vesicles can be seen remote from the primarily affected dermatome in immunocompetent individuals, which probably results from hematogenous spread of the virus.¹³ On rare occasion, zoster can occur without a rash, an entity known as *zoster sine herpette*.¹⁴ The prodromal stage, dermatomal pain and serologic or virologic evidence of zoster appears without visible skin findings.

Complications

Acute and chronic complications of herpes zoster which involve the skin, eye and central nervous system are relatively frequent; whereas, complications involving inner organs are considered rare.¹² Neurological complications of herpes zoster can occur simultaneously with the acute eruption or can appear weeks to months after the rash has resolved and can involve any level of the neuraxis.

Postherpetic Neuralgia (PHN)

The most common and debilitating complication of herpes zoster is postherpetic neuralgia.¹ PHN is defined as pain persisting for longer than four weeks or occurring four weeks after a pain-free interval.¹² The duration of pain may vary from one to six months depending on several factors. Age and relative immunosenescence play a major role in the incidence and duration of PHN. Other factors that correlate with PHN include a severe rash during the acute phase or a multi-dermatomal rash distribution. The presumptive mechanism behind PHN is thought to be hypersensitization of nociceptors, which exhibit a slow return to baseline.⁴ PHN is a chronic condition with serious

associated morbidity. Symptoms associated with PHN include chronic fatigue, anorexia, weight loss and insomnia. The sensory symptoms associated with PHN include spontaneous aching, burning, throbbing or stabbing pain, allodynia (pain precipitated with movement in the affected dermatome), hyperalgesia, and intense itching.⁴

Meningoencephalitis/Encephalitis

Acute VZV encephalitis is a relatively rare complication of herpes zoster that mostly occurs a few days after the appearance of rash. It has also been reported from days to weeks before or after the skin eruption.⁵ Apart from the immunocompromised population, which is at increased risk, herpes zoster in a cranial nerve dermatome also increases the risk of encephalitis. The clinical presentation is most often an acute or subacute delirium accompanied by a few focal neurological signs.⁵

Chronic VZV encephalitis is seen almost exclusively in patients with AIDS who have marked depletion of CD4⁺ T cells or other conditions with depressed cellular immunity. The clinical presentation is usually subacute with headache, fever, mental status changes, and seizures. Patients may present with focal neurologic defects which include aphasia, hemiplegia, and visual field cuts.⁵ Onset maybe several months after the herpes zoster episode, which makes the diagnosis difficult. In about 30-40% of patients, there may be no reliable history of recent VZV skin disease, further complicating the diagnosis. MRI studies may reveal infarcts of cortical and subcortical grey and white matter (multifocal leukoencephalopathy) and small vessel vasculitis. CSF analysis reveals mild mononuclear pleocytosis and is usually PCR-positive for VZV-DNA.¹⁵ It should be noted, however, that CSF pleocytosis is present in about 50% of patients with uncomplicated herpes zoster, reflecting the local

leptomeningitis that regularly accompanies the disease.

Myelitis

VZV invasion of the spinal cord leads to herpes zoster myelitis. The virus spreads along the central axons of the infected primary sensory neurons. The most common initial presentation is bladder dysfunction (e.g. urinary retention), which is often accompanied by weakness of the lower limbs, asymmetric reflexes, and sensory disturbances.¹⁶ Myelitis most commonly follows thoracic herpes zoster, resulting in weakness affecting the same spinal cord segment as the rash.⁵ Just like other complications of herpes zoster, myelitis is well described in patients with AIDS. MRI is useful for diagnosing myelitis, with abnormal signal evident in the spinal cord at the level of inflammation.⁵ Diagnosis is confirmed by the presence of VZV DNA, anti-VZV IgG or both in the CSF. Most recently, a case of VZV spinal cord infarction was identified by diffusion weighted MRI.¹⁷

Cranial Nerve Palsies

The extra spinal nerve most commonly affected by herpes zoster is the trigeminal nerve. Herpes zoster ophthalmicus (HZO) or ophthalmic zoster arises from VZV reactivation in the first division of this nerve.¹⁵ It classically begins with flu like symptoms and the development of a painful unilateral rash in the distribution of one or more branches of V1. While HZO does not specifically affect the structures of the eye (as it has a different innervation), many of the acute and long term complications associated with HZO result from direct viral toxicity to the eye or the ensuing inflammatory response within the eye.¹⁸ Ophthalmic zoster accounts for 1-10% of all herpes zoster cases. The rate of complication is high; 50-90% of patients develop ocular complications if left untreated.¹⁵ The nasociliary division of the ophthalmic branch is affected

in about 30% of with vesicles on the side and the tip of the nose, known as Hutchinson's sign (a powerful predictor of ocular complications).²

Cranial nerves and ganglia adjacent to the trigeminal nerve can also be affected by HZ. Ramsay Hunt Syndrome or herpes zoster *oticus* involves facial and auditory nerves (geniculate ganglia) and is the second most common cause of non-traumatic peripheral facial nerve paralysis after Bell's Palsy. Symptoms include unilateral facial weakness accompanied by a vesicular rash in the external ear canal.¹⁵ Other symptoms included sensorineural hearing loss, tinnitus, vertigo, otalgia, and pharyngeal pain. Zoster involvement of the vagus nerve can cause dysphagia, nausea, vomiting, and irregularity of the heart rate.

Ocular Complications

Ocular sequelae can involve the eyelid/conjunctiva resulting in conjunctivitis or may involve the episclera/sclera resulting in episcleritis/scleritis. Corneal involvement may result in epithelial and stromal keratitis or possibly endothelitis.⁴ Ocular herpes zoster infection may cause uveitis (anterior chamber) with the risk of secondary glaucoma. Chorioretinitis and neuritis of the optic nerve are more common in AIDS patients.¹² VZV induced necrotizing retinitis manifests as two clinical syndromes: acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN). ARN is seen in both immunocompetent and immuno-compromised hosts. It usually presents with periorbital pain, floaters with hazy vision, and loss of peripheral vision.¹⁷ ARN is a full thickness retinal necrosis characterized by focal and well demarcated areas of necrosis in the retina secondary to an occlusive vasculopathy located beyond the major temporal vascular arcades.¹⁹ PORN is the second most common opportunistic retinal infection among patients with AIDS, who have CD4⁺ counts lower than 10 cells/mm³.

Patients with PORN present with sudden painless loss of vision, floaters, and constricted visual fields due to retinal detachment.²⁰ There is a third form of necrotizing retinitis designated RPHRN, for rapidly progressive herpetic retinal necrosis. RPHRN involves outer and inner retinal layers and may also occur with CNS disease.²¹ RPHRN and PORN are more common variants of retinitis than ARN in advanced HIV.

Delayed Contralateral Hemiparesis

Stroke is a rare but serious complication, thought to arise from direct VZV invasion of the large cerebral arteries by extension from smaller vessels traversing the trigeminal innervated meninges.⁵ This can occur weeks or months after the initial episode. It usually presents as headache and hemiplegia secondary to stroke, contralateral to the original rash. CT or MRI studies show evidence of infarction. Angiography may reveal granulomatous inflammation and narrowing of middle or anterior cerebral arteries.¹⁵

Skin Complications

Acute and chronic complications involving the skin are frequent. The skin is predominantly affected by bacterial secondary infections in the acute stage. Ecthymiform ulcerations may develop.¹² Other cutaneous complications include: hemorrhages (zoster hemorrhagicus), purulent gangrene (zoster gangrenosus), and persistence of lesions and dissemination (zoster disseminatus) in immunocompromised patients.¹² A manifestation of psoriasis vulgaris (Kobner's phenomenon) may occur with chronic hypo-pigmented and depigmented scar formation.

Diagnosis

The diagnosis of herpes zoster is made clinically based on prodromal symptoms and the characteristic rash. Laboratory testing is useful for differentiating

zosteriform herpes simplex, suspected organ involvement, and for atypical presentation such as zoster *sine herpette*.²² Tzanck smear may suggest VZV infection, but it cannot differentiate herpes zoster from zosteriform herpes simplex infection. A viral culture is 30 to 70% sensitive and 100% specific for VZV. The yield of diagnostic testing is highly dependent on the stage of the lesions, the quality of the specimen collected, and the time elapsed. For maximum yield, fluids from fresh vesicles should be aspirated and immediately sent to the laboratory. Growth of varicella zoster in a tissue culture may take 3 to 14 days.²³ VZV DNA detection by PCR is very sensitive (nearly 100%) and can be used to detect the DNA in fluid taken from the vesicles or cerebrospinal fluid (CSF). PCR on CSF along with antibody testing for VZV are the tests of choice for neurologic disease. Immunofluorescence antigen detection of VZV antigens in vesicle scrapings, or other specimens such as a tissue biopsy or CSF is a good test because it is rapid, specific and sensitive (nearly 90%). It is a suitable alternative when PCR is not available.²² Although some patients will show a “boost” in VZV antibody titer after an episode of

herpes zoster, serology is not a very sensitive or specific diagnostic method. The commonly used methods are ELISA or latex agglutination, the latter being more sensitive.²³

Treatment

The goals of treatment for herpes zoster are: reduce acute/chronic pain, accelerate healing of cutaneous lesions, and prevent any further complications.¹⁰

Treatment of Symptoms

Pain control can be achieved by appropriately-dosed analgesics (e.g. tramadol), often in combination with a neuroactive agent (e.g. amitriptyline). Local treatment of the rash can be achieved through drying and antiseptics with wet dressings, *lotio alba*, vioform zinc mixture or later by crust removal.¹²

Indications for Antivirals

Antiviral treatment hastens the healing process and is important when a complicated clinical course is anticipated (see Table 2). Zoster in young individuals without risk factors is a self-limiting

Table 2. Indications for systemic antiviral therapy of zoster.

Urgent Indications

Zoster of any localization in patients beyond the age of 50

Zoster in the head/neck area of patients at any age

Severe zoster on the trunk/on the extremities

Zoster in immunodeficient patients

Zoster in patients with severe atopic dermatitis and severe eczemas

Relative Indications

Zoster on the trunk/on the extremities in patients younger than 50 years

Table derived from Gross et al., 2003¹²

disease, expected to heal without complications.¹² Antiviral medications have a small window of opportunity and the success of antiviral treatment depends on the timely initiation of therapy. In the normal host, most viral replication ceases by 72 hours after the onset of rash. This warrants initiation of systemic virostatic therapy as soon as possible. In immunocompromised patients however, the duration of replication and viral shedding may be substantially prolonged. Thus, antiviral treatment even after the 72 hour window period may be beneficial.⁹ Four medications are approved for treatment of zoster including acyclovir, valacyclovir, famciclovir [approved in the United States] and brivudin licensed in Europe. All four of these drugs are nucleoside analogs and can be given orally except acyclovir which has a parenteral form.²⁴

Acyclovir

Acyclovir is an analogue of the nucleoside guanosine, which *in vivo* is phosphorylated, initially by viral thymidine kinase, followed by cellular kinases, into acyclovir triphosphate. This compound subsequently acts as a competitive inhibitor of guanosine triphosphate, thereby inhibiting viral DNA polymerase.¹³ In placebo controlled trials, when given orally as 800 mg five times daily for seven days, shorter viral shedding times were observed which halted lesion formation, accelerated healing, and reduced pain severity. However, no clear reduction in frequency and duration of post herpetic neuralgia was observed.³ Side effects include headache, nausea, and diarrhea in a few percent of patients. Renal toxicity is an important consideration in renal patients and dose adjustments should be made prior to administration. CNS toxicity is rare, but may include disorientation, delirium, seizures, tremor or slurred speech.¹³ Disadvantages of acyclovir include

poor bioavailability for oral administration and the resulting need for five times daily administration.²⁵ (injectable acyclovir will be discussed below).

Valacyclovir

Valacyclovir, a prodrug of acyclovir, produces serum acyclovir levels three to five times as high as those achieved with oral acyclovir therapy. The standard dose of oral valacyclovir is 1,000 mg every eight hours for seven days for uncomplicated herpes zoster. The benefits of valacyclovir compared to acyclovir were noted in a randomized trial of patients 50 years of age and older: There were equivalent rates of cutaneous healing, with the median time to zoster associated pain shortened by valacyclovir (38 days versus 51 days, $P=0.001$).³

Famciclovir

Famciclovir is a prodrug of penciclovir with a similar mechanism of action as acyclovir. The usual dose for famciclovir is 500 mg every eight hours for seven days in uncomplicated herpes zoster. It was shown significantly superior to placebo in reducing the duration of viral shedding, limiting new lesion formation, and hastening healing in a placebo controlled trial of subjects at least 50 years of age. In addition, famciclovir reduced the median duration of postherpetic neuralgia from 163 days in the placebo group to 63 days in the famciclovir group.³

Because of the superior pharmacokinetic profiles and easier dosing regimens, valacyclovir and famciclovir are preferred to acyclovir for the treatment of herpes zoster. There are no absolute contraindications to the use of these drugs, although, a dose adjustment is required in patients with renal insufficiency. None of the above three medications are approved for use in pregnant women.³

Brivudin

Brivudin is a virostatic agent activated by viral enzymes phosphorylation. In Europe, it is primarily used for the early treatment of acute herpes zoster in immunocompetent adults. The active form of the drug, brivudin triphosphate, prevents viral replication by blocking the VZV DNA polymerase. It is 200 to 1,000 times more effective at inhibiting viral replication *in vitro* than acyclovir or penciclovir.¹⁵ Brivudin is known to have a greater potency and a long elimination half-life. Therefore, it is administered as a single 125 mg tablet once daily for seven days in the treatment of uncomplicated herpes zoster. Additional advantages include both the hepatic and renal elimination, obviating the need for dose modifications in patients with renal or hepatic impairment. In a randomized double-blind multicenter study, brivudin was shown to be more effective than acyclovir in reducing the duration of rash and severity of pain in 1,227 immunocompetent patients.¹⁵ A disadvantage to the use of this medication is its life threatening drug interaction with 5-fluorouracil and other 5-fluoropyrimidines.

Intravenous Acyclovir

Intravenous (IV) acyclovir is recommended in severely immunocompromised patients (e.g. acute leukemia or transplant recipients).¹⁰ IV acyclovir has been shown to prevent disease progression in patients at high risk for dissemination. The dose for IV acyclovir in immunocompromised patients/disseminated disease is 10 mg/kg every eight hours until resolution of cutaneous/visceral disease.²⁶ Potential side effects of intravenous acyclovir are more significant than the oral formulation, and include decreased renal function, gastrointestinal irritation, phlebitis or tissue damage at the IV site, central nervous system dysfunction and hypersensitivity reactions. Decreased renal function mostly occurs in patients from deposition of the drug in

the kidneys of patients whose renal function/hydration is inadequate. When the concentration of the drug exceeds 1.7 mg/mL at 37°C, the drug may crystallize *in vivo*. The best way to avoid renal dysfunction is by infusing acyclovir slowly over one hour and ensuring that patients receive one liter of fluid per gram of medication. Dose adjustments should be made according to creatinine levels.²⁷

Corticosteroids

Corticosteroids are recommended for use in conjunction with antiviral therapy. Prednisone may be dosed at 60 mg orally for seven days, tapering over the next two weeks.²⁶ The use of corticosteroids in the treatment of herpes zoster has been evaluated in a large placebo-controlled clinical trial.²⁸ The findings justified the use of steroids in persons older than 50 years of age, with severe symptoms and without relative contraindications (e.g. diabetes, hypertension, or glaucoma).⁹ Combination therapy resulted in an improved quality of life, as measured by reduction in the use of analgesics, the time to uninterrupted sleep, and the time to resumption of usual activities.³

Treatment of Postherpetic Neuralgia (PHN)

Treatment of PHN is complex, often requiring a multifaceted approach. There is no intervention that reliably relieves the pain of PHN. Effective therapy often requires multiple medications.²⁶ Opioids play a significant role in pain management, despite some of the well known complications of therapy. A clinical trial with oxycodone for patients affected by PHN resulted in a significant reduction of pain from 67% to 11% in placebo and treated recipients, respectively.²⁴ Longer acting opiate preparations may be more suitable than shorter acting analgesics. Other reasonable pain treatment options include oxycodone with acetaminophen or morphine.²⁶ Non-narcotic

medications, such as tramadol, may be a good choice for patients with risk factors for substance abuse. Several randomized controlled clinical trials have documented benefit from tricyclic antidepressants (TCA), either as a single agent or in combination with other drugs.²⁴ TCAs are often associated with sedation, a variety of anticholinergic side effects and potential cardiac dysrhythmias. Thus, treatment is started with a low dose at bedtime and gradually increased as tolerated. Patients who are unable to tolerate TCAs may benefit from selective serotonin and norepinephrine reuptake inhibitors (SSRIs).²⁶ Several newer generation anticonvulsants, such as gabapentin and pregabalin, are approved by the Food and Drug Administration (FDA) for the treatment of PHN. Gabapentin is initiated at a dose of 300 mg once daily, and increased as tolerated to a maximum of 1,800 mg per day. Pregabalin dosed 150 mg to 300 mg per day, taken either two or three times a day. These medications have fewer adverse effects and require less hematologic monitoring than older anticonvulsants. Other approaches to management of chronic pain include topical applications of capsaicin or lidocaine patches. Topical therapy with capsaicin should be continued for at least four weeks until substantial pain relief occurs.²⁶ The burning sensation associated with application of capsaicin often limits clinical use, however. Recent advances in PHN therapies, while more invasive, include electrical stimulation of the thalamus, anterolateral cordotomy, cryotherapy of the intercostal nerves and ablation of the dorsal roots using pulsed radiofrequency. Because limited data is available to support these therapies, referral to a pain medicine specialist is recommended.²⁶

Resistance of Varicella Zoster Virus to Antivirals

Mutations in the thymidine kinase (TK) gene or mutations in the polymerase gene are responsible for

resistance of VZV to antivirals. Viral strains with mutations in the TK gene are usually resistant to acyclovir, famciclovir, and ganciclovir due to the lack of phosphorylation required for their activation. Such viral strains have been isolated from several HIV-1 infected patients who had been treated for acyclovir for long periods. The treatment of choice in such cases is intravenous foscarnet, 40 mg three times or 50 mg two times per kilogram of body weight per day.¹² Viral strains with polymerase gene mutations may be ineffective to foscarnet as well. In such cases, the only effective treatment is intravenous cidofovir.¹²

Prevention

Currently, a live attenuated vaccine is approved by the FDA for the prevention of herpes zoster, however it is not available in Thailand. The vaccine is administered as a single 0.65 mL dose subcutaneously in the deltoid region.²⁹ The vaccine dose contains a minimum of 19,400 plaque-forming units (PFU) about 14 times the amount present in the childhood chicken pox vaccine.³⁰ The vaccine also contains sucrose, hydrolyzed porcine gelatin, monosodium L-glutamate, human diploid human culture cells, and trace quantities of neomycin and bovine calf serum.²⁹ The zoster vaccine is given to individuals who have already been exposed to the virus, and hence is a "therapeutic vaccine".³⁰ The safety and efficacy of the herpes zoster vaccine was evaluated in a shingles prevention study performed in 2005. In this randomized double blinded multicenter, placebo-controlled study 38,456 adults aged 60 and older were followed for a median of 3.1 years.³¹ The researchers found that the vaccine reduced the incidence of shingles by 51.3%, reduced illness severity by 61.1%, and decreased the incidence of PHN by 66.5%. Following these published findings, the FDA in 2006 approved the zoster vaccine for prevention of HZ in individuals 60 years or older.³² More

recently, the FDA revised its recommendations for herpes zoster vaccine to be given to adults aged 50 to 59 years, as well as for those aged 60 years or older. The FDA based this change on a multicenter, placebo controlled study that included 22,000 individuals aged 50 to 59 years. These individuals were followed for a year post immunization with a noted risk reduction of shingles by about 70%.³³ The herpes zoster vaccine is indicated irrespective of whether the person has had a previous episode of herpes zoster. However, patients with active herpes zoster should wait until the rash has healed.²³ The Advisory Committee on Immunization Practices (ACIP) does not recommend any bounds on the upper age limit for the vaccine.³⁴ The zoster vaccine does not contain thimerosal, a mercury based preservative used in other vaccines. Due to this reason, it must be kept frozen at an average temperature of -15°C. It should be reconstituted immediately upon removal from the freezer and should be used within 30 minutes. In July 2009, the FDA approved storage and or transportation at a temperature from 2°C to 8°C for up to 72 hours prior to reconstitution.²⁹ The contraindications for the zoster vaccine include a history of life threatening allergic reaction to gelatin, neomycin or any other component of the vaccine, people with HIV/AIDS with CD4 cell counts less than 200, patients undergoing chemo/radio therapy for cancer treatment, leukemia or lymphoma, organ transplantation, active untreated tuberculosis, pregnancy or breastfeeding. Patients with leukemia who are in remission and have not received chemotherapy or radiation for at least 3 months can receive the zoster vaccine. Chronic diseases such as diabetes, hypertension, chronic renal failure, chronic lung disease, and rheumatoid arthritis are not considered contraindications.³⁴

Future Directions

Currently, MERCK is conducting clinical studies

to test a heat treated VZV vaccine, which has been safely administered to autologous bone marrow transplant recipients. In these patients, the vaccine accelerated the recovery of VZV cell mediated immunity, and reduced the occurrence of herpes zoster. Based on these results, several groups are currently exploring the potential benefits of inactivated VZV vaccines in immunocompromised patients who cannot receive the current live attenuated vaccine.^{29,35}

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