Herpes Zoster: Diagnostic, Therapeutic, and Preventive Approaches

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Abstract: Herpes zoster (Hz), which generally presents as a localized, painful cutaneous eruption, is a common clinical problem, particularly among adults ≥ 50 years of age and immunocompromised patients. The diagnosis of Hz is mainly made clinically, except in patients with atypical manifestations or certain complications, such as central nervous system involvement, in which laboratory virologic testing is required. In addition to having a higher mortality rate, immunocompromised individuals have atypical and severe clinical findings and are at greater risk for complications and recurrence of Hz. Treatment of Hz includes the use of antiviral agents, analgesics for control of acute zoster pain, good skin care for healing, and prevention of secondary bacterial infection. Antiviral agents, preferably valacyclovir or famciclovir, should be started within 72 hours of onset to reduce the severity of the infection, the duration of the eruptive phase, and the intensity of acute pain. Herpes zoster has been associated with several complications, of which post-herpetic neuralgia (PHN) is the most common and debilitating. Varicella-zoster virus vaccine and early treatment with either famciclovir or valacyclovir are the only measures proven to prevent PHN. The options for treating PHN include topical agents, such as lidocaine patches, and systemic agents, such as the anticonvulsants gabapentin and pregabalin. Measures for preventing Hz include infection control through routine hand hygiene and appropriate use of isolation precautions and personal protective equipment; immunoglobulins, such as the varicella-zoster virus immunoglobulin and vaccine; and antiviral agents. The zoster vaccine has been shown to be effective in reducing the incidence of Hz and PHN. The vaccine is recommended for all individuals aged ≥ 60 years who have no contraindications, including individuals who report a previous episode of Hz.

Keywords: antiviral agents; herpes zoster; post-herpetic neuralgia; varicella-zoster virus vaccine

Introduction

Herpes zoster (Hz), or shingles, results from reactivation of varicella-zoster virus (VZV) infection. Varicella-zoster virus is one of the alphaherpesviruses that initially infect somatic cells (mucoepithelial). Replication in these cell types is then followed by the transmission of viral infection into the neurons. Viral particles enter at the termini of the sensory neurons of the peripheral nervous system and then transport long distances along axons in the retrograde direction toward cell bodies, where the genomes are deposited into the nucleus to establish lifelong latency. The virus establishes latency in cells of the cranial nerve, dorsal root, and autonomic ganglia. Latency is characterized by the presence of viral DNA in ganglionic neurons, with limited virus gene transcription. Following reactivation from latency, new viral particles are assembled and spread in the anterograde direction back out toward the periphery, producing the characteristic bandlike rash in the involved dermatome. Rarely, viral particles spread

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trans-synaptically from the neurons of the peripheral nervous system into higher-order neurons of the central nervous system (CNS).[1,2]

Primary infection with varicella stimulates VZV antibody production and activates VZV-specific T cells, which control later stages of reactivation. Varicella-zoster virus occasionally reactivates due to a decline in the specific cell-mediated immunity to VZV with aging, immunosuppression (due to diseases with immune system dysfunction or drugs that suppress the immune system), or both. Herpes zoster occurs equally in men and women and without seasonal variation. Although it usually occurs once during a lifetime, second episodes may occur in immunocompromised individuals and, rarely, in immunocompetent individuals.[3]

The incidence of Hz ranges from 1.5 to 4 cases per 1000 persons per year, with up to 1 million new cases per year in the United States. The incidence of Hz increases with aging; the incidence in individuals aged > 75 years has reached up > 10 to 12 cases per 1000 person-years. More than 50% of cases of Hz occur in individuals aged ≥ 60 years.[4,5] In approximately 10% to 20% of individuals with Hz, herpes zoster ophthalmicus (HZO) may develop. A retrospective, population-based cohort study among patients enrolled in a US private health plan reported that the overall incidence of HZO was 30.9 per 100 000 person-years, and for the population aged ≥ 65 years, the incidence was 104.6 per 100 000 person-years, approximately 5-fold that of the rest of the population.[6] The incidence of Hz is also high in individuals with certain medical conditions (Table 1).[7–16]

Recent literature indicates that the prevalence of Hz and its complications (eg, disseminated disease and ocular, neurologic, and visceral organ involvement) are decreasing in patients with human immunodeficiency virus (HIV), probably due to immune system improvement with combination antiretroviral therapy. A retrospective cohort study reported that the Hz incidence rate during the study period (2002–2009) was 9.3 new Hz cases per 1000 person-years of follow-up, whereas between 1997 and 2001, the incidence rate was 32 new Hz cases per 1000 person-years of follow-up. The incidence of Hz and its complications in HIV-infected individuals are still higher than those in the general population. Low CD4 cell counts and detectable viral loads have been associated with an increased risk for Hz. Individuals with HIV are at high risk for immune reconstitution syndrome on starting combination antiretroviral therapy.[17–19]

Table 1. Common Risk Factors for Herpes Zoster

Older age (≥ 50 years of age)
Untreated depression
Inflammatory bowel disease[a]
Rheumatologic disorder (eg, rheumatoid arthritis, SLE, giant cell arteritis, dermatomyositis[a])
Chronic kidney disease and hemodialysis
HIV infection
Dermatologic disorder (eg, psoriasis treated with systemic corticosteroids)[a]
Solid and hematologic malignancy, particularly when undergoing chemotherapy (eg, bortezomib)
PBSCT or SOT
Diabetes mellitus
Treatment with a systemic corticosteroid agent
Micronutrient deficiency

[a]A recent study showed that treatment with anti-tumor necrosis factor agents does not increase the risk for herpes zoster.[12]

Abbreviations: HIV, human immunodeficiency virus; PBSCT, peripheral blood stem cell transplantation; SLE, systemic lupus erythematosus; SOT, solid organ transplantation.

Clinical Manifestation

The clinical presentation of Hz varies widely, ranging from localized cutaneous dermatomal involvement to visceral organ involvement, including the CNS and the eyes (Table 2). Herpes zoster often manifests spontaneously. An age-matched case–control study using Medicare claims data found that patients with Hz were 3.4-fold (95% CI, 2.8–4.2) as likely as controls to have experienced trauma in the week before Hz onset. The association was even stronger in cranial zoster, in which patients were 27.5-fold (95% CI, 5.4–140.3) more likely than controls to have had cranial trauma in the week before Hz onset.[20]

Cutaneous Hz is characterized by the eruption of an erythematous maculopapular rash, followed by the appearance of clear vesicles and new vesicle formation for 3 to 5 days, followed by pustulation and scabbing of the lesion. Skin lesions usually heal within 2 to 4 weeks, often leaving skin scarring and permanent changes in pigmentation. The lesions, which appear in the skin segment innervated by a single sensory ganglion (dermatome), are unilateral and do not cross the midline. However, simultaneous involvement of > 1 dermatome, contiguous or noncontiguous, and lesions crossing the midline may occur in immunocompromised patients, but virtually never in immunocompetent individuals. The most frequently involved dermatomes are thoracic, followed by cranial (especially trigeminal), lumbar, and cervical. Acute pain from the Hz-involved dermatome ranges from mild itching, tingling, or allodynia (pain provoked by light touch) to severe pain. It occurs in ≥ 95% of patients aged > 50 years, and 60% to 70% of patients continue to have persistent pain 1 month after the episode.[21]

Table 2. Clinical Presentations of Herpes Zoster

Type of Infection	Clinical Manifestation	Diagnosis	Treatment
Cutaneous Hz (localized or disseminated)[a]	Localized pain, erythematous vesicular rash following dermatomal distribution	Usually, clinical diagnosis but occasionally requires laboratory diagnosis, as in viral culture, DFA, and PCR	Systemic antiviral agents, eg, valacyclovir, famciclovir, with skin care and pain control
Zoster sine herpete	Localized neuropathic pain, meningoencephalitis, vasculopathy, myelitis, cerebellar ataxia, polyneuritis cranialis (involvement of cranial nerves IX, X, and XI), or ocular involvement (eg, acute retinal necrosis, retinal periphlebitis, uveitis, iridocyclitis, and disciform keratitis) without rash	Diagnosis based on distribution/ characteristics of prolonged radicular pain, other neurologic or ocular symptoms and signs, exclusion of similar conditions, testing for anti-VZV IgG antibody and PCR for VZV DNA in CSF, and PCR for VZV DNA in blood mononuclear cells	Systemic antiviral agents IV or orally for 1–12 wk based on organ involved and immune status of patient; analgesics
Herpes zoster ophthalmicus	Localized neuropathic pain, erythematous vesicular rash that follows distribution of ophthalmic division of trigeminal nerve with/ without ocular manifestation (epithelial, stromal, and disciform keratitis, anterior uveitis; acute retinal necrosis, cranial nerve palsies, and optic neuritis)[b]	Clinical diagnosis, based on inspection and an ophthalmologic exam	Systemic antiviral agents, analgesics, topical lubricants, topical or systemic corticosteroids in case of eye involvement (after consultation with an ophthalmologist); topical antivirals effective only for corneal epithelial disease
Ramsay Hunt syndrome[c]	Acute otalgia, unilateral facial paralysis, hyperacusis, taste disturbances in the anterior two thirds of tongue; reduction of tear, nasal and saliva secretion; vesicular lesions can appear on concha, ear canal, postauricular skin, tympanic membrane, ipsilateral anterior two thirds of the tongue, or palate; cranial nerve VIII can be affected in ~40%–50% of patients, manifesting as nausea, vomiting, vertigo, ataxia, falls, nystagmus, tinnitus, hearing loss	Diagnosis made clinically with audiometry and without need for MRI	Systemic antiviral agents either po or IV, based on severity, for 10–14 d, analgesics, 2–3-wk tapering course of prednisone (starting dosage, 60–80 mg/d)
Vasculopathy			
Large vessel unifocal granulomatous arteritis	Occurs in immunocompetent, older adults; stroke-like symptoms with hemiparesis occurring contralateral to antecedent Hz within few weeks to ≤ 6 mo from onset of Hz	Diagnosis confirmed by MRI showing ischemic or hemorrhagic infarct; angiography or MRA demonstrating inflammation, narrowing, thrombosis of proximal branches of anterior or middle cerebral artery; abnormal CSF findings (mild lymphocytic pleocytosis, increased protein, sometimes oligoclonal bands), and PCR for VZV DNA, and anti-VZV IgG antibody (more sensitive than PCR testing) both in CSF	Acyclovir 10 mg/kg IV 3 ×/d, 2–3 wk may help; role of systemic corticosteroids not clear
Small vessel multifocal vasculopathy	Usually occurs in immunocompromised individuals; may occur from 30 days pre- to 6 mo post-onset of Hz; often presents as TIA, stroke, or acute or subacute delirium that may be accompanied by headache, meningismus, fever, ataxia, or seizures	Diagnosis confirmed by MRI showing multifocal infarcts, abnormal CSF findings (increased opening pressure, mild lymphocytic pleocytosis, increased protein, sometimes oligoclonal bands), and PCR for VZV DNA, and anti-VZV IgG antibody (more sensitive than PCR testing) both in CSF	Treatment with IV acyclovir 10 mg/kg 3 ×/d, 2–3 wk may be helpful

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Table 2. (*Continued*)

Type of Infection	Clinical Manifestation	Diagnosis	Treatment
Meningitis/ meningoencephalitis[d]	Characterized by headache, fever, somnolence, stiff neck; presence of cognitive dysfunction, alterations in state of consciousness, behavioral changes, focal neurologic abnormalities, or seizures suggestive of encephalitis; cranial nerve palsy, eg, III, IV, or VII, can occur; additional signs may include autonomic and hypothalamic disturbances, diabetes insipidus, and SIADH	Diagnosis confirmed by MRI of brain (for encephalitis), abnormal CSF findings (mononuclear pleocytosis with elevated protein), anti-VZV IgG antibody and PCR for VZV DNA in CSF; in undiagnosed severe cases, CSF PCR for VZV DNA should be repeated after 3–7 d; CSF anti-VZV IgG antibody test repeated after 2–4 wk	Acyclovir 10 mg/kg IV 3 ×/d for 2–3 wk in immunocompetent/ immunocompromised individuals; role of systemic corticosteroids as adjuvant treatment for VZV encephalitis controversial but may help (3–5-d course), IV acyclovir in immunocompetent individuals with severe VZV encephalitis; surgical decompression indicated for impending uncal herniation/increased intracranial pressure refractory to medical management
Myelopathy[e]	Spectrum of VZV myelopathy is broad, from acute to chronic, rarely recurrent; may occur with acute episode of Hz spontaneously or triggered by surgery, eg, spinal surgery (majority within 3 month of onset of acute Hz); common manifestations include paraparesis, impaired sensation with a level compatible with the segment of VZV reactivation (most commonly thoracic), sphincter dysfunction. Atypical presentations (myelopathy developing without preceding Hz, zoster sine herpete, skin lesion developing after myelopathy, irrelevant anatomic distribution of myelopathy and zoster) often occur in immunocompromised individuals susceptible to VZV myelitis. Concomitant complications, eg, disseminated Hz, encephalitis, meningo-myelo-radiculitis, ventriculitis, polyneuropathy can occur	Diagnosis is confirmed by MRI of spine (showing longitudinal serpiginous enhancing lesions), abnormal CSF findings (mononuclear pleocytosis with elevated protein), anti-VZV IgG antibody (detectable after 1–3 wk of onset of disease), PCR for VZV DNA (detectable within days of onset of disease) in CSF	Systemic antiviral agents IV or orally for 2–3 wk; benefit of systemic corticosteroids in addition to antiviral agents unknown; antiviral agents not indicated for postinfectious myelitis in immunocompetent individuals when systemic corticosteroids may be beneficial
Focal motor weakness[f]	Usually occurs within 1 d to 4 mo after onset of Hz and often involves same segment affected by rash (eg, arm or leg weakness following cervical and lumbosacral Hz, respectively)	Diagnosis usually made by close temporal and anatomic relation between rash and focal neurologic deficit	Treatment with systemic antiviral agents in presence of active Hz rash
Acute retinal necrosis	Visual changes (blurred vision, loss of peripheral vision, periorbital pain) usually occur weeks to months after episode of Hz in both immunocompetent immunocompromised individuals; other eye becomes involved in 30%–50% of patients; visual changes have been reported as a complication of VZV vaccine	Characteristic fundoscopic examination reveals granular, yellowish, nonhemorrhagic retinal lesions with prominent intraocular inflammation in anterior chamber/ vitreous; diagnosis confirmed by detection of VZV in vitreous humor/ retinal tissue, taken by biopsy, by viral culture, DFA, anti-VZV IgG antibody, and PCR	Acyclovir, 10–15 mg/kg IV q8h for 10–14 d, followed by oral valacyclovir, 1 g, 3 ×/d for 4–14 wk, can be used in immunocompetent individuals. Improved preservation of vision in patients treated with combination IV ganciclovir plus foscarnet, with/without intravitreal antivirals (foscarnet), has been reported in immunocompromised individuals. Laser photocoagulation may halt progression of acute retinal necrosis. Systemic corticosteroids may help; should be prescribed and monitored by ophthalmologist

(Continued)

Table 2. (*Continued*)

Type of Infection	Clinical Manifestation	Diagnosis	Treatment
Progressive outer retinal necrosis	Usually occurs in immunocompromised individuals, including HIV-infected patients with low CD4 count (< 10 cells/μL); common presentation includes sudden, painless loss of vision; floaters; constricted visual fields with resultant retinal detachment	Characteristic fundoscopic examination reveals diffuse retinal hemorrhages, detachment, whitening with macular involvement bilaterally and relative lack of intraocular inflammatory changes. Diagnosis confirmed by detection of VZV in vitreous humor, retinal tissue, taken by biopsy, by viral culture, DFA, anti-VZV IgG antibody, and PCR testing	Combination of IV ganciclovir and foscarnet or ganciclovir recommended; acyclovir should not be used due to poor/inconsistent results

[a]Disseminated VZV is defined as involvement of ≥ 2 noncontiguous dermatomes, or ≥ 20 vesicles in multiple dermatomes that occur within a week of the onset of local eruption.

[b]Hutchinson's sign, skin lesions involving the tip, side, or root of the nose, is a predictor of ocular complications.

[c]Ramsay Hunt syndrome mainly affects cranial nerve VII (geniculate) ganglion and cranial nerve VIII within bony facial canal. Rarely affects cranial nerves V, VI, IX, and X.

[d]Electroencephalography is recommended for all patients with encephalitis or meningoencephalitis.

[e]A benign self-limiting type (called *postinfectious myelitis*), presenting as monophasic spastic paraparesis, with or without sensory features and sphincter dysfunction usually occurs in immunocompetent individuals, days to weeks after acute Hz.

[f]Lower motor neurons type weakness and the site of lesions is at the root, plexus, or peripheral nerve level. Prognosis is generally good and > 50% of patients regain full motor power.

Abbreviations: CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; DFA, direct fluorescent antigen assay; HIV, human immunodeficiency virus; Hz, herpes zoster; IgG, immunoglobulin G; IV, intravenous; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; po, orally; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TIA, transient ischemic attack; VZV, varicella-zoster virus.

Patients with cutaneous Hz may have low-grade fever, headache, photophobia, and malaise before eruption of the rash. The rash is sometimes preceded by paresthesia, itching, and pain for 1 to 5 days, a condition termed pre-herpetic neuralgia (PHN).[18]

Differential diagnoses for Hz include acute herpes simplex, contact dermatitis, impetigo, folliculitis, scabies, insect bites, drug-induced rash, and varicella infection. Herpes simplex can sometimes present in a band that mimics a dermatome (zosteriform herpes simplex), which should be considered in the differential diagnosis in patients with recurrent localized, grouped vesicles, especially involving the mouth or genital regions.[22]

There are several Hz-associated neurologic complications, such as PHN, meningitis, meningoencephalitis, cerebellitis, isolated cranial nerve palsies, that produce ophthalmoplegia or the Ramsay Hunt syndrome, Bell's palsy, multiple cranial nerve palsies (polyneuritis cranialis), vasculopathy, myelitis, acute disseminated encephalomyelitis, acute inflammatory demyelinating polyneuropathy (Guillain-Barré syndrome), focal motor weakness, and various inflammatory disorders of the eye, the most serious of which is acute retinal necrosis (Table 2).[23–29]

Subclinical invasion of VZV into the CNS is relatively common; approximately one third and 46% of neurologically asymptomatic immunocompetent individuals with cutaneous Hz have a cerebrospinal fluid (CSF) polymerase chain reaction test result that is positive for VZV and CSF leukocytosis, respectively.[30]

Post-herpetic neuropathy, the most common complication of Hz, is defined as a neuropathic pain that persists for > 3 months after the complete resolution of the cutaneous lesions of Hz. The pathogenesis of PHN is unknown but may be due to either the excitability of ganglionic or spinal cord neurons or persistent low-grade infection resulting from viral invasion of the nerve roots, with subsequent inflammation and destruction.[20] The prevalence of PHN increases with aging and other risk factors and ranges from 5% to 22% (Table 3).[31–34]

Post-herpetic neuropathy can persist from a few months to years. The pain of PHN can manifest as burning, throbbing, an episodic sharp electric shock–like sensation, tactile allodynia, or hyperalgesia (exaggerated response to a painful stimulus). It is associated with long-term psychological distress and physical disabilities that lead to loss of workdays, interference with sleep and daily activities, and loss of quality of life. It is also associated with a substantial health care cost.[34]

Diagnosis

The diagnosis of Hz is based on the characteristic cutaneous eruption (a vesicular rash that follows a defined dermatomal pattern and is accompanied by neuropathic pain). The clinical diagnosis of cutaneous Hz may not be obvious, particularly in immunocompromised patients, and may mimic other cutaneous diseases, such as herpes simplex virus (HSV) infection, drug reaction, and contact dermatitis.[22]

Confirmatory testing is required in patients with atypical cutaneous lesions, such as painless skin lesions, lesions

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Table 3. Patient Risk Factors for PHN

Older age (≥ 50 years of age)
Immunocompromised
Micronutrient deficiency
Low income
Involvement of trigeminal dermatomes or brachial plexus during the acute episode of Hz
Hz ophthalmicus with keratitis, conjunctivitis, or uveitis
Severe prodromal pain
Acute severe pain
Involvement of larger surface area by skin lesions
Numerous lesions
Not receiving antiviral drugs

Abbreviations: Hz, herpes zoster; PHN, postherpetic neuralgia.

not conforming to a dermatomal distribution, or persistent neuropathic pain without the appearance of typical skin lesions. Laboratory testing is also required in patients with CNS and visceral organ involvement and zoster sine herpete (Table 2). Confirmatory testing includes direct fluorescent antigen assay, viral culture, or quantitative polymerase chain reaction for the detection of VZV DNA in skin lesion/visceral organ samples, whereas polymerase chain reaction of body fluids such as CSF, along with antibody testing (immunoglobulin G) for VZV in CSF, are first-choice tests in patients with suspected CNS and visceral organ involvement.[35] The advantages of direct fluorescent antigen (which involves staining cells that have been scraped from the base of the lesions with a scalpel blade using fluorescein-conjugated monoclonal antibodies) are that it is more sensitive than viral culture and it can distinguish between HSV and VZV.[36]

A thorough history and physical examination should be performed in all patients with Hz to identify risk factors such as underlying malignancy or immunodeficiency. However, routine additional laboratory and imaging studies should not be performed unless otherwise clinically indicated. An age-based cancer screening should be performed in patients with Hz (eg, a yearly mammogram is recommended in all women starting at age 40 years).[37,38]

Herpes zoster is more common among HIV-infected individuals, particularly among young adults, compared with age-matched individuals in the general population. Therefore, adults with a new diagnosis of Hz should be screened for HIV by undergoing an assessment for risk factors and serologic testing.[19]

Treatment

The primary objectives of the treatment of Hz are to soothe and protect the involved skin, accelerate the healing of skin lesions, reduce the duration of zoster-associated pain (defined as pain from the onset until resolution), prevent bacterial superinfection, and improve patients' functioning and quality of life.

Determining whether a patient can be treated safely as an outpatient or requires hospitalization is the first essential step in the treatment of Hz. Patients with severe, disseminated infection, severe herpes zoster ophthalmicus with ocular involvement, or visceral involvement such as CNS, should be hospitalized for therapy with intravenous acyclovir and supportive care.[22,23]

Soothing and protecting the involved skin can be achieved using compresses and a sterile, occlusive, nonadherent protective dressing. The skin lesions should be kept clean and dry to reduce the risk for bacterial superinfection.

It is recommended that treatment with antiviral agents be started in patients with Hz who present within 72 hours of lesion onset. Initiating treatment with antiviral agents within 72 hours of lesion onset results in shorter duration of viral shedding and new lesion formation, reduction of the duration of zoster-associated acute pain, and acceleration of cutaneous healing.[39] However, antiviral agents can still be prescribed in certain patients who present > 72 hours after lesion onset. These patients include older adults (≥ 60 years of age) with severe pain and a large area of skin involvement; immunocompromised patients; those with continued new vesicle formation; and those with visceral, neurologic, or ocular complications, including HZO. In approximately 50% of patients with HZO, ocular complications will develop if antiviral treatment is not administered.[40] Therapy with antiviral agents has been reported to reduce the frequency of late ocular inflammatory complications such as keratopathy, episcleritis, iritis, and stromal keratitis in patients with HZO.[41–43]

Acyclovir, valacyclovir, and famciclovir have been approved in the United States for the treatment of Hz (Table 4). They are all effective for the treatment of Hz, although the latter 2 drugs are preferred because of a simplified dosing schedule, improved pharmacokinetic characteristics, and superiority to acyclovir in the reduction of herpes zoster-associated pain and PHN duration in immunocompetent adults aged ≥ 50 years.[41,44]

Oral antiviral agents are commonly used for the treatment of uncomplicated Hz. Intravenous acyclovir should be used for the treatment of disseminated Hz; severe HZO; and ocular, visceral organ, and CNS involvement.[23]

Topical acyclovir or penciclovir should not be used for the treatment of any type of Hz infection, except as therapy

Table 4. Antiviral Drugs for Treatment of Patients With Hz

Drug	Dosage	Side Effects	Comments
Acyclovir	800 mg po 5 ×/d (with creatinine clearance > 25 mL/min);10–15 mg/kg TID IV (with creatinine clearance > 50 mL/min)	GI side effects, eg, nausea, vomiting. Acute kidney injury secondary to precipitation of insoluble acyclovir crystals in renal tubules. CNS side effects (agitation, hallucinations, disorientation, tremors, myoclonus)	Dose adjustment required for patients with renal dysfunction. Probenecid prolongs half-life of acyclovir. Topical acyclovir should not be used to treat Hz
Famciclovir	500 mg po TID (with creatinine clearance > 60 mL/min)	GI side effects, eg, nausea. Headache	Famciclovir is a prodrug of penciclovir. Alternative dosage of famciclovir is 750 mg po once daily, 500 mg po BID, or 250 mg po TID. Famciclovir can reduce duration of PHN. Dosage adjustment is required for patients with renal dysfunction. Probenecid prolongs half-life of famciclovir. Topical penciclovir should not be used for Hz
Valacyclovir	1 g po TID (with creatinine clearance > 50 mL/min)	GI side effects, eg, nausea Headache Thrombotic microangiopathy syndrome	Valacyclovir is a prodrug of acyclovir and produces serum acyclovir levels 3- to 5-fold higher than those achievable with oral acyclovir. The alternative dosage of valacyclovir is 1.5 g po BID. Valacyclovir can reduce the duration of PHN. Dosage adjustment is required in patients with renal dysfunction. Probenecid prolongs half-life of valacyclovir

Abbreviations: BID, twice daily; CNS, central nervous system; GI, gastrointestinal; Hz, herpes zoster; IV, intravenous; PHN, postherpetic neuralgia; po, orally; TID, 3 times daily.

adjuvant to systemic antiviral agents for corneal epithelial disease.[23]

In a large, nationwide cohort study from Denmark that included 1804 pregnancies, exposure to acyclovir, famciclovir, or valacyclovir in the first trimester of pregnancy was not associated with an increased risk for major birth defects.[45]

One of the essential elements of the treatment of Hz is adequate control of both acute Hz-related pain and chronic pain associated with PHN. Controlling acute Hz-related pain not only will improve functional status and health-related quality of life but also will reduce the risk for PHN. Only treatment with amitriptyline, ganglion blockade with bupivacaine and dexamethasone, and repetitive epidural injection of methylprednisolone acetate and bupivacaine during the acute illness has been reported to prevent PHN in clinical trials.[46–48]

The use of systemic corticosteroids has not been reported to prevent PHN in clinical trials, but it reduced the duration of acute neuritis, as measured by a reduced need for analgesics and by a more rapid return to usual activities and uninterrupted sleep. Therefore, it is recommended that a 10- to 14-day tapering course of oral prednisone (eg, starting at 60 mg/d) be added to a regimen of antiviral agents in patients with Hz who are aged > 50 years, have moderate to severe pain at presentation, and have no contraindications for its use.[49–51]

Acute Hz-related pain can be controlled with the use of a short-acting narcotic analgesic agent (eg, oxycodone) given on a scheduled rather than on an as-needed basis, a 5% lidocaine patch, gabapentin or amitriptyline in addition to oral analgesic agents, oral prednisone in addition to an antiviral agent and an analgesic agent, an epidural injection of methylprednisolone acetate and bupivacaine (once or repetitive) in addition to an oral analgesic agent, ganglion blockade with bupivacaine and dexamethasone, and/or acupuncture. Topical capsaicin should not be used in patients with active Hz because it can exacerbate pain, but it can be used for the treatment of PHN.[48,49,52–57]

The management of PHN often requires a multifaceted therapeutic approach due to symptoms that vary in nature and severity, a long disease duration, and a potential for psychological and physical debilitation. Options for the treatment of PHN are summarized in Table 5. In cases of uncontrolled pain or intolerable adverse effects with monotherapy, combination therapy may be required.[58–69] In addition to drug therapies, several other modalities have been employed to treat PHN. These modalities include

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Table 5. Treatment Options for PHN

Drug Class	Drug/Dosage	Clinical Indication/Evidence	Major AEs/Precautions
Opioid agonists	Fentanyl patch 12 μg/h; morphine 15 mg q6h as needed; oxycodone 5 mg q6h as needed. Titrate at weekly intervals or shorter as tolerated	Considered one of the second- or third-line therapies for PHN due to potentially treatment-limiting AEs. Long-acting opioid preparations (oral or transdermal) preferable to short-acting analgesics for management of chronic pain associated with PHN	All drugs in class may cause nausea, vomiting, constipation, sedation, cognitive dysfunction, bronchospasm, orthostatic hypotension, and itching. Use with precaution in elderly patients and patients with cognitive dysfunction, sleep apnea, or asthma. All opioid agonists have additive sedative effects with TCAs, gabapentin, and pregabalin. Dosage adjustment required in patients with renal dysfunction. Regular assessment recommended using 5 As approach: Analgesia, Activity, Adverse effects, Aberrant use, Affect
TCAs	Amitriptyline, nortriptyline, or desipramine; starting dose, 10–25 mg at bedtime, increased by 10–25 mg every 7 d, up to 75–150 mg once daily	Drug class is one of the first-line therapies for PHN	All drugs in class may cause somnolence, anticholinergic effects (sedation, cognitive impairment, orthostatic hypotension, urinary retention, constipation) weight gain. Nortriptyline and desipramine slightly better tolerated than amitriptyline due to less anticholinergic effects. Baseline ECG recommended before starting TCAs. Use with precaution in patients with cardiac disease (eg, prolonged QT interval), glaucoma, BPH, seizure, or with use of tramadol or SSRIs (risk for serotonin syndrome)
Calcium channel α-2-δ ligands	–	Drug class is one of first-line therapies for PHN	All agents in drug class may cause sedation, dizziness, blurred vision, ataxia, peripheral edema, weight gain. Titrate drugs slowly in elderly patients. Do not discontinue the drugs suddenly. Reduce doses of both drugs in patients with renal dysfunction
Gabapentin	Starting dose, 100–300 mg taken at night, titrated as needed by 100–300 mg every 3–7 d, to as much as 1800–3600 mg/d, in 3 or 4 divided doses	Effective in treating PHN when used alone or in combination with other modalities	Pharmacokinetic properties of gabapentin are variable; therefore, dosage is patient dependent
Extended-release gabapentin	Starting dose, 600 mg po, once daily for 3 d, followed by 600 mg TID. It can be used at 1800 mg once daily	Mixed results regarding the efficacy of extended-release gabapentin in the treatment of PHN	Pharmacokinetic properties of gabapentin are variable; therefore, dosage is patient dependent
Pregabalin	Starting dose, 25–75 mg, titrated up as needed by 75 mg every 3–7 d, to 300–600 mg/d, in 2 divided doses as tolerated	Pregabalin more effective in controlling pain than amitriptyline. Pregabalin more effective and cost-effective than gabapentin in treating PHN	Pharmacokinetic properties of pregabalin are linear and more predictable
Topical lidocaine	Lidocaine 5% patch once daily or BID; lidocaine 5% gel once daily or BID	Effective and well tolerated in controlling pain, particularly allodynia, for long duration (> 1 y) and one of first-line therapies for PHN. Use associated with relatively fewer AEs than oral therapies for PHN. Lidocaine patch is preferable to gel	Common AEs include local erythema, itching, rash. Contraindicated in patients with hypersensitivity to amide local anesthetics (eg, bupivacaine, mepivacaine). Patch should be off for 6–12 h
Capsaicin patches	Apply 0.025% and 0.075% cream 3–4 ×/d over affected region; single 60-min application of 8% capsaicin patch	Single 60-min application of 8% capsaicin patch more effective than 0.04% capsaicin patch in treatment of PHN. Efficacy of 8% patch can last up to 3 mo if its application is repeated. One of the second- or third-line therapies for PHN	Common AEs include pain, burning, erythema, elevated BP due to initial increase in pain. Apply topical local anesthetic before the 8% patch application

(Continued)

Table 5. (*Continued*)

Drug Class	Drug/Dosage	Clinical Indication/Evidence	Major AEs/Precautions
Serotonin–norepinephrine reuptake inhibitors	–	Efficacy has been established mainly in diabetic painful polyneuropathy	Avoid use of this class with tramadol due to risk for serotonin syndrome
Duloxetine	Starting dose, 30 mg/d, titrated up to 60 mg/d after 1 wk, then as tolerated up to 120 mg/d	–	May cause nausea, dry mouth, constipation, reduced appetite, diarrhea, sedation, dizziness. Use with precaution in patients with hepatic disorder and uncontrolled hypertension
Venlafaxine	Starting dose, 37.5 mg once daily or BID, increased by 37.5–75 mg each wk as tolerated, up to 225 mg daily	–	May cause nausea, prolonged QT interval, and hypertension at high dosages. Use with precaution in patients with cardiac disease and hypertension
Atypical opioids	–	One of the second-line therapies for PHN. When used alone or with other therapies both drugs are effective in treating PHN	All drugs in class may cause nausea, vomiting, constipation, headache, drowsiness, dizziness. Use with precaution in patients with seizure disorder and concomitant use of SSRIs and TCAs. Adjust the doses of both drugs in patients with hepatic or renal disease
Tramadol	Starting dosage is 50 mg q6h as needed, titrated up by 50–100 mg every 3–7 d, to maximal dosage of 400 mg/d, in 4 divided doses. Starting dose of sustained-release tramadol, 100 mg/d, titrated up to 400 mg once daily	Tramadol may be better tolerated than opioid analgesics.	–
Tapentadol	Starting dose is 50 mg every 4–6 h as needed, titrate up as tolerated to maximum daily dose of 600 mg, divided into 4 to 6 doses	–	–

Abbreviations: AEs, adverse events; BID, twice daily; BP, blood pressure; BPH, benign prostatic hypertrophy; ECG, electrocardiogram; PHN, postherpetic neuralgia; SSRIs, selective serotonin reuptake inhibitor; TCAs, tricyclic antidepressants; TID, 3 times daily.

invasive interventions such as sympathetic nerve blocks, intercostal nerve block, pulsed radiofrequency, intrathecal injection of methylprednisolone acetate, spinal cord stimulation, cryotherapy, botulinum toxin A injection, acupuncture, and transcutaneous electrical nerve stimulation.[70–77]

Prevention

Varicella-zoster virus can be transmitted from a person with Hz to a person who is VZV seronegative, resulting in varicella. The virus can be transmitted through direct contact with lesions from a patient with dermatomal Hz. It can also be transmitted through the airborne route, particularly from patients with disseminated Hz. Patients should be isolated until all lesions are crusted. Most authorities recommend standard precautions and the use of gloves when touching the lesions of patients with localized Hz. Severely immunocompromised patients in whom dermatomal Hz has developed should be placed on both airborne and contact isolation until it is clear that dissemination is not developing. All patients with disseminated Hz should be placed in airborne and contact isolation.[78] Patients with active Hz should be especially careful to avoid contact with infants and small children, pregnant women, and immunocompromised individuals, all of whom are potentially susceptible.

Health care workers, family members, household contacts, and visitors who are healthy and who do not have a reported history of varicella infection or who are VZV seronegative should receive varicella vaccination before any direct contact with recipients of a peripheral blood stem cell transplant (PBSCT) or a solid organ transplant (SOT). The vaccination schedule should be completed at least 4 weeks before PBSCT. While undergoing conditioning therapy, PBSCT recipients should avoid contact with any VZV vaccine recipient who experiences a rash after vaccination.[79]

Several studies, including randomized, double-blinded, placebo-controlled trials, have shown that live attenuated VZV vaccine reduced the incidence of Hz (among adults aged 50–59 and ≥ 60 years), PHN (among adults aged ≥ 60 years), HZO, hospitalization, Hz-related interference with activities of daily living, and health-related quality of life (only in individuals who did not develop Hz). The vaccine was more efficacious in preventing Hz among adults aged 60 to 69 years

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than among those aged ≥ 70 years; however, it prevented PHN to a greater extent among adults aged ≥ 70 years.[13,80–84] The vaccine was found to be less effective in untreated, depressed individuals than in nondepressed and depressed individuals treated with antidepressant medications.[13]

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention recommends that the VZV vaccine be given as a single 0.65-mL dose subcutaneously in the deltoid region of the arm in immunocompetent adults aged ≥ 60 years, regardless of history of varicella infection.[85] Serologic testing for past exposure is not required prior to vaccination. In 2011, the US Food and Drug Administration expanded the age indication for the VZV vaccine to include adults aged 50 to 59 years. Although the protection of VZV vaccine declines gradually, a booster dose is not recommended.[86] The vaccine is effective through year 5 after vaccination, and the postvaccination antibody concentrations are similar after either 1 or 2 doses of the vaccine.[87,88] Because it is a live vaccine, VZV is contraindicated in people with active, untreated tuberculosis; pregnant women; in immunocompromised adults, such as those with leukemia, lymphoma, or advanced malignancy; and in patients receiving chemotherapy, radiotherapy, and large doses of corticosteroids. The vaccine also should not be given to persons with a history of anaphylactic reaction to any vaccine components, such as gelatin and neomycin. Antiviral agents such as acyclovir should not be used for at least 24 hours before and 14 days after vaccination.[89] The vaccine is effective and well tolerated in older adults (aged ≥ 60 years) taking anti-tumor necrosis factor or other biologic therapies, in individuals with hematologic malignancies (in remission), and in PBSCT recipients.[90,91] However, live vaccines should not be given to PBSCT recipients who are < 24 months post-transplantation, who still require immunosuppressive therapy, or who have evidence of graft-versus-host disease (GVHD).[92]

The vaccine is well tolerated. Common adverse effects are injection-site reaction, itching, and headache. The vaccine can be given concurrently with influenza and pneumococcal vaccines in older adults without altering the immune response to either vaccine.[93,94]

Despite reported efficacy, and despite being recommended by the ACIP since 2006, the VZV vaccine is still underutilized, particularly among minority groups such as Hispanic patients and non-Hispanic black patients.[95]

The cost-effectiveness of the vaccine is affected mainly by age at vaccination, incidence of Hz, price and duration of protection of the vaccine, and duration of PHN. The vaccine is likely to be cost-effective if the duration of protection is > 10 years.[96]

Herpes zoster reactivates commonly in certain immunocompromised patients, particularly in PBSCT recipients, and it is associated with a high risk for PHN.[97,98] Long-term prophylaxis with low-dose oral acyclovir (400–800 mg/d) or valacyclovir (2000 mg/d) for the prevention of recurrent VZV infection is routinely recommended for the first year after transplantation in VZV-seropositive, allogeneic and autologous PBSCT recipients and in patients with multiple myeloma receiving bortezomib-based therapy.[99–103] Patients with multiple myeloma treated with bortezomib and who are undergoing long-term acyclovir prophylaxis are at increased risk for severe renal and neurologic toxicity. Therefore, renal function and neurologic condition should be closely monitored.[104] In allogeneic PBSCT recipients who have chronic GVHD or who require systemic immunosuppression at persistent risk for VZV reactivation, the optimal duration of prophylaxis is poorly defined. Prophylaxis with acyclovir or valacyclovir is commonly continued until, or 6 months after, the discontinuation of all systemic immunosuppressive drugs and until CD4 count reaches > 200 cells/mm^3. Prophylaxis should be restarted with the resumption of systemic immunosuppressive drugs for either rejection or GVHD.

In SOT recipients, prophylaxis for cytomegalovirus (CMV) with valganciclovir, ganciclovir, acyclovir, or valacyclovir also prevents VZV reactivation. SOT recipients not receiving prophylaxis for CMV prevention but who are HSV-1 or HSV-2 seropositive are usually undergoing low-dose acyclovir prophylaxis (for ≥ 1 month), which prevents VZV reactivation. However, the risk for VZV reactivation persists for years after SOT, and prophylaxis with antiviral agents is unlikely to prevent the majority of cases of Hz. Starting antiviral agents once Hz develops is a practical option after the discontinuation of CMV or HSV prophylaxis.[99]

In SOT candidates who are VZV seronegative and who have no contraindications for the use of live attenuated varicella vaccine, 2 doses of the vaccine should be administered, with a minimum interval of 4 to 6 weeks between the 2 doses, and with the second dose given ≥ 2 weeks (and preferably > 4 weeks) prior to transplantation. Seroprotection should be confirmed after vaccination, with consideration of subsequent doses in patients who do not respond to the initial series.[105]

Any individual exposed to a potential case of contagious varicella or Hz (household contact, face-to-face contact) should have a thorough assessment that includes status of the source, the exposure itself, and the exposed person's susceptibility

to the infection and risk for severe infection. Evidence of immunity to varicella in adults includes any of the following: documentation of 2 doses of varicella vaccine ≥ 4 weeks apart; history of varicella or Hz based on diagnosis by a health care provider; serologic evidence of either immunity or disease; or birth in the United States before 1980, except in health care workers and pregnant women.[86] Nonimmune, immunocompetent, exposed individuals should be given varicella vaccine as early as possible, and up to 5 days after exposure. Administration of varicella vaccine within the first few days after exposure to wild-type VZV produces a protective (or partially protective) immune response. The ACIP recommends that, during an outbreak of varicella, all nonimmune, immunocompetent individuals be given the first or second dose of varicella vaccine, provided that the appropriate interval has elapsed (3 months in individuals aged 12 months to 12 years and ≥ 4 weeks in individuals aged ≥ 13 years).[106] However, in exposed pregnant women and in immunocompromised individuals, live varicella or VZV vaccine is contraindicated. These groups of individuals should receive passive immunization with varicella-zoster immunoglobulin (VZIG) 125 U per 10 kg (maximum, 625 U; minimum, 125 U) as a deep intramuscular injection within 10 days of the exposure. If VZIG is unavailable, intravenous immunoglobulin 400 mg/kg should be given. In immunocompromised, susceptible individuals, postexposure prophylaxis with antiviral agents can be used as an adjuvant to immunoprophylaxis with VZIG, or alone if VZIG is either unavailable or cannot be used. Acyclovir or valacyclovir should be given from days 3 to 22 after known exposure to either varicella or Hz, and from days 3 to 28 if given with immunoprophylaxis.[107] All exposed, susceptible individuals should undergo airborne and contact precautions from days 10 to 21 after exposure to the index case, and those who receive VZIG should undergo precautions until day 28.[107,108]

Conflict of Interest Statement

Mazen S. Bader, MD, MPH, discloses no conflicts of interest.

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