

Herpes Zoster: Clinical Manifestation, Treatment, and Prevention

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Abstract

Herpes zoster (HZ, shingles, zoster) is a disease due to reactivation and multiplication of persistent varicella zoster virus (VZV) after suffering from previous varicella with characteristics of dermatomal rashes, pain, and unilateral. Dermatomes most often involved in HZ lesions are thoracic, trigeminal, lumbal, and cervical. The first lesion is usually erythematous macule or papule, which then turns into vesicle, then to pustule and to become crust, and persists for 2-3 weeks. The main goal of antiviral therapy in HZ patients is to reduce the expansion, duration, and severity of rashes and pain in primary dermatomes; prevent the spread of HZ to other places; and prevent post-herpes neuralgia. One of the prevention strategies for HZ in the elderly and high-risk individuals is vaccination using the varicella zoster virus vaccine that is live zoster vaccine or recombinant zoster vaccine.

Keywords : Herpes zoster, clinical manifestation, treatment, prevention

Introduction

Herpes zoster (HZ) (shingles, zoster) is a disease with a characteristic rash and unilateral dermatomal pain distribution caused by reactivation and multiplication of endogenous varicella zoster virus (VZV), persisting in latent phase in sensory ganglia after previous episode of varicella.^{1,2}

Several classical clinical manifestations include painful herpetiform clustered vesicles, with an erythematous base, which is limited in one or two dermatomal areas. HZ occurring in healthy, immunocompetent individuals will reach spontaneous resolution and disappear without interventions. HZ on children may be of lighter severity compared to adults. Patients over 50 years of age and immunocompromised individuals harbor higher

risk of acquiring HZ with clinical manifestations of rash, pain, and severe complications, causing distress and reducing quality of life.^{3,4}

Medications will be the most effective for patients having the risk of bearing long and severe symptoms, especially immunocompromised individuals and those over 50 years of age. In general, drug choices differ by immunity status and personal clinical manifestations.^{3,4}

One of the preventive strategies of HZ in general population, especially elderly and high-risk groups, is to stimulate immunity against VZV by vaccination.³

Clinical Manifestation

A few days before rash eruption, fever, malaise, myalgia, headache, pain and paresthesia around dermatom occur. Most often, constant or intermittent pain is experienced by those older than 60, which varies from superficial tingling or itching, burning, till lancinating pain. Onset of pain is 48-72 hours before the first rash appear. Some patients may experience zoster sine herpetic with the form of acute segmental neuralgia without skin lesions.^{1,4,6}

The most common clinical manifestation is unilateral distribution of rash, usually limited to one or two dermatoms. The first lesion is usually erythematous macule or papule, which then 12-24 hours after turns into vesicle, then to pustule by the third day. After 7-10 days, the pustule dries off to become crust, and persists for 2-3 weeks. New lesions may appear for the first 1-4 days (sometimes up to 7 days).¹ Classical rash appear as painful herpetiform grouped vesicles sitting on an erythematous base, and is limited to one or two dermatoms.^{3,6} Skin lesions usually heal without residual rash, but may turn into hypo/hyperpigmentation following inflammation or scarring. Skin rash will be more severe and longer in older individual; therefore it is less severe and shorter in pediatric population.¹ Sometimes, regional lymphadenopathy may occur.³

Clinical manifestations can highly vary. HZ most often occurs in dermatoms with the most number of varicella lesions.¹ Dermatom related to HZ lesion are usually within centripetal distribution of the initial varicella lesion. During varicella, virus spreads from skin lesion to sensory nerve endings, then ascends to ganglion. Other hypothesis believes that the ganglion is infected by hematogen route during viremia phase of varicella, and

reactivation stimulus occurs most often in these ganglions.^{3,6} Dermatomes most often involved in HZ lesions are thoracic, trigeminal, lumbal, and cervical.¹⁰

HZ oticus (geniculate zoster, zoster auris, Ramsay Hunt syndrome, Hunt syndrome) occurs with involvement of geniculatum ganglion. The classic appearance is otalgia with herpetiform vesicles in external auricular canal or tympanic membrane, with or without facial paralysis, auditory symptoms (hearing disturbance), and vestibular symptoms. Ramsay Hunt syndrome triad consists of HZ lesion on ear, ipsilateral facial palsy, and anesthesia in 2/3 anterior of the tongue. This syndrome is caused by involvement of N. VII, IX, and X.³

HZ involving the eyelids signifies the involvement of the first branch (ophthalmicus) of trigeminal nerve, and is named HZ ophthalmicus. This type is often experienced by the elderly. HZ lesions on the bridge of the nose (Hutchinson's sign) is a predictor of ocular involvement. On occasions, blepharoconjunctivitis, keratitis, uveitis, and secondary glaucoma may occur.^{3,6}

The involvement of second branch (maxillaris) and third branch (mandibularis) of trigeminal nerve causes intraoral HZ lesions accompanied with tooth pain. Maxillary branch involvement causes lesions in ipsilateral cheek, upper and lower lid, side of nose, nose mucose membrane, nasopharynx, tonsils, upper teeth, palatum, uvula, and tonsillar fossa. Involvement of mandibular branch causes lesions on the side of the head, external ear, external auricular canal, lower lip, base of mouth, buccal mucose membrane, and tongue.^{3,6}

Disseminated HZ is a generalized eruption with more than 10-12 extradermatomal vesicles, 7-14 days after the onset of classic dermatomal HZ. Disseminated HZ indicate decreased cellular immunity with various causes, including malignancy, radiation therapy, cancer chemotherapy, organ transplantation, or long term corticosteroid medications.³ In the immunocompromised, new lesions may appear till up to 2 weeks, and viremia with disseminated rash may occur with complications involving skin necrosis, scar, and visceral organ involvement including lungs, liver, and brain. HZ patient with active HIV infection may experience recurrent HZ in the same dermatome or other dermatomes. HZ patients with AIDS may experience severe HZ with dissemination to the skin and visceral organs, including acyclovir-resistant VZV with verrucous or hyperkeratotic lesions.^{1,8,10}

HZ complications don't happen often in healthy children and adults, and most commonly reserved to the immunocompromised. The frequently reported complication is post herpetic neuralgia (PHN), which is a persistent pain for more than 4 weeks after HZ onset, and occurring 60% in patients >60 years old. Some skin complications include secondary bacterial infection, scar, zoster gangrenosum, and cutaneous dissemination. Ocular complications include conjunctivitis, keratitis, corneal ulcer, iridocyclitis, glaucoma, and blindness. Some visceral complications include pneumonitis, hepatitis, esophagitis, gastritis, cystitis, and arthritis. Neurological complications involve meningoencephalitis, cranial nerve palsy, sensory loss, deafness, peripheral nerve palsy.¹

Diagnosis

HZ diagnosis is mainly based on anamnesis and physical examinations, with focus on the characteristic location and rash appearance with local pain.⁶ Laboratory diagnosis confirmation is done on atypical HZ patients, visceral organ and central nervous system involvement, or zoster sine herpette. Some laboratory diagnosis confirmation involve Tzanck smear, polymerase chain reaction (PCR), direct immunofluorescence assay (DFA), skin biopsy, and culture.

Tzanck smear is a simple and affordable laboratory confirmation test, but it cannot differentiate VZV with other herpesviruses. PCR may detect VZV DNA in skin lesion samples and visceral organs. PCR and VZV IgG test with cerebrospinal fluid sample are the first line laboratory examinations on HZ patients with visceral organ and central nervous system involvement. Skin biopsy and PCR can assist diagnosis on zoster sine herpetic cases.^{3,6}

Treatment

During acute phase, in order to subside local symptoms and hasten vesicular lesion drying, a patient may do a compress with sterile saline solution, Burowi solution, or lotio calamin, which is applied on the involved skin for 30-60 minutes, 4-6 times a day. Topical antiviral therapy is proven not effective, thus is not recommended.^{1,3,6,8}

The main objective of antiviral therapy on HZ patients is to limit spread, duration, and severity of lesion and pain on primary dermatom, reduce distribution of HZ to other locations, and prevent PHN.¹

Most complications are caused by prolonged replication and VZV spread from the involved ganglion. Therefore it should be prevented by quick and effective antiviral therapy.¹ Nucleoside analogues such as acyclovir, famcyclovir, and valacyclovir, and pyrophosphate analogue phoscarnet has been proven to be effective to treat VZV infection. Afterwards, cellular enzymes will transform acyclovir monophosphate to acyclovir triphosphate which inhibits DNA polymerase virus to stop virus DNA synthesis.¹ Phoscarnet is an inorganic pyrophosphate analogue which inhibits viral replication. Antiviral activity is brought forward by selective inhibition on DNA polymerase and reverse transcriptase pyrophosphate-binding site, but it doesn't influence cellular DNA polymerase. Phoscarnet antiviral activity doesn't require phosphorylation by thymidine kinase, thus proven effective for acyclovir-resistant VZV.^{1,8}

Herpes Zoster on Immunocompetent Adolescents and Adults

Antiviral therapy is recommended to reduce time of lesion healing, duration and severity of acute pain on adult patient. Medication is administered in ≤ 72 hours after rash onset. Antiviral therapy is recommended, even for those with lesion onset of >72 hours, if new vesicles still emerge, any cutaneous lesions exist, disseminated visceral or neurological involvement is suspected, HZ subtype is ophthalmicus or oticus, and all immunocompromised patients.^{1,3,9,11}

Antiviral drug regimen recommended for immunocompetent adolescents and adults are:¹

- Those <50 years old: symptomatic therapy; or oral famcyclovir 3dd 500 mg for 7 days; or oral valacyclovir 3x1 gram for 7 days; or oral acyclovir 5x800 mg for 7 days.
- Those ≥ 50 years old, and any age with cranial nerve involvement (for example, HZ ophthalmicus): oral famcyclovir 3x500 mg for 7 days; or oral valacyclovir 3x1 gram for 7 days, or oral acyclovir 5x800 mg for 7 days.

The choice of drug depends on the price of the medicine and frequency of dosages in a day. Famcyclovir and valacyclovir are preferred compared to acyclovir for oral therapy due to their pharmacological advantages, less frequency of administration in a day, and higher antiviral activity in the bloodstream.^{1,3,12}

Ophthalmicus HZ is better treated alongside ophthalmologists to prevent ocular complications, especially when the eye is involved.^{8,9}

Herpes Zoster on Immunocompromised Patients

Less severe HZ on immunocompromised patients or those with local HZ may be given oral acyclovir, famcyclovir, or valacyclovir.^{1,3,9} Treatment regimen for immunocompromised individuals involve:¹

- Mild immunocompromise, involving HIV infection: oral famcyclovir 3x500 mg for 7-10 days; or oral valacyclovir 3x1 gram for 7-10 days; or oral acyclovir 5x800 mg 7-10 days.
- Severe immunocompromise: intravenous acyclovir 10 mg/kg, 3x daily for 7-10 days.
- Acyclovir-resistant (AIDS end stage): intravenous foscarnet 40 mg/kg 3x daily till resolution.

Herpes Zoster on Pregnant Women and Children

Pregnant women with HZ should be considered to be treated as soon as possible, to hasten lesion healing and reduce intensity and length of pain period. The recommended antiviral therapy for pregnant women are oral acyclovir 5x800 mg/day for 7-10 days and oral valacyclovir 3x100 mg/day for 7 days.^{4,13,14} Famcyclovir isn't recommended for pregnant and breastfeeding women.¹⁴ Intravenous acyclovir therapy is given to pregnant women with HZ involving cranial nerves, ocular nerve, mucose membrane, hemorrhagic lesion, disseminated lesion, and pneumonitis. Intravenous dosage ranges from 10-15 mg/kg, or 500 mg/m² every 8 hours, for 5-10 days.^{13,14}

Herpes zoster doesn't occur often in children, and if it does, it is majorly mild. Antiviral therapy is recommended if complications are present, if they are immunocompromised, or new lesions keep emerging after 3 weeks course of disease. Acyclovir is given orally, with dosage 20 mg/kg/dosage (maximum of 800 mg/dosage), 5 times per day, for 5-7 days. For immunocompromised children with severe HZ, they are given intravenous acyclovir 10 mg/kg or 500 mg/m² every 8 jam, for 7-10 days.^{4,9,15}

Anti-inflammatory Therapy

Corticosteroid usage for HZ is still debated. Inflammation happening in sensory ganglia plays a role in PHN, thus for its prevention, one may be given corticosteroid during acute phase of HZ. Initiation of corticosteroid must be hand-in-hand with antiviral therapy.^{1,4,10,16} The duration of corticosteroid treatment should not exceed antiviral therapy.¹ Combination of acyclovir and corticosteroid is recommended for healthy adult HZ patients with moderate – severe pain, if neurological symptoms are significant, or if central nervous system, Ramsay-Hunt syndrome, or ocular complications are involved.^{3,4,9,10}

The studies about acyclovir and corticosteroid combination therapy reported various dosage, route of administration, and treatment period. Dworkin reported prednisolone usage at 60 mg/day for 1 week, then tapered off to 30 mg/day for 1 week, followed by 15 mg/day for 1 week.^{10,11} Murakami reported Ramsay-Hunt syndrome medication using acyclovir 250 mg IV 3 times daily, or oral acyclovir 5x800 mg/day for 7 days, combined with intravenous or oral prednisolone 1 mg/kg/day with two divided doses for 5 days, tapered off slowly and stopped in 10 days. Coulson reported treatment of Ramsay-Hunt syndrome using oral acyclovir 5x200 mg/day for 21 days, followed with oral prednisolone 1 mg/kg/day for 14 days then tapered off to 10 mg/day before stopped.⁴

Treatment of Acute Pain in HZ

Most of HZ patients experience acute pain, and it is usually the most reported symptom. Analgetics are necessary as adjuvants to antiviral therapy.⁹ Choice and dosage of drug depends on pain severity, underlying diseases, and response to medication.^{1,9} Patients with HZ and mild pain may be given oral acetaminophen for 325-1000 mg 4-6 times per day, or nonsteroidal anti-inflammatory drugs (NSAIDs) like oral ibuprofen 400 mg 4- times daily. Acetaminophen and NSAIDs are the drugs of choice to control HZ acute pain.^{10,11,17} Healthy HZ patient reporting moderate – severe acute pain on presentation, or with risk factors for PHN (women, age over 50 years old, lesion count >50, location in cranial/sacral area, hemorrhagic lesion, or dermatomal pain during prodromal phase) are recommended to be given tricyclic antidepressant analgetic, anticonvulsant or opioid/non-opioid.⁹ If pain control is still inadequate, doctors may consider to administer nerve block or local anesthesia.¹

Anticonvulsant medications gabapentin and pregabalin are reported to reduce 50% of acute pain in HZ.¹⁷ Gabapentin is used with initial dosage 100 – 300 mg before night sleep, and can be increased by 100 – 300 mg, 3 times daily until 3-7 days and pain is tolerable (maximum dosage of 3600 mg/day). Pregabalin is used with initial dosage 25 – 75 mg, 1-2 times daily, and can be increased by 75 mg, 2 times daily for 3-7 days until pain is tolerable (maximum dosage of 600 mg/day). Side effects range from somnolence, dizziness, ataxia, and peripheral edema.^{1,10,11,16}

Tricyclic antidepressants (amitriptyline, nortriptyline, and desipramine) can reduce 44-67% HZ acute pain.¹ Initial dosage is 10-25 mg before night sleep, and can be increased 10 – 25 mg weekly until pain is tolerable (maximum dosage of 150 mg/day). Side effects include somnolence, dry mouth, blurred vision, sedation, orthostatic hypotension, constipation, heart arrhythmia, and urinary retention.^{7,10,16,17}

Opioid/non-opioid analgetics are reported to be effective to reduce acute HZ pain, some of the medications being oxycodone and tramadol. Oxycodone is used with initial dosage of 5 mg every 4 hours, and can be increased 5 mg 4 times daily every week until pain is tolerable (maximum of 120 mg/day). Some reported side effects are nausea, vomiting, constipation, sedation, cognitive dysfunction, bronchospasm, orthostatic hypotension, and itching. Tramadol is used with initial dosage of 50 mg, 1-2 times daily, and can be increased 50 – 100 mg/day, given in two divided doses until pain is tolerable (maximum of 400 mg/day; 300 mg/day for age >75 years old).^{10,11,16}

Prevention of HZ:

Varicella Zoster Virus Vaccination

The prevention of HZ aims to avoid reactivation and spread of latent VZV virus. One of the preventive strategies of HZ in the general population, especially the elderly and high-risk individuals is to stimulate immunity against VZV.³

In the year 2006, the US Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) recommended the higher potency live attenuated vaccine VZV (Zostavax®) to prevent HZ on immunocompetent non-pregnant population, aged ≥ 60 years old, including those who have had previous HZ episode. It is given in a single subcutaneous dose on the deltoid area.^{7,18} Protection spans till 3 years.

Several contraindications to this medication is those severely immunocompromised, pregnant women, and children.^{3,10,20}

In the year 2018, CDC recommended immunization on adults using zoster vaccine:

- 2 doses of recombinant zoster vaccine (RZV) (Shingrix®) 2-6 months apart, is used for those aged ≥ 50 years old, regardless of previous HZ episode, or have received live zoster vaccine (ZVL) (Zostavax®).
- 2 doses of RZV, 2-6 months apart for adults having received ZVL, minimal of 2 months after ZVL.
- Administration of one of RZV or ZVL for those aged ≥ 60 years (RZV is preferred).^{3,20}

Varicella Zoster Immune Globulin (VZIG)

The Centers for Disease Control and Prevention (CDC) recommended passive immunization using VZIG to prevent or modify clinical manifestation of VZV infection on high risk individuals, children, pregnant women, or immunocompromised individuals exposed to varicella or herpes zoster. VZIG is given intramuscularly, with dosage of 125 U/10 kg (maximum of 625 U; minimum 125 U) or 0,5-1 mg/kg. The best effect is achieved if administered as soon as possible from exposure, and at least ≤ 96 hours after exposure. Protection after VZIG lasts for around 3 weeks.^{3,7,10}

Conclusion

Classic clinical characteristics of HZ are painful herpetiform grouped vesicles, sitting on top of an erythematous base, limited to one or two dermatoms. Skin rash is more severe and longer in the elderly, but milder and shorter in children. Dermatoms most often involved are thoracal, trigeminal, lumbal, and cervical. Clinical manifestations may vary.

HZ diagnosis is based on clinical appearance, and laboratory diagnosis confirmation is done on atypical HZ patients.

HZ treatment is recommended for those with risk of experiencing long and severe symptoms, especially immunocompromised populations and those over 50 years old. Acyclovir, famcyclovir, valacyclovir, and phoscanet is proven to be effective to treat VZV infection. Medication is administered in ≤ 72 hours after onset of rash. Combination

therapy acyclovir and corticosteroid is recommended for acute moderate – severe pain, those experiencing significant neurological symptoms or with central nervous system manifestation, Ramsay-Hunt syndrome, and ocular complications.

Analgetic medications are given as adjuvants to antiviral therapy to treat acute pain in HZ. HZ patients with acute mild pain can be given acetaminophen or NSAIDs. HZ patients with moderate – severe pain may be given tricyclic antidepressants analgetic, anticonvulsant or opioid/non-opioid.

One of the strategies of prevention of HZ in the elderly and high-risk individuals is to vaccinate using zoster vaccine live or recombinant zoster vaccine. Passive immunization using VZIG is recommended to prevent or modify clinical manifestation of VZV infection on high-risk individuals, children, pregnant women, or immunocompromised exposed to varicella and herpes zoster.

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