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Review Article

A Review on Herpes Zoster

Shraddha Nimse*, Shrikant Kavitake, Dhananjay Mundhe

Dattakala College Of Pharmacy

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ABSTRACT

HZ is secondary to varicella, its incidence increases with age. In children and youngsters, HZ is rare and associated to metabolic and neoplastic disorders. In adults, advanced age, distress, other, and immunosuppression are the most common risk factors. The disease shows different clinical stages of variable clinical manifestations. Some of the manifestations bear a higher risk of complications. Among the possible complications, postherpetic neuralgia, a chronic pain disease, is one of the most frequent. HZ vasculitis is associated with morbidity and mortality. Renal and gastrointestinal complications have been reported. The cornerstone of treatment is early intervention with acyclovir or brivudine. Second line treatments are available. Pain management is essential. This review focuses on manifestations of HZ and its management. Although several articles have been published on HZ, the literature continues to evolve, especially in regard to patients with comorbidities and immune compromised patients. The objective of this review is to discuss current updates related to introduction, History, diagnosis, clinical presentations, complications, etiology, epedemiology and management of Herpes Zoster. Studies in which the diagnosis was confirmed by lab tests have shown that the diagnosis of herpes zoster solely based on clinical evaluation has a specificity of 60–90 %, depending on severity and site.

This is especially true in cases in which,

- The Patient Does Not Report A Typical Prodromal Phase.
- The Lesions Involve More Than One Dermatome Or Cross The Midline.
- A Site Other Than The Thoracic Region Is Affected.
- The Temporal Course Is A Typical. The Affected Individual Has A Prior History Of Herpes Zoster.
- The Affected Individual Has Received A Vzv Vaccine.

HZ is associated with higher long-term risk of a major cardiovascular event. These findings suggest there are long-term implications of HZ and underscore the importance of prevention.

***Corresponding Author:** Shraddha Nimse
Address: *Dattakala College Of Pharmacy*
Email : snnimse123@gmail.com

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INTRODUCTION

Herpes zoster (HZ) is caused by reactivation of the varicella-zoster virus from a latent state and is usually characterized by a unilateral, acutely painful vesicular rash that affects a single dermatome and is self-limiting, typically resolving in a few weeks. Postherpetic neuralgia (PHN) is a common clinical complication of HZ that presents as severe, often persistent, pain that occurs after the rash has resolved. The risk of developing PHN in patients with HZ varies from 5% to more than 30%, as recently reported in a systematic review of 30 studies in26 countries. The occurrence of both HZ and PHN increases with age, and incidence rates appear to be increasing over time.[1] Herpes zoster (HZ) is a cutaneous disease secondary to HZ virus infection in spinal nerves and cranial nerves, characterized by vesicular rashes with burning, tingling or stabbing pain along the affected innervated area. The reported annual morbidity of HZ ranges from 3.9 to 42/100,000 person-years and the incidence is even higher in elderly patients because of the decreased immunity.[1] Herpes zoster (HZ), or shingles, is a painful vesicular rash,usually unilateral, caused by the varicella zoster virus (VZV). The pain and potential long-term effects associated with HZ, including post-herpetic neuralgia (PHN) and cranial nerve damage, can be debilitating, with a serious impact on quality of life. In 2006, the zoster vaccine received Food and Drug Administration (FDA) approval for use in healthy adults aged 60 and older. Zoster vaccine can increase cell-mediated immunity to VZV and reduce the risk of HZ. [2]

Herpes zoster (HZ), or shingles, is caused by the reactivation of the varicella zoster virus (VZV). People who had a primary infection of VZV (chickenpox) or received a varicella vaccine could develop HZ later during their lifetime. About 1 million people develop HZ annually in the United States [1]. The risks of developing HZ, as well as post-herpetic neuralgia and being hospitalized for complications, increase with age; those who are immune compromised are particularly at increased risk. As such, the Centers for Disease Control and Prevention (CDC) recommends the recombinant zoster vaccine (RZV) in adults aged 50 years and older to prevent HZ and its complications; RZV is also recommended to adults aged 19 years and older who are immune compromised.[3]

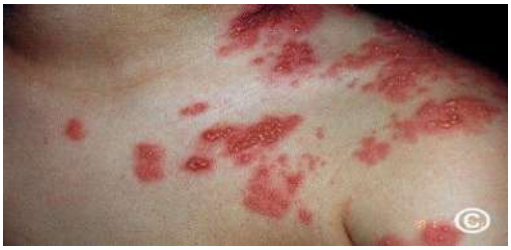

Fig.No.1 HZ skin infection

NATURAL HISTORY OF HERPES ZOSTER

The clinical presentation of herpes zoster is variable. In the majority of patients, a prodrome of dermatomal pain or abnormal sensations precedes the appearance of the characteristic rash. This prodrome may also present with fatigue, headache, and other flu-like symptoms. It begins several days before rash onset in almost all cases, but a series of patients with prodromal pain preceding the appearance of the rash by 7 to more than 100 days has been reported. Unfortunately, it is not possible to reliably identify individuals with a herpes zoster prodrome. In a series of 57 patients presenting to their general practitioners with acute unilateral pain, only 2 developed a herpes zoster rash, and there was no correlation between clinical evaluations and VZV reactivation as determined by the development of a rash or the results of serology and polymerase chain reaction. The unilateral dermatomal rash of herpes zoster begins with the appearance of macules and papules on an erythematous base. The resulting clustered vesicles progress to pustules and crusts over the next 7 to 10 days, and complete loss of scabs occurs within 2 to 3 weeks. Thoracic dermatomes are the most commonly affected sites in herpes zoster and account for up to 50% of all

bases.6,30,49 Cranial (especially the ophthalmic division of the trigeminal nerve), cervical, and lumbar dermatomes each account for 10% to 20% of cases, and sacral dermatos are affected in 2% to 8% of cases. Because herpes zoster can occur in any dermatome, it may be misdiagnosed as herpes simplex when it affects dermatomes in which such infections are common, especially lumbar, sacral, maxillary, and mandibular dermatomes. In addition to involvement of the primary dermatome, patients commonly develop lesions in adjacent dermatomes. Older age is associated with a greater likelihood of a more severe herpes zoster rash, but cutaneous disseminatio defined as 20 lesions outside the primary and immediately adjacent dermatomes rare in immune competent patients.42 Cutaneous dissemination and atypical or prolonged rash can occur in immune compromised patients, and a sub stantial number of these patients also have evidence of visceral involvement. Herpes zoster without a rash but with dermatomal pain, referred to as zoster sine herpete, has also been described. Although the finding of VZV DNA, but not herpes simplex virus DNA, in the cerebrospinal fluid of 2 patients with prolonged and recurrent radicular pain and no rash provides support for the existence of this condition, its prevalence is currently unknown. Because of the difficulty of diagnosing herpes zoster (and its complications, especially PHN) in the absence of the characteristic rash, this diagnosis should be reserved for patients who have been evaluated in specialist centers with a diagnosis confirmed by the results of laboratory tests such as acute and convalescent serology. In some patients, pain does not resolve when the herpes zoster rash heals but can continue for months or years. This persisting pain is the most common complication of herpes zoster. Patients typically describe several different types of pain, including continuous burning or throbbing pain, intermittent sharp or electric-shock–like pain, and allodynia. Chronic pain has substantial effects on quality of life, and physical disability and emotional distress are common in patients with PHN. Unfortunately, there have been no systematic attempts to investigate the prevalence of PHN, and estimates of the number of cases have ranged up to 1 million in the United States. Numerous studies have established that older age is a potent risk factor for PHN; greater acute pain intensity, greater severity of the rash, and presence and greater severity of a painful prodrome receding the rash are additional well-replicated risk factors. [4]

ETIOLOGY

The VZV is a neurotropic human herpes virus belonging to the genus alpha herpesviridiae. It shows a worldwide distribution. The virus is responsible for primary infection resulting in varicella and HZ representing a reactivation of latent infection. The VZV genome consists of about 125,000 base pairs of linear double-stranded DNA, and its nucleocapsid consists of 162 capsomers. The virus is highly cell-associated and only infects human cells, such as epithelial cells, T lymphocytes, and ganglionic neurons. Virus entry into neural cells is mediated by heparan sulfate proteoglycan and the glycogen synthase kinase 3 (GSK-3) pathway. Viral core glycoproteins B, H, and L participate in the core fusion complex. New virus particles can be released as soon as 9 to 12 h after cellular entry. Varicella is acquired by airway contact with respiratory droplets or smears from vesicular varicella lesions and is one of the most contagious human disorders. The initial viral replication occurs in the respiratory tract, followed by invasion of local lymph nodes. Eventually, viremia occurs, associated with cutaneous vesicular eruptions. These lesions present a colorful picture of different stages, from early vesiculation to crusted lesions and possibly scars. The incubation period for varicella varies between 10 and 21 days. Varicella is contagious from 1 to

4 days before the cutaneous rash and until all vesicular cutaneous lesions have dried up. Varicella infection in pregnancy can spread via placenta, leading to fetal infection. Fetal varicella infection leads to disseminated life-threatening diseases. Vaccination protects the fetus. While HZ is uncommon among children, the HZ risk could be diminished by 64% in children after vaccination for varicella, as shown in a Canadian study. Varicella vaccination in the youth does not seem to reduce HZ risk during aging. After primary infection, the VZV virus becomes latent in nerval tissue. VZV has been detected in dorsal root ganglia, cranial nerve ganglia, and various autonomic ganglia in the enteric nervous system, and in astrocytes. Nectin-1, which is highly expressed in neurons, seems to be involved in viral entry of axons and cell bodies. VZV-infected neurons overexpress anti-apoptotic proteins such as Bcl2 and Bcl-XL.VZV latency has been associated to open reading frame (ORF). VZV latency is controlled largely by cell-mediated immunity, and reactivation is considered a result of loss of such immune surveillance. Upon reactivation, VZV replicates within cell bodies of neurons. In the next step, virus particles shed from the cell bodies down the nerve to the correlating dermatome. In the affected dermatome, the virus provokes inflammation and vesiculation. The pain caused by HZ is due to inflammation of nerves affected by VZV. HZ does not pose a risk to a developing fetus due to specific maternal antibodies that are transmitted di placental to the fetus. [6]

EPIDEMIOLOGY OF ZOSTER AND COMPLICATIONS

HZ occurs worldwide without seasonal variations of incidence. The incidence of HZ is age-dependent and ranges from 1.2 to 3.4 per 1000 persons per year among younger adultsto 3.9 11.8 per 1000 persons per year in elderly patients (i.e., >65 years). According to a systematic review of studies from 2002–2018, the cumulative incidence has been estimated between 2.9–19.5 cases per 1000 population with female predominance. Common risk factors for HZ are age > 50 years, immunosuppression, infections, and mental stress A meta-analysis of 16 studies till January 2021 confirmed that patients with diabetes mellitus also have a higher risk (pooled relative risk 95% confidence interval (CI). A recently published (2021) Indian study reported a significant association between pediatric HZ and megaloblastic anemia. A major cause of megaloblastic anemia is vitaminB12 or folic acid deficiency. According to the Global Burden of Disease database, the mortality rate due to HZ inpatients >65 years ranges from 0.0022 to 82.21 per 100,000 population. According to2007 and 2008 HZ-outpatient incidence data from Germany, the annual mortality rate of HZ has been estimated as 0.29 (women) and 0.10 (males) per 100,000 patient years. It is important to note possible heterogeneity in epidemiological data due to differences in reporting. It is possible that countries without efficient and effective reporting systems may not have lower numbers than those with efficient reporting systems. [6]

Risk Factors

Infection with VZV Wild-type VZV: zoster reflects reactivation of latent VZV, the primary risk factor and a necessary precondition for zoster is previous VZV infection. Approximately 99.5% of the U.S. population aged >40 years has serologic evidence of previous infection, including all evaluated subgroups; therefore, all older adults are at risk for zoster, although many cannot recall a history of varicella. Varicella vaccine is effective at preventing initial wild-type VZV infection in persons not previously infected. Any wild type VZV infections prevented cannot reactivate as zoster. The age at the time of initial VZV infection influences the age at which zoster occurs. Persons acquiring an intrauterine or early childhood

infection with VZV are at increased risk for pediatric zoster. When VZV infections occur before age 2 months, the risk for zoster occurring by the age of 12 years is increased >35-fold compared with the risk for VZV infections occurring after infancy. Other case series suggest that the risk for pediatric zoster also might be increased in children who experienced varicella at older ages. Conversely, the risk for zoster might be diminished in persons born in countries or living in communities where varicella infection tends to occur at later ages. These observations suggest that changes in the epidemiology of varicella caused by varicella vaccination or by other factors can alter the epidemiology of zoster, particularly pediatric zoster. [7] Oka/Merck Strain VZV: Among vaccine recipients, the attenuated Oka/Merck strain of VZV included in varicella vaccine also can establish a latent infection and clinically reactivate as zoster. Zoster caused by Oka/Merck strain VZV cannot be distinguished on clinical grounds from zoster caused by wild-type VZV. The risk for zoster caused specifically by Oka/Merck strain VZV is unknown because recipients of varicella vaccine might have already been infected with wild-type VZV or might have become infected with wild-type VZV following vaccination (i.e., due to vaccine failure) that could also reactivate. Therefore, the rate of all episodes of zoster among varicella vaccine recipients define the upper bound for the risk of the subset of episodes caused by Oka/Merck strain VZV. The risk for zoster in immune compromised children was approximately 65% less for those who had received the varicella vaccine compared with those with previous wild-type varicella infection. In immunocompetent children, the risk also appears to be reduced among 1-dose vaccine recipients compared with children with a history of wild-type varicella, although longer follow up is needed. The risk for zoster in immunocompetent children following 2 doses of varicella vaccine has not been studied. Collectively these studies suggest that the risk for Oka/Merck strain zoster following varicella vaccination is no higher, and likely considerably lower, than that following wild type varicella infection, even though the acquisition of the Oka/Merck VZV through vaccination generally occurs at a young age (i.e., varicella vaccination is recommended for children aged >12 months, which might be a risk factor for pediatric zoster. As varicella vaccine recipients age, the risk for and manifestation of Oka/Merck strain zoster in older persons at greater risk for zoster complications can be evaluated. [7]

Age

Influence on zoster. Age is the most important risk fac-tor for development of zoster (Figure 1) Virtually all studies conducted in numerous settings and with various study designs have indicated an association between age and increasing zoster incidence, extending to the oldest cohorts. One study indicated that zoster incidence increased with age by a factor of >10, from 0.74 per 1000 person years in children aged <10 years to 10.1 per 1000 person years in persons aged 80–89 years, with much of the increase beginning at age 50–60 years . Approximately 50% of persons who live to age 85 years will have experienced zoster. The important role of age as a risk factor for zoster is presumably related to a loss of components of VZV specific CMI response because of aging (i.e., immunesenescence) possibly combined with waning immunity that might occur over time following initial varicella infection. Loss of specific immunity allows VZV to complete the process of reactivation and spread to the epidermis to produce the fully expressed clinical illness. Although precise correlates of protection against zoster have not been identified, certain CMI responses to VZV antigen decline with age. [7]

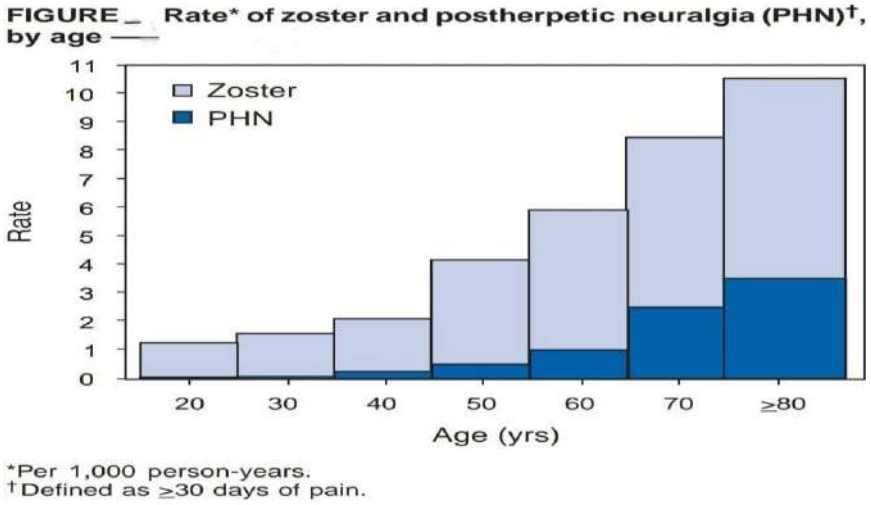

Fig. No.2 Rate of Zoster and PHN

Influence on PHN

Among persons experiencing zoster, the primary risk factor for the development of PHN is age. Several studies have indicated that the risk for PHN among persons with zoster increases with age, particularly for per-sons aged >50 years (Figure 1). In one study, the risk for experiencing at least 2 months of pain from PHN increased 27.4-fold among patients aged>50 years compared with those aged <50 years. Approximately 80%-85% of PHN occurs in zoster patients aged >50 years.

Sex

Results from a large, randomized, controlled vaccine trial in the India indicated that the incidence of confirmed zoster cases in a cohort of immunocompetent persons aged >60 years was 11% higher among the women (11.8 versus 10.7 cases per 1000 person years in women and men, respectively). A prospective cohort study in the Netherlands documented 38% more cases among women than men (odds ratio = 1.38 [95% confidence interval [CI] = 1.22–1.56) after controlling for age and other zoster risk factors. Other studies using a variety of methods also demonstrated an age-standardized excess of zoster among women. However, some researchers did not find a difference by sex. Women with zoster might also be at increased age-specific risk for developing PHN compared with men.[7]

METHODS

Study Population, Enrollment Criteria, And Exposure

We used the IBM Market Scan Research Databases (Market Scan; International Business Machines Corporation, Armonk, New York), among the largest proprietary US claims databases available for health-care research, and likely highly representative of the commercially insured population. The databases capture person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services. Paid claims and encounter data are linked to detailed patient information across sites and types of providers collected from approximately 350 payers (mainly large employers and health plans; predominantly fee-for-service data). We extracted data on persons aged 50 years or older who were vaccinated from January 1, 2018, through a maximum of May 5, 2020. To be included, an individual had to have been enrolled from 400 days prior through 56 days after RZV vaccination. RZV was identified using current Procedural Terminology code 90750 and National Drug Codes 58160081912, 58160082311, 58160082801, 58160082803, 58160082901, and 58160082903. RZV doses

received within 42 days of a prior dose were excluded. [8]

Study Design and Participants

Individuals with MBL and CLL cared for at Mayo Clinic, Rochester, MN, who were naïve to RZV were eligible to participate in this study (patients who received prior live attenuated zoster vaccine were allowed). Two cohorts were enrolled: Cohort 1 consisted of individuals with MBL and previously untreated CLL; and Cohort 2 consisted of CLL participants who were on BTKi therapy. The pre vaccination characteristics at the time of study entry and history of prior vaccination with the live attenuated herpes zoster vaccine were ascertained. Individuals who participated provided written consent after the study was approved by the mayo Clinic Institutional Review Board. Since the study was conducted after the Food and Drug Administration approval of RZV, all patients received the vaccine as a standard of care. Participants received two doses of RZV separated by 2 months. Blood samples were collected prior to vaccination, 1 month after the second dose of RZV (3 months From the first dose of RZV), and at 12 and 24 months after the first dose of vaccine. Blood sample collection at the 24-month time point is still ongoing and results from this interval are not included in this report.[9]

Assessment of Immunogenicity

Antibody was measured by ELISA designed to detect anti-gE antibodies at pre vaccination and 3 and 12 months after the first dose of RZV administration. Assays were conducted at the Centers for Disease Control and Prevention (Dr. Scott Schmid) as previously described. Results are reported in ELISA units/μL after interpolation of the optical density values onto a standard curve constructed using a laboratory control serum and Prism 9.1 software (Graph pad LLC). We defined a humoral response to vaccination as the proportion with anti-gE antibody concentration after vaccination that was ≥ 4 times the pre vaccination concentration, as previously described.18,20,26 Antibody responses were also reported as the geometric mean titer in each group. The gE-specific T-cell response was measured by dual-color interferon γ (IFN- γ) and interleukin 2 (IL-2) FLUOROSPOT (Mabtech) on peripheral blood mononuclear cells (PBMCs) depleted of ≥ 50% leukemic of B cells using magnetic beads coated with anti-CD19 monoclonal antibodies (STEMCELL technologies, Catalog # 17854). Results are reported as spot-forming cells (SFCs)/106 PBMC in wells stimulated with overlapping gE peptides as previously described. We also report the geometric mean count (GMC) of SFCs/106 PBMC at pre vaccination and 3 months after the first dose of vaccine and calculated the geometric mean fold rise (GMFR) in SFCs during this interval. GMFR was calculated as anti-log10 (mean [log10 SFC3 month/SFC0 month]). Cell-mediated immune response assays were conducted at the University of Colorado (Dr. Adriana Weinberg). The FLUOROSPOT well reader (MJJ) was blinded to cohort allocation of the samples. The cell-mediated immune response rate was defined as the proportion of participants who achieved a ≥ 2-fold increase in IFN- γ and IL-2 SFC/106 PBMC 3 months after the first dose of RZV compared with pre vaccination levels, as previously described.18 We compared the response data to a historic cohort of age- and sex-matched healthy con-trols who received RZV, a previously described.[9]

CLINICAL STAGES

Clinical symptoms appear in three stages—pre-eruptive, acute exsudative, andchronic. The pre-eruptive stage presents with burning or pain within the affected dermatome at least 2 days prior to cutaneous eruptions. Non cutaneous symptoms such as experiencing headaches, general malaise, and photophobia may also be present. In the acute eruptive phase, multiple umbilicated and painful vesicles develop. The vesicles often burst,

ulcerate, and eventually dry out. This is the most contagious stage. Pain is often severe and unresponsive to non steroidal pain medications. The acute eruptive phase may last 2–4 weeks. Pain can continue longer. Chronic HZ infection is characterized by severe pain that lasts >4 weeks. Patients experience dysesthesias, paresthesias, and sometimes shock-like sensations. The pain is disabling and may last for several months. In most patients, diagnosis is made clinically. Due to variable clinical presentation and atypical cases, the diagnosis of HZ may be challenging in some patients. Polymerase chain reaction (PCR) is useful for confirmation of suspected HZ-type pain without a rash.[6]

SIGNS AND SYMPTOMS

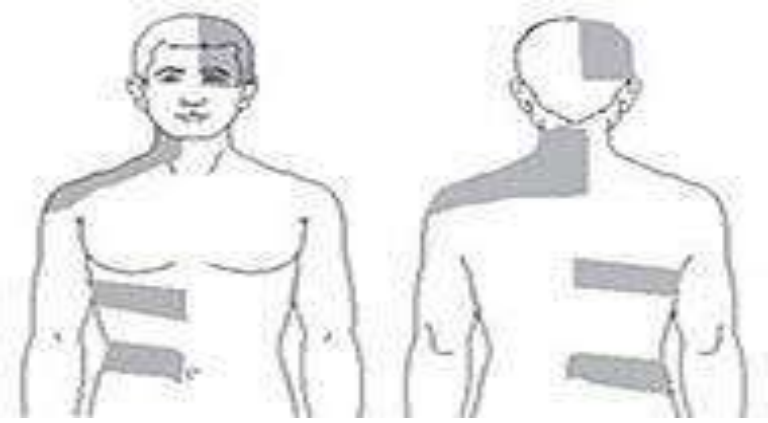

Fig.No.3 Rashes

- Pain, Itching, or Tinging of the Skin.
- Painful rash of blister like sores usually on one side of the body often on the face or torso
- Fever
- Headache
- Upset stomach .[13]
- Fever, malaise, warmth, redness, increased sensation in the affected dermatome. The rash of begin as macules-> papules ->vesicles -> pustules

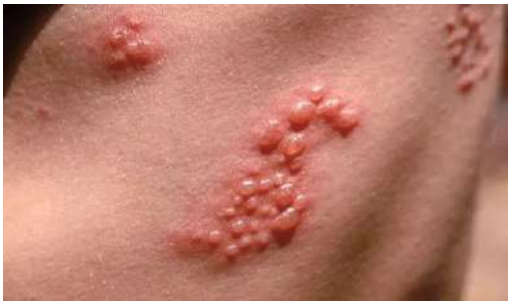

Fig.No.4 Signs

CLINICAL PRESENTATION OF HERPES ZOSTER OPTHALMICUS

Inflammation of almost any ocular tissue can occur and recur in HZO.

Eyelid-

- Vesicular eruption
- Secondary bacterial infection,
- Eyelid scarring,
- Marginal notching,
- Loss of cilia,
- Trichiasis,
- Cicatricial entropion or ectropion.
- Scarring and occlusion of the lacrimal puncta

Conjunctiva

- Follicular conjunctivitis

Sclera

- Episcleritis, Scleritis

Cornea

- Punctate and dendritic keratitis
- Decreased corneal sensation
- Nummular corneal infiltrates
- Interstitial keratitis
- Disciform keratitis

- corneal vascularization
- Lipid keratopathy
- Corneal opacity

Ant Chamber-

- Trabeculitis, Raised IOP

Iris

- Iritis

Choroid

- Focal choroiditis.

Retina

- Occlusive retinal vasculitis, RD

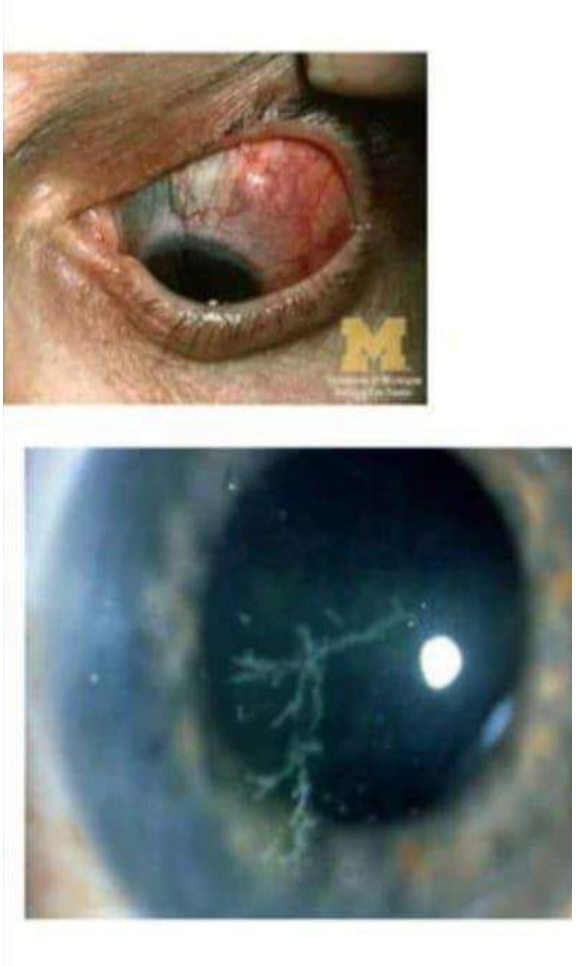

Fig.No.5 Opthalmicus HZ infection

DIAGNOSIS

Zoster diagnosis might not be possible in the absence of rash (e.g., before rash or in cases of zoster sine herpete). Patients with localized pain or altered skin sensations might undergo evaluation for kidney stones, gallstones, or coronary artery disease until the zoster rash appears and the correct diagnosis is made (62). In its classical manifestation, the signs and symptoms of zoster are usually distinctive enough to make an accurate clinical diagnosis once the rash has appeared (63). Occasionally, zoster might be confused with impetigo, contact dermatitis, folliculitis, scabies, insect bites, popular urticaria, candidal infection, dermatitis herpetiformis, or drug eruptions. More frequently, zoster is confused with the rash of herpes simplex virus (HSV), including eczema herpeticum . The accuracy of diagnosis is lower for children and younger adults in whom zoster incidence is lower and its symptoms less often classic. In some cases, particularly in immunosuppressed persons, the location of rash appearance might be atypical, or a neurologic complication might occur well after resolution of the rash. In these instances, laboratory testing might clarify the diagnosis. Tzanck smears are inexpensive and can be used at the bedside to detect multinucleated giant cells in lesion specimens, but they do not distinguish between infections with VZV and HSV. VZV obtained from lesions can be identified using tissue culture, but this can take several days and false negative results occur because viable virus is difficult to recover from cutaneous lesions. Direct fluorescent antibody (DFA) staining of VZV-infected cells in a scraping of cells from thease of the lesion is rapid and sensitive. DFA and other antigen-detection methods also can be used on biopsy material, and eosinophilic nuclear inclusions (Cowdry type A)Are observed on histopathology. Polymerase chain reaction (PCR) techniques performed in an experienced laboratory also can be used to detect VZV DNA rapidly and sensitively in properly-collected lesion material, although VZV PCR testing is not available in all settings. A modification of PCR diagnostic techniques has been used at a few laboratories to distinguish wild-type VZV from the Oka/Merck strain used in the licensed varicella and zoster vaccines. In immune

compromised persons, even when VZV is detected by laboratory methods in lesion specimens, distinguishing chickenpox from disseminated zoster might not be possible by physical examination or serologically. In these instances, a history of VZV exposure, a history that the rash began with a dermatomal pattern, and results of VZV antibody testing at or before the time of rash onset might help guide the diagnosis.[7] HZ diagnosis is mainly based on anamnesis and physical examinations, with focus on the characteristic location and rash appearance with local pain. Laboratory diagnosis confirmation is done on atypical HZ patients, visceral organ and central nervous system involvement, or zoster sine herpete. Some laboratory diagnosis confirmation involve Tzanck smear, polymerase chain reaction (PCR), direct immunofluorescence assay (DFA), skin biopsy, and culture. Tzank smear is a simple and affordable laboratory confirmation test, but it cannot differentiate VZV with other herpes viruses. 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.[14]

TREATMENT OF HERPES ZOSTER

Herpes zoster (HZ), also known as shingles, is the secondary manifestation of an earlier infection with the varicella-zoster virus in one or more dermatomes. The reported incidence varies from 2.2 to 3.4 per 1000 people per year.1-3 As reactivation of the virus is linked to an age-related diminished virus-specific and cell-mediated immunity, HZ develops mainly in elderly people. Immunocompromised patients are also at increased risk of developing HZ. As it has not yet been proven that HZ is provoked by any serious underlying pathologic condition (eg, malignancy),4 a search for possible risk factors is not warranted in otherwise healthy patients in whom HZ develops. The main complications of HZ include postherpetic Neuralgia (PHN) and ophthalmic problems, the latter in cases of ophthalmic HZ. Postherpetic neuralgia is usually defined as pain in the involved dermatome that is still present 1 month after rash onset.5,6 Sometimes, however, a period of 3 months is applied.7,8 A large prospective study identified 4 independent predictors of PHN: older age, severe acute pain, severe rash, and a shorter duration of rash before consultation.9 Although PHN can disappear after a few months, it can also develop into a lasting persistent pain syndrome. A recent double-blind placebo-controlled trial showed that vaccination of immunocompetent persons 60 years of age and older with an investigational live attenuated zoster vaccine markedly decreased HZ morbidity and PHN incidence. The aim of this article is to review the evidence regarding treatment of immune competent HZ patients, focusing on short-term as well as on long-term (prevention of PHN) effects. [2]

Antiviral Medication

Most of the placebo-controlled RCTs of antiviral therapy were summarized in a meta- analysis. A sub analysis (4 studies11-14 comprising 692 patients) showed that acyclovir (800 mg 5 times daily for 7-10 days) had no statistically significant effect on acute pain after 1 month (pooled odds ratio 0.83, 95% confidence interval [CI] 0.58 to 1.21). Because the various studies used measurement methods that could not be compared, no overall effect on the duration of acute pain could be established. From the separate studies, however, it appeared that the effect of acyclovir on the duration of acute pain did reach statistical significance in a few instances. Pain relief was seen at most few days earlier. Another placebo-controlled RCT with acyclovir, published after this meta-analysis, also did not demonstrate a statistically significant effect on pain reduction

after 1 month. A double-blind placebo-controlled RCT with famciclovir (500 or 750 mg 3 times a day for 1 week) reported that the median length of time to the disappearance of acute pain did not differ significantly among the 3 groups.16 It only reported a statistically significant effect on pain in the subgroup of patients with more than 50 skin lesions given famciclovir in the lowest dose. The median length of time for pain to disappear was 20 days in this subgroup compared with 30 days in the placebo group (hazard ratio 1.9, 95% CI 1.3 to 3.0). Data from a double-blind acyclovir-controlled RCT showed that famciclovir administered once (750 mg) or twice (500 mg) daily was as effective as famciclovir (250 mg) 3 times daily, and as effective as acyclovir (800 mg) 5 times daily, in cutaneous healing and reduction of acute pain. A small double-blind acyclovir-controlled RCT showed that famciclovir (250 mg 3 times a day) was as effective as acyclovir (800 mg 5 times a day) for healing skin lesions and decreasing acute pain. Another study compared valacyclovir with acyclovir. The design of that study does not allow for conclusions on the reduction of acute pain. In most individual studies the time necessary for the vesicles, ulcers, and crusts to disappear was shorter when antiviral medication was used than when placebo was used. The time gain was only 1 or 2 days. Antiviral medication might relieve acute pain and speed healing of skin lesions. These effects are only marginal, though, and thus have little clinical relevance. Dr Opstelten is a general practitioner and Dr.Verheij is a Professor of General Practice, both at Utrecht University in The Netherlands. Dr. Eekhof and Knuistingh Neven are general practitioner-epidemiologists, both at Leiden University in The Netherlands. [2]

Analgesics

It has been predicted that combining antiviral therapy with effective relief of acute pain in herpes zoster will further reduce the risk of PHN beyond that achieved by antiviral therapy alone. The basis for this hypothesis is provided by the well-replicated relationship between acute pain severity and PHN and by recent research on the pathophysiology of PHN. The efficacy of opioid analgesics, anticonvulsants, tricyclic antidepressants, or nerve blocks during the acute phase of herpes zoster in reducing the risk of PHN requires investigation in randomized placebo-controlled clinical trials. Rven if there were no benefit of aggressive analgesic treatment in patients with herpes zoster in reducing their likelihood of developing PHN, the effective relief of acute pain in herpes zoster is clearly a desirable treatment goal in itself. Clinicians should use the principles of state-of-the-art pain management for herpes zoster acute pain, such as scheduled analgesia, use of standardized pain measures, and consistent and frequent follow-up. The choice of analgesic treatment approaches depends on the patient's pain severity, underlying conditions, and response to the drug. Patients with mild pain may be treated adequately with acetaminophen or non-steroidal agents, whereas patients with moderate to severe pain usually require treatment with a strong opioid analgesic. One approach to the use of opioids in herpes zoster pain is to start with a short-acting medication scheduled 4 times daily and titrating the dose until pain reduction and tolerability are achieved. Long-acting opioids are more convenient and may also provide a more consistent level of pain relief, so treatment can be switched from a short-acting to a long-acting medication if an effective and tolerable dose is found, depending on cost and patient preference. Providers can prescribe rescue doses of a short-acting opoid for exacerbations of pain as needed with the long-acting opioid. Opioids have multiple adverse effects including nausea, constipation, and sedation that maybe intolerable in some older adults. In most cases, constipation should be anticipated and managed with laxative therapy. If

moderate to severe herpes zoster pain is not adequately relieved by antiviral agents in combination with oral analgesic medications and/or corticosteroids, then adjuvant agents such as anticonvulsants (eg, gabapentin or pregabalin) or tricyclic antidepressants (eg, nortriptyline or desipramine) can be considered.13 Although neither gabapentin nor pregabalin has been tested for the prevention of PHN or relief of acute pain in herpes zoster in randomized, controlled trials, these agents have known efficacy in relieving chronic neuropathic pain, and a single-dose (900 mg) gabapentin trial in herpes zoster acute pain showed pain reduction. If prescribed, gabapentin and pregabalin must be dose adjusted for renal insufficiency and can cause sedation, dizziness, ataxia, and peripheral edema, which can be particularly problematic in frail elderly patients. It is best to give starting doses at bedtime and carefully increase subsequent doses to 3 times daily for gabapentin and twice daily for pregabalin. Tricyclic antidepressants have not been tested for relief of herpes zoster acute pain in randomized, controlled trials. However, tricyclic antidepressants have known efficiencacy in relieving chronic neuropathic pain and a small study that used amitriptyline 25-mg daily during acute herpes zoster was associated with lower rates of pain at 6 months from rash onset. Amitriptyline has greater anticholinergic properties and associated adverse effects than nortriptyline or desipramine. The use of tricyclic antidepressants must be weighed carefully against significant potential adverse effects, particularly in frail elderly patients. These agents should be used with extreme caution, if at all, in patients with QT prolongation, with atrioventricular block or bundle-branch block, or with a recent acute myocardial infarction. Baseline and follow-up electrocardiograms are necessary when prescribing these agents. Other important anticholinergic adverse effects include urinary retention, dry mouth, constipation, dizziness, orthostatic hypotension, visual impairment, drowsiness, cognitive impairment, and balance problems.[2]

Zoster Vaccine

Vaccine Composition, Dosage, and Administration The zoster vaccine licensed in the United States (ZOSTAVAX®, Merck & Co., Inc.) is a lyophilized preparation of the Oka/Merck strain of live, attenuated VZV, the same strain used in the varicella vaccines (VARIVAX®, PROQUAD®). The Oka strain was isolated in Japan in the early 1970s from vesicular fluid from a healthy child who had varicella; the strain was attenuated through sequential propagation in cultures of human embryonic lung cells, embryonic guinea-pig cells, and human diploid cells (WI-38). Further passage of the virus was performed at Merck Research Laboratories in human diploid cell cultures (MRC-5). The cells, virus seeds, virus bulks, and bovine serum used in the manufacturing are all tested to provide assurance that the final product is free of adventitious agents. Zoster vaccine, when reconstituted as directed in the package label using the supplied diluent, is a sterile preparation for subcutaneous administration. Each 0.65-mL dose contains a minimum of 19,400 PFU (4.29 log10) of Oka/ Merck strain of VZV when reconstituted and stored at room temperature for up to 30 minutes. Zoster vaccine is similar to VARIVAX®. However, its minimum potency is at least 14-times the potency of VARIVAX®, which contains a mini-mum of 1,350 (approximately 3.13 log10) PFU. PROQUAD® contains 3.993 log10 PFU, similar in potency to ZOSTAVAX®. Each dose of zoster vaccine also contains additional VZV antigenic component from nonviable Oka/Merck VZV. Additional vaccine components in each dose include 31.16 mg of sucrose, 15.58 mg of hydrolyzed porcine gelatin, 3.99 mg of sodium chloride, 0.62 mg of monosodium L-glutamate,

0.57 mg of sodium phosphate dibasic, 0.10 mg of potassium phosphate monobasic, 0.10 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of neomycin and bovine calf serum. The product contains no thimerosal or other preservatives. Zoster vaccine should be administered as a single 0.65-mL dose subcutaneously in the deltoid region of the upper arm; a booster dose is not licensed for the vaccine. The vaccine should not be injected intravascularly or intramuscularly and should only be reconstituted and injected using a sterile syringe free of preservatives, anti-septics, and detergents, which can inactivate the vaccine virus. [7]

Efficacy

The efficacy of zoster vaccine was evaluated in a phase 3 vaccine trial termed the Shingles Prevention Study, a double blind randomized, placebo-controlled trial involving 38,546 healthy adults aged >60 years who had a history of varicella or at least 30 years of residence in the continental United States (as a marker of previous infection). Persons excluded from the trial included those with a history of zoster, with allergies to components of the vaccine, with immune compromising conditions, or with conditions that might have interfered with study evaluations (e.g., cognitive impairment, <5 year life expectancy, dermatologic disorders, chronic pain, hearing loss, or lack of mobility). The study population ranged in age from 59–99 years (median: 69.4 years), and comprised 41.0% females, 95.4% white, 2.1% blacks, 1.3% Hispanics, and 1.2% other or unknown race/ethnicity. On enrollment, approximately 90% of the participants had at least one underlying chronic medical condition. Persons were randomized to receive a single subcutaneous dose of zoster vaccine or placebo; the mean duration of follow up was 3.1 years. Active case ascertainment was conducted through monthly telephone contact supplemented by a close-out interview. Zoster cases were confirmed by PCR testing (93%), viral culture (1%), or evaluation by a panel of five physicians with expertise in zoster diagnosis (6%). Patients with confirmed zoster were followed for at least 182 days to assess the outcome of the condition, including presence and severity of pain. Approximately 95% of persons were followed to completion of the study. Outcomes evaluated included incidence of zoster, incidence of PHN (defined as pain level of three or more [on a numerical rating scale of 0-10] persisting at least 90 days after rash onset), and burden of illness (BOI), measured using a mean value of severity-by-duration index for each treatment group, thus incorporating the incidence, severity, and duration of pain and discomfort from zoster). A total of 957 confirmed cases of zoster occurred among study participants: 315 among vaccine recipients and 642 among placebo recipients. The proportion of vaccine and placebo recipients that received antiviral treatment within 72 hours of rash onset, as clinically indicated, was 64.1% and 65.9%, respectively. The vaccine reduced the risk for developing zoster by 51.3% (95% CI = 44.2–57.6; $p<0.001$. The vaccine was 66.5% (95% CI = 47.5–79.2; $p<0.001$) efficacious for preventing PHN. When the definition of PHN was changed from 30 days of pain to 182 days of pain following rash onset, vaccine efficacy increased from 58.9% to 72.9%. Zoster vaccine had an independent effect of reducing PHN among patients who developed zoster (39% [95% CI = 7%–59%]) . The mean severity-by-duration of zoster was reduced by 57% ($p = 0.016$) in vaccine recipients who developed PHN. Zoster vaccine reduced BOI by 61.1% (95% CI = 51.1– 69.1; $p<0.001$). The vaccine reduced the degree of interference in activities of daily living (ADLI) caused by zoster, in part because of the reduction in zoster itself, but also because of a decrease in ADLI among those vaccine recipients who did develop zoster . No evidence indicated

that vaccine recipients experiencing zoster were protected from other sequelae such as scarring, bacterial superinfection, palsies, or ocular or visceral complications.[7]

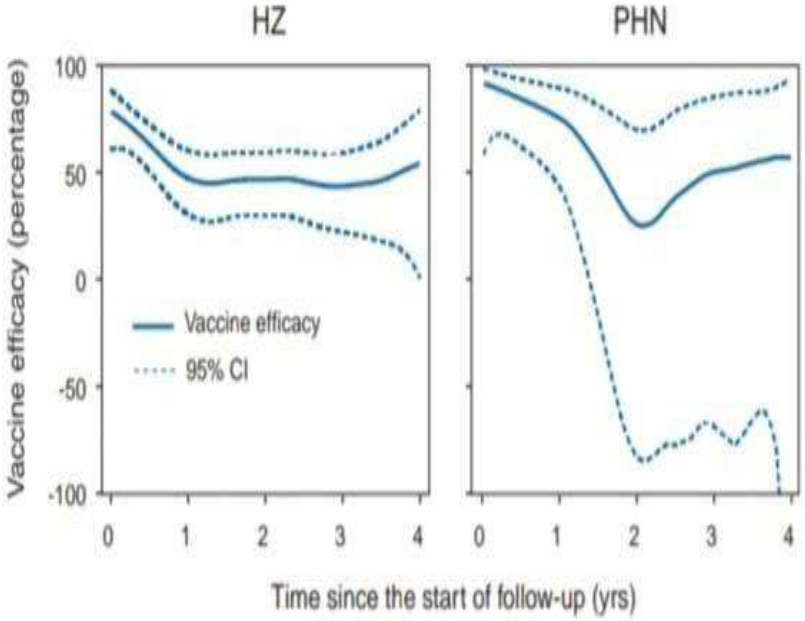

Fig.No.6. Duration of zoster vaccine efficacy for preventing zoster and PHN

Table No.1 Summary of duration and dosage of standard antiviral therapy for herpes zoster

Sr. No.	Agent	Individual Dose	Frequency of Intake/ administration	Duration
1	Valacyclovir PO	1000mg	Three times daily	7 days
2	Acyclovir PO	800mg	Five times daily	7 days
3	Acyclovir IV	8-10mg/kg	Three times daily	7 - 10 days
4	Famciclovir PO	250mg	Three times daily	7 days
5	Brivudine PO	125mg	Once a day	7 days

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