

## **Varicella-Zoster Virus**

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## Introduction

The human herpesvirus 3 (HHV-3) or known as the varicella-zoster virus (VZV), is a type of virus that belongs to the  $\alpha$ -herpesvirus family.<sup>1</sup> This virus is highly infectious and can cause varicella and herpes zoster (HZ), commonly known as chickenpox and shingles, respectively. Varicella affects mostly young children and adolescents; however, adults may be able to contract it as well.<sup>2</sup> Due to the varicella vaccination, infections have declined in the United States and are much rarer. The Center for Disease Control (CDC) states that since the vaccination program began in 1995, there has been over a 90% decrease in varicella cases. Although with the varicella vaccination, it is still possible to be infected with the disease, however the symptoms will be milder.

Once a person has been exposed to and recovered from varicella, the virus can remain inactive for many years or decades before reemerging as herpes zoster.<sup>3,4</sup> HZ largely affects adults over the age of 50 that have had varicella at one point during childhood. The CDC reports that one in three adults will develop HZ during their lifetime. The risks and complications associated with getting HZ are directly proportional with age.

## Brief History

The first documentation of VZV was described as a rash of unknown cause in many ancient civilization writings.<sup>5</sup> In 1888, it was suggested that there was a correlation between HZ and varicella; it was not until the 1950s, that this correlation was proven correct.<sup>5,6</sup> Ever since the correlation was made between varicella and HZ by Thomas Weller, a considerable amount of advancements have been made in the prevention and treatment of the diseases associated with VZV.

From the introduction of a vaccine by Michiaki Takahashi in 1974 to the complete DNA sequencing in 1986, many are hopeful that it will eventually lead to the eradication of the virus.

### **Organism's Appearance**

Mature VZV virions are 180 - 220 nm in diameter and are made up of four main parts: the envelope, tegument, capsid, and core.<sup>7,8,9</sup> The outer covering or envelope is composed of a lipid bilayer with glycoproteins, and these glycoproteins help bind to the cell receptors of the host cell. The next layer is composed of viral proteins, which reside inside the envelope and is known as the tegument. The inside layer is the capsid or nucleocapsid, as it contains the DNA protein needed for replication. Its shape is an icosahedron with 162 capsomere proteins and a 5:3:2 axial symmetry. In the capsid is the core, containing the genetic information of the virus in a linear double strand DNA, having one copy per virion. The DNA contained in the core is only released when the virion infects a host cell.

### **Life Cycle and Replication**

The varicella-zoster virus (VZV) is a highly contagious human herpesvirus and can establish its dormancy in the dorsal root ganglia.<sup>10</sup> The reactivation of VZV virion can cause HZ after being dormant for many years, though it usually occurs in older adults and those that are immunocompromised. VZV stimulates the production of new infectious virus particles in the host cells and is governed by DNA synthesis proteins.

VZV is a human-specific virus infection that is spread from one person to another through close or direct contact with the fluid from the rash or blisters.<sup>2,3,11</sup> Once VZV infects the host via the entry of the mucosal epithelial sites, local replication of the virus begins and is then spread to the tonsil and other regional lymphoid tissues before targeting T-lymphocytes (T-cells).<sup>11</sup> The infected

T-cells then deliver the virus to cutaneous sites for replication. At this point, a small, itchy, blister-like rash may start to appear on the infected individual's body. VZV can then be transported to neuronal nuclei along the neuronal axons where it can establish latency in the sensory ganglia.

Once the host has been infected, for VZV to replicate, the VZV virion attaches to the cell membrane of a host T-cell in circulation and remodels it to produce more of the VZV protein.<sup>1,11</sup> It attaches at the nuclear pore of the cell, and the genomic DNA material is then introduced into the nucleus of the cell, where it is then duplicated. These DNA proteins can be expressed as immediate early (IE), early (E) and late (L) proteins in the host T-cell. Once the DNA is replicated, nucleocapsids then encase the newly synthesized DNA and move to the inner nuclear membrane. After the encasement, they start budding across the nuclear membrane, and the capsids then enter the cytoplasm, where virion glycoproteins mature in the trans-Golgi region. In the vesicles, tegument proteins start being assembled; there, the capsids undergo a secondary envelopment and are transported to the cell surface, where the newly assembled virion is released and begin to make their way to other T cells to repeat the replication once again. This cycle of viral replication will cause cell damage and eventually cause the cell to lyse.

## **Symptoms**

VZV causes different diseases; varicella and HZ. The initial infection is varicella with the symptoms appearing as a rash of itchy red blisters.<sup>2</sup> This disease is usually seen affecting younger children, with the rash showing up on the chest, back, and face, before spreading to the entire body. Other symptoms may include fever, tiredness, loss of appetite, and/or headache one to two days before the rash.

After the initial infection, VZV will be dormant for many years before possibly reemerging as HZ.<sup>3,12</sup> HZ can appear later in life and is a painful rash with shooting pain that can appear as blisters

on either side of the body, neck area, and in some cases, on one side of the face. If herpes zoster does develop on the face, it can affect the eye and can lead to vision loss if not treated. The blisters can develop to scabs over 7 to 10 days and within 2 to 4 weeks can fully clear up. Many have often experienced pain, itching, or tingling in the area where the rash will develop several days prior to it appearing. Other signs and symptoms may include fever, headache, chills, and upset stomach.

### **Statistics**

Since VZV is a highly contagious human disease, the distribution of it is worldwide.<sup>11</sup> In the United States, the incidence of varicella can range 13 to 16 cases per 1,000 persons per year.<sup>1</sup> More than 90% of people become infected before adolescence, and only a small proportion of less than 5–10% of adults remain susceptible to VZV. In the United States, the incidence of varicella was equivalent to the annual birth rate of 4 million before the vaccine was introduced in 1995.<sup>2,10</sup> According to the CDC, more than 3.5 million cases of varicella, 9000 hospitalizations, and 100 deaths were prevented by the vaccination.

In the general population, the annual incidence of herpes zoster is 1.5 to 3.0 cases per 1,000 persons.<sup>12</sup> It has been estimated that 99% of Americans born before 1980 have had varicella and are now at risk for herpes zoster.<sup>3</sup> It is believed that 1/3 of the VZV infected individuals in the United States will develop HZ in their lifetime and an estimated 1 million people will get HZ each year. The risk of getting HZ and having serious complications increases as one gets older. For those that do develop herpes zoster, about 1 in 10 people will develop nerve pain that may last months or years after the rash has gone away. This nerve pain known as postherpetic neuralgia (PHN), is the most common complication with HZ.

### **Complication - PHN**

Postherpetic neuralgia (PHN) is caused by the reactivation of VZV resulting in HZ.<sup>1,3</sup> Because the cell is damaged and lysed, it will cause some nerve pain, which can last months to years after the rash has gone away. PHN is one of several serious neurological disorders associated with HZ. About 40% of HZ patients over age 60 have experienced chronic PHN.<sup>10,13</sup> PHN is characterized by constant, severe, stabbing or burning pain.<sup>13</sup> Though the cause of PHN is unknown, it is speculated that alteration of the excitability of the ganglionic or even spinal cord neurons or that there is a persistent or low-grade productive of virus infection is present in the ganglia. Although PHN is not a threat to life, it is difficult to manage. There is supportive treatment with the use of neuroleptic drugs and various analgesics, like opiates to alleviate pain, but no universally accepted treatment exists.

## **Diagnosis**

In diagnosing varicella and HZ, both have typical clinical presentations that allow for a probable diagnosis.<sup>12</sup> Varicella presents a rash extending from the face to the abdomen of the body to the hand and soles of the feet. HZ presents a painful rash on one side of the body. In immunocompromised patients with HZ, they may develop dispersed skin lesions that can mimic varicella.

For a more definitive diagnosis of varicella and HZ, laboratory testing can be used for atypical cases of VZV or HZ. The most sensitive diagnostic methods include the use of polymerase chain reaction (PCR) and direct fluorescent assays (DFA).<sup>2,3,12</sup> PCR can be used to detect the disease using vesicle fluid or skin lesions. Other sources are less likely to provide an adequate sample, such as saliva, blood, or cerebrospinal fluid and may often lead to false-negative results.<sup>2</sup> DFA is performed on scrapings taken from the skin lesion. These two methods are both rapid and reliable for diagnosing the disease.<sup>12</sup> One other test includes the viral culture test. However, it

provides slower results and is much less sensitive, although it can be specific and can help distinguish VZV from other viral pathogens.

### **Prevention/Treatment**

The best way to prevent varicella and HZ is to get vaccinated with the varicella vaccine.<sup>2</sup> Even if a vaccinated person does get varicella, the symptoms can be milder with fewer to no lesions. This vaccine has prevented many cases of severe illness, and in the United States, it has led to over a 90% decrease in varicella cases, hospitalizations, and deaths. Even with the vaccination, there are treatments for those that do contract the infection.

Varicella is treated with acyclovir and can be done intravenously.<sup>12</sup> If initiated within 24-hours of the onset of the rash, it would help maximize the efficacy of this treatment. Several treatments can be done at home to help relieve the symptoms and prevent further spread of the infection.<sup>2</sup> Calamine lotion and a cool bath with added baking soda may help relieve some of the itchiness. It is best to avoid using aspirin or aspirin-containing products for the fever symptom in children, because it has been associated with Reye's syndrome.

The treatment for HZ can be acyclovir, valacyclovir, or famciclovir.<sup>3,12</sup> These medications can help treat HZ and shorten the length and severity of the illness and are most effective if taken as soon as possible after the rash appears. In one case study, the infected individual was prescribed oral valacyclovir when he was diagnosed with HZ. Wet compresses, calamine lotion, and pain medications may help relieve the pain or itchiness caused by HZ.

### **Case Study**

One example of someone who benefited from valacyclovir treatment was a 75-year-old male who was referred to his physician after experiencing itching and burning sensations on the left side

of his back and chest for two-days.<sup>5</sup> It was noted that a few days prior to this, he also experienced numbness and tingling in the same area. During a medical history questioning the patient he mentioned that during his childhood, he contracted a varicella zoster virus infection. Along with his medical history, he also mentioned that he had a coronary artery bypass graft (CABG) procedure that was performed several years earlier.

Upon a physical examination, the patient's skin showed clusters of vesicles on the left side of his chest, back, and side.<sup>5</sup> Some tenderness along with increased itching and burning was noted after the physician conducted a palpation. After further testing, the patient was diagnosed with HZ and precautions were made to prevent the spread of the infection. He was prescribed an oral prescription of valacyclovir to be taken 3 times a day and his symptoms were later relieved.

## **Conclusion**

The varicella-zoster virus (VZV) can cause varicella and herpes zoster (HZ), but thanks to the varicella vaccine, the number of varicella infections have substantially decreased, resulting in HZ decrease as well. There is a small percentage of adults in the United States that are still susceptible to VZV, but because of the advancements made in prevention and treatment of the disease, physicians are able to treat many of the symptoms, even if just by reducing the pain for the individual. Postherpetic neuralgia (PHN), one of many serious complications associated with HZ, is still being studied, as this does not have a definite cause. PHN may not be a threat to life but can pose some difficulty to an individual's quality of life depending on the severity. If a patient is diagnosed with VZV, the best diagnostic testing to confirm prognosis is the use of polymerase chain reaction (PCR) and direct fluorescent assays (DFA). These two tests are more sensitive, fast, and reliable for diagnosing.

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