Advances in the Understanding of the Pathogenesis and Epidemiology of Herpes Zoster

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Advances in the understanding of the pathogenesis and epidemiology of herpes zoster

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SUMMARY

The primary varicella zoster virus (VZV) infection results in chickenpox (varicella), which is transmitted via the airborne route. VZV is highly infectious, but in the USA the incidence of varicella has been reduced by 76–87% as a result of the varicella vaccine.

The virus establishes latency in the dorsal root ganglia during varicella and, when reactivated, travels along the sensory nerve axons to cause shingles (herpes zoster [HZ]). There are over 1 million cases of HZ in the USA each year, with an estimated lifetime attack rate of 30%. The incidence of HZ, which causes significant morbidity, increases with age and reaches approximately 10 cases per 1,000 patient-years by age 80. Cell-mediated immunity (CMI) is known to decline with age as part of immunosenescence, and decreased CMI is associated with reactivation of VZV.

This article provides an overview of our emerging understanding of the epidemiology and pathogenesis of varicella and HZ, in addition to exploring the current theories on latency and reactivation. Understanding the risk factors for developing HZ and the complications associated with infection, particularly in older people, is important for prompt diagnosis and management of HZ in primary care, and they are therefore also reviewed.

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Conflict of interest

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Keywords
Zoster; VZV; Epidemiology; Pathogenesis

1. Introduction

Varicella zoster virus (VZV) causes two distinct diseases, chickenpox (varicella) and shingles (herpes zoster [HZ]). The link between these two diseases has been understood for over 100 years and is based on two observations: (a) VZV remains latent in human neurons for decades after varicella infection and (b) sufficient VZV-specific cell-mediated immunity (CMI) is necessary to maintain latency.

The segmental nature of HZ and its origin in individual sensory ganglia were appreciated when ganglionitis was observed during autopsies performed on patients with HZ in the early 20th century. In 1892, von Bokay recorded cases of varicella in children exposed to adults with HZ, and the link between varicella and HZ was later proven by an analysis of isolates from a patient who had had varicella followed by HZ some years later. These isolates had identical molecular profiles.

Before the introduction of varicella vaccination, there were 4 million cases of varicella per year in the USA, with an incidence of 15–16 cases per 1,000 population. The varicella vaccine was licensed in the USA in 1995, and consequently the incidence of varicella has been reduced by 76–87% in the period 1995–2000. There are over 1 million cases of HZ in the USA each year, with an estimated lifetime attack rate of 30%.

This article reviews the epidemiology of varicella in temperate and tropical climates, and the ability of current diagnostic techniques to provide information about its molecular epidemiology. Our contemporary understanding of viral pathogenesis and the major theories explaining latency and reactivation will also be examined. An understanding of the risk factors and complications associated with HZ, particularly in older people, will be discussed in relation to primary healthcare management.

2. Epidemiology

VZV is unique among the human alphaherpes viruses in that it is transmitted via the airborne route, leading to a typical winter-spring seasonality pattern of primary infection for varicella. VZV can also be transmitted by fomites from skin lesions of varicella and HZ. HZ does not follow a seasonal pattern and does not occur in epidemics because it results from the reactivation of each patient’s latent endogenous virus; therefore, the incidence rate of HZ is generally more stable than that of varicella (Figure 1).

The incidence of HZ increases with age, with an inflection point at around age 50 and an incidence of approximately three cases per 1,000 patient-years. By age 80, the incidence reaches about 10 cases per 1,000 patient-years (Figure 2).

In many temperate countries, varicella predominantly affects children under 10 years of age, and the incidence of HZ across these countries is very similar. In contrast, in many tropical...
countries, the incidence of varicella in children is low and the virus frequently occurs in late adolescence or early adulthood. Hence, the cumulative proportion of people who develop varicella approaches that of temperate climates by 30 years of age. There are no data available for the incidence of HZ in tropical countries.

2.1. Molecular epidemiology of VZV

Many laboratories have developed polymerase chain reaction (PCR) methodologies for the diagnosis of HZ and to better understand the pathogenesis of VZV. In one study, VZV was detected by PCR in the saliva of patients with HZ, which persists in the host after the HZ rash disappears; 20% of saliva specimens were positive for VZV at 15 days after rash onset.11 There are significant correlations between the presence and amount of virus in saliva and high pain score ($p < 0.005$).11 Similarly, recent research has shown that VZV DNA remains detectable in the blood by PCR for up to 6 months in 80% of patients with HZ, and the viral load shows a trend towards higher levels in people with pain (Breuer J, personal communication, 2009).

Isolates from varicella (acquired as an exogenous infection) and HZ (resulting from endogenous reactivation) can be studied as five distinct genotypes of VZV from specific geographical areas: Clade 1, genotype C (E1/A); Clade 2, genotype J (C); Clade 3, genotype B (E2/D); Clade 4, genotype J2 (M2/B); Clade 5, genotype A1 (M1). These five genotypes differ in their global distribution: genotypes B and C are found mainly in Europe and North America, genotypes J2 and A1 are found mainly in Africa and Asia, and viruses of genotype J are mostly found in Japan. This distribution has remained stable; for example, VZV genotyping from Caucasians with HZ who have lived in the UK all their lives revealed a prevalence of 85–90% of the European genotypes.12

The five distinct genotypes of VZV can be separated into two groups by a single restriction-site difference (Figure 3).13–17 Advanced genotyping techniques have demonstrated that co-infection with more than one genotype can occur in a child,18 which provides an opportunity for virus recombination.16 It is also possible that both co-infecting genotypes can establish latency within the host, and both have the potential for reactivation. This suggests that immunity to VZV following chickenpox may not always protect against re-infection (albeit subclinical) with another strain.19 The biological significance of re-infection was investigated in a genotyping study of adults with HZ in east London, UK. The results suggested that up to 30% of HZ cases could have resulted from re-infection with VZV.20

3. Pathogenesis of VZV infection

The highly infectious VZV enters the body via the respiratory tract and spreads rapidly from the pharyngeal lymphoid tissue to circulating T lymphocytes. During the incubation period of 10–21 days, the virus arrives at the skin, causing the typical vesicular rash of varicella. Infection results in lifelong immunity against clinically apparent second episodes of varicella in the vast majority of individuals.21

The immune response to VZV infection has three components:
1. Innate immunity. Experiments on severe combined immunodeficiency mice with human skin grafts (SCIDhu mice) infected with VZV led to the hypothesis that innate immunity, mediated by IFN-α, in the skin is eventually overcome by the virus. The virus then spreads (within memory T cells) to other parts of the body as cell-associated viraemia.22

2. Humoral immunity. This is very important for viral neutralization of the cell-free virus. Although VZV-specific antibodies are formed during a varicella infection, this response is not necessary for recovery from varicella. Children with congenital agammaglobulinaemia experience uncomplicated varicella, and other diseases associated with defects in antibody synthesis are not associated with excess HZ.21

3. CMI. This is an essential component of the host response to varicella because VZV is a cell-associated virus and T-cell-mediated immunity is needed to eliminate intracellular pathogens. Consequently, varicella and HZ are more severe in patients with defects in CMI, and HZ is both more frequent (age-specific) and more severe in T-cell-immunocompromised patients.23

Immune evasion provides an advantage to VZV. Down-regulation of major histocompatibility class (MHC) I and II expression in T cells, and fibroblasts infected with VZV, may initially allow VZV to establish highly productive infections, thereby increasing the likelihood of transmission to new hosts.24 Ultimately, the host immune response can compensate, despite the presence of viral immune evasion mechanisms.

VZV also evades recognition by CD4+ T cells, which recognize peptides presented by MHC II molecules. During a varicella infection, CD4+ T cells release IFN-γ, which stimulates CD8+ T cells and up-regulates the expression of MHC II on cells that do not usually express this molecule. This increase in MHC II in skin cells enables CD4+ T cells to lyse infected cells within the skin lesions. Latently infected cells do not show this increase in MHC II even in the presence of IFN-γ. The exact viral genes encoding both of these processes are not yet known.25

In the immunocompetent host, VZV may spread to other organ systems in the body but is ‘nullified’ without any serious detrimental effect. However, in immunocompromised individuals, including neonates, VZV cell-associated viraemia lasts longer, and the virus can be disseminated and cause organ damage, including hepatitis, pneumonia and encephalitis. There are two mechanisms of VZV transmission as described in Figure 4:

1. Within the superficial epidermis, cell-free VZV is shed and virions can be transmitted from host to host.

2. Outside the suprabasal epidermis, VZV spreads by cell-to-cell contact.

4. Latency

All herpesviruses have the ability to establish latency, thereby providing a reservoir to facilitate the infection of new generations of susceptible individuals.
Two hypotheses have been proposed to explain how VZV gains access to the dorsal root ganglia (DRG) and cranial root ganglia (CRG) to establish latency:

1. Cell-free VZV is produced in the epidermis and infects the intraepidermal projections of sensory neurons. The virus then travels by retrograde transport in axons to reach cell bodies, where latency is established. This theory is supported by the observation that the distribution of HZ reflects the relative distribution of varicella skin lesions.\(^{26-28}\)

2. VZV is carried to the DRG/CRG within infected T cells during the viraemic stage of the varicella infection. The infected T cells fuse with neurons and infect neuronal cell bodies. The virus begins proliferation within the neurons, but cell death is prevented, proliferation ceases and latency is established. This hypothesis is based on the anti-apoptotic action of the gene ORF63.\(^{27,29}\)

VZV gene expression is highly restricted during ganglionic latency. No viral antigens are presented on the surface of latently infected neurons, thus protecting latently infected cells from immune detection.

T-cell immunity is essential for the maintenance of latency. The incidence of HZ correlates with depressed VZV-specific CMI in lymphoma patients\(^{30}\) and in bone marrow transplant recipients,\(^{31}\) but not with levels of VZV antibody. Onozawa et al.\(^{32}\) also showed that the incidence of HZ in stem-cell transplant recipients did not correlate with humoral immunity. Although these transplant recipients received intravenous immunoglobulins, which contain a high titer of VZV antibodies, HZ is very common after transplantation, indicating that VZV-specific CMI, not VZV antibody, is necessary to maintain latency.

5. Reactivation

Viral gene transcription products are required to establish and maintain latency, but host factors subsequently determine whether or not the virus remains latent. There are a number of potential triggers of reactivation, including expression of the ORF61 protein and the presence of mediators of inflammation. Different viral genes are expressed during latent and lytic infection. The ORF61 gene product is necessary and sufficient to induce the switch between the two states: latency and lytic infection. In latent VZV infection, six genes are regularly expressed, whereas in lytic infection, 71 genes are expressed.\(^{34}\)

When VZV is reactivated, it is transported along microtubules within sensory axons to infect epithelial cells, usually without viraemia. The resulting infection of the skin causes a rash within the dermatome innervated by a single sensory nerve. Trigeminal (cranial nerve), cervical and thoracic sensory nerves are most commonly involved in VZV reactivation. There is also inflammation and necrosis of all other cell types within the affected ganglion. Inflammation has been implicated in the reactivation of VZV in a guinea pig neuron model, based on the ability of mast cell extract to trigger reactivation in this model.\(^{35}\)

VZV reactivation is associated with a decline in CMI (Figure 5),\(^{33}\) either as a natural consequence of aging (the ability of VZV-specific T cells to proliferate decreases with age) or as a result of immunosuppression.\(^{27}\) HZ also occurs in infants whose mothers were
infected with varicella during late pregnancy or who had a varicella infection during the first year of life, because infants in these situations have not developed adequate VZV-specific CMI.\textsuperscript{28}

It is hypothesized that the occurrence of HZ correlates with a decline below an unknown, perhaps host-specific, threshold level of VZV-specific CMI, whereas the severity of zoster correlates with the residual level of this VZV-specific CMI at the time of reactivation.

6. Risk factors for HZ

Risk factors for HZ are shown in Table 1, the most important being older age.\textsuperscript{36–44}

In the general population, the incidence of HZ is two to three per 1,000 patients per year. Lifetime risk in the general population is about 30\% and, in those surviving to 85 years of age, at least 50\% will have had HZ. The lifetime risk increases with age, with an odds ratio (OR) of 1.20 (1.10–1.31) per 5-year interval in those aged >65 years.\textsuperscript{45} This is most likely due to declining VZV-specific CMI.

Epidemiological data show that HZ normally occurs in young individuals, but not as frequently as in older people,\textsuperscript{46} so it is not imperative to investigate young people who develop HZ. However, there should be a higher index of suspicion for underlying immunosuppressive disease in younger people with HZ. The following criteria should be considered for further investigation:

- Risk factors for HIV
- Rash confluent throughout the dermatome
- Rash present in multiple dermatomes
- New lesions appearing after 6 days
- Extracutaneous presentation.

In individuals with reduced CMI, HZ rates are substantially higher. The incidence in HIV-positive patients and in transplant recipients can be more than 10 times that observed in the general population.\textsuperscript{47}

Some data suggest that women have a greater incidence of HZ than men at all ages. This pattern is observed in some other diseases but may represent a bias resulting from the fact that women consult their physician regarding post-herpetic pain more often than men.\textsuperscript{40}

Ethnicity is also a risk factor in the development of HZ. The prevalence of HZ in African Americans is only one third of that in Caucasians,\textsuperscript{36} although this difference is lost if the individual becomes infected with HIV. The cause of this disparity between ethnic groups is unknown. Other risk factors include psychological stress and mechanical trauma.

Psychological stress within the previous 6 months more than doubles the risk of developing HZ,\textsuperscript{38} and mechanical trauma was found to be highly associated with the development of HZ in the same site (OR 8.02 within 6 months, \( p = 0.0002 \), and 12.07 within 1 month, \( p = 0.002 \)) in a case-controlled study matched for age, sex and ethnicity.\textsuperscript{40}
The observation that patients with HZ are more likely to have a first-degree relative with the virus than matched controls without it (39.3% in cases vs. 10.5% in controls; \( p < 0.001 \)) suggests that genetics plays a role.\(^4^2\) An association between human leukocyte antigen (HLA) and post-herpetic neuralgia (PHN) has been reported,\(^4^3\) and polymorphisms in the IL-10 gene promoter have recently been associated with an increased risk of HZ.\(^4^4\)

Lack of exposure to varicella is also a risk factor for HZ. The incidence of HZ was lower among individuals who lived in a house with children (exposure to children being a surrogate for exposure to VZV that would result in a boost of their VZV-specific CMI).\(^4^8\)

### 7. Complications of HZ

The complications of HZ can be divided into four groups – cutaneous, visceral, neurological and ocular (Table 2),\(^4^9\) with the incidence of all complications increasing with age. After PHN, ocular complications are the most common,\(^4^6\) and the virus can infect any of the structures within the eye.\(^5^0\)

Neurological complications associated with HZ are common. PHN, defined as pain lasting after the rash has disappeared (often considered when pain is present for 90 days after the onset of rash), is common. Around 15% of HZ patients will have PHN lasting for more than 3 months, and PHN may be more severe (as measured by opioid use) in patients with diabetes mellitus\(^4^1\) or HIV infection.\(^5^1\) The prevalence and duration of pain increases with age in accordance with the general age-related decline in immune response (immunosenescence) (Figure 6).\(^5^2\)

### 8. Summary

Primary infection with VZV causes varicella, whereas reactivation of the latent virus causes HZ. The recent demonstration of co-infection of the same host (and indeed even the same cell) with different strains of VZV, and the further possibility of recombination between the viruses, adds complexity to our understanding of the natural history of VZV infection.

VZV evades the host’s immune system and spreads throughout the body, with the potential to cause serious problems in the immunocompromised host. The virus establishes latency in the DRG and CRG of an infected individual; latency is maintained by the presence of VZV-specific CMI, even as the virus evades the host’s CMI.

As an individual ages, decreasing VZV-specific CMI due to immunosenescence often leads to viral reactivation, which manifests as HZ. Apart from older age, other risk factors for HZ include immunosuppression, female gender, white race, mechanical or psychological stress, lack of exposure to children, and genetic susceptibility. Understanding the significance of these risk factors, in addition to the basic pathogenesis and epidemiology of VZV, will help physicians to promptly diagnose and manage HZ effectively within primary healthcare.

As populations throughout the world sustain increasing numbers of older people, the incidence and epidemiology of HZ will be expected to change. These changes will be modulated by the medium- and long-term effects of the varicella vaccine and HZ vaccine in...
countries where these vaccines are available. Hence, it becomes even more imperative to continue the research into the epidemiology and pathogenesis of VZV in order to further reduce the incidence of varicella and HZ in both temperate and tropical countries.

Acknowledgments

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Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>VZV</td>
<td>varicella zoster virus</td>
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<td>HZ</td>
<td>herpes zoster</td>
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<tr>
<td>CMI</td>
<td>cell-mediated immunity</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>MHC</td>
<td>major histocompatibility class</td>
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<td>IFN</td>
<td>interferon</td>
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<td>MSGP4</td>
<td>Fourth Morbidity Survey in General Practice</td>
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<td>RCGP</td>
<td>Royal College of General Practitioners</td>
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<tr>
<td>DRG</td>
<td>dorsal root ganglia</td>
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<tr>
<td>CRG</td>
<td>cranial root ganglia</td>
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<td>OR</td>
<td>odds ratio</td>
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<td>HLA</td>
<td>human leukocyte antigen</td>
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<td>PHN</td>
<td>post-herpetic neuralgia</td>
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References


44. Haanpää M, Nurmikko T, Hurme M. Polymorphism of the IL-10 gene is associated with susceptibility to herpes zoster. scand J Infect Dis. 2002; 34:118–9. [PubMed: 11928840]


Fig. 1.
Fig. 2.
The incidence of HZ increases with age. Figure adapted from Edmunds et al, 2001 and Gauthier et al, 2009.9,10 Abbreviations: MSGP4, Fourth Morbidity Survey in General Practice; RCGP, Royal College of General Practitioners.
Fig. 3.
Phylogeny of VZV.\textsuperscript{13–17} Figure adapted from Loparev et al, 2007.\textsuperscript{13}
Fig. 4.
Intercellular spread of VZV. Numbers indicate the steps in synthesis of VZV in the basal epidermis (no release of infectious VZV) and the superficial epidermis (release of infectious VZV). Figure courtesy of Gershon A and Gershon M.
Fig. 5.
VZV-specific CMI declines with age.\textsuperscript{33}
Fig. 6. Prevalence of PHN according to age.\textsuperscript{52} Reproduced from Kost RG, Straus SE. Postherpetic neuralgia-pathogenesis, treatment, and prevention. \textit{N Engl J Med} 1996 Jul 4;335(1):32–42. © 1996 Massachusetts Medical Society. All rights reserved.
Table 1

Risk factors for HZ.  

<table>
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<tr>
<td>Older age</td>
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<tr>
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<td>Diabetes</td>
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<td>Female gender</td>
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<td>Genetic susceptibility</td>
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<td>Mechanical trauma</td>
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<td>Recent psychological stress</td>
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<td>White race</td>
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Table 2

Complications of HZ.49

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<th>Cutaneous VZV dissemination</th>
<th>Visceral</th>
<th>Neurological</th>
<th>Ocular</th>
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<td>Neural extension of VZV infection:</td>
<td>PHN</td>
<td>Loss of corneal sensation</td>
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<td>Panophthalmitis</td>
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<td>Uveitis</td>
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