

CLINICAL REVIEW

Varicella Zoster Virus: Two Lives of a Pathogen

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ABSTRACT

Varicella zoster virus is the etiological agent of both varicella ("chickenpox") and herpes zoster ("shingles"). The ubiquitous and infectious nature of this virus underlies the high incidence of varicella among young individuals. Subsequent to primary infection causing varicella, the virus enters a state of dormancy within the sensory ganglia. These latent viral particles will persist for the lifetime of the individual. Several factors, chiefly advancing age, are correlated with an increased risk of viral reactivation and secondary infection causing herpes zoster. A common complication of herpes zoster is a chronic pain syndrome called post-herpetic neuralgia, which involves viral-mediated damage to the sensory neurons. The present paper provides a brief overview of the epidemiology, known mechanisms and available treatment options for the dual manifestations of varicella zoster virus. Additionally, the clinical evidence for a recently developed herpes zoster vaccine is discussed.

UNLIKELY SIBLINGS

Outwardly, the similarities between chickenpox and shingles may be difficult to identify. What could this relatively benign illness of childhood share with such a potentially debilitating affliction of adulthood?

The clinical manifestations of these diseases are notably dissimilar. Varicella ("chickenpox") is recognized as a highly contagious and widespread itchy rash, while herpes zoster ("shingles") is characterized by dermatomally distributed pain and localized eruption of painful vesicles. Although disease complications of varicella are relatively rare in immunocompetent patients, herpes zoster is associated with a complication risk of nearly 50% in persons over age fifty.¹ Keeping these clinical disparities in mind, it may be surprising to learn that varicella and herpes zoster are in fact rooted in the same infectious agent. For an overview of the two lives of varicella zoster viral infection, please see Figure 1.

The First Hit: Varicella

Varicella zoster virus (VZV), a ubiquitous pathogen, is an alphaherpesvirus with subfamily ties to the herpes simplex virus.² When a person is first exposed to VZV, most often during childhood, they exhibit the classical signs of varicella: fever, flu-like symptoms and a generalized vesicular rash

on the face, scalp and trunk. Varicella is usually self-limited in the immunocompetent host, resolving within approximately fourteen days.³

A Dormant Threat

Although the symptoms of varicella soon resolve, the causative agent does not vanish. Rather, VZV retreats from the amplified immune activity of the host by seeking refuge in the dorsal and/or cranial sensory ganglia. These clusters of neuron cell bodies are the bridge between peripheral sensory receptors and the internal processing of the central nervous system.

VZV persists in a latent form within the sensory ganglia until host conditions are conducive to its reactivation and proliferation.⁴ Cell-mediated immune defenses are critical to the maintenance of this state of viral dormancy.

Exodus

Unfortunately, cell-mediated immunity slowly fades over the course of a lifetime.⁵ When this protection falls below a certain threshold, latent VZV can become active and infectious once more. This secondary infection of VZV manifests as a distinct clinical entity called herpes zoster, or "shingles." See Figure 2 for a conceptual interpretation of VZV

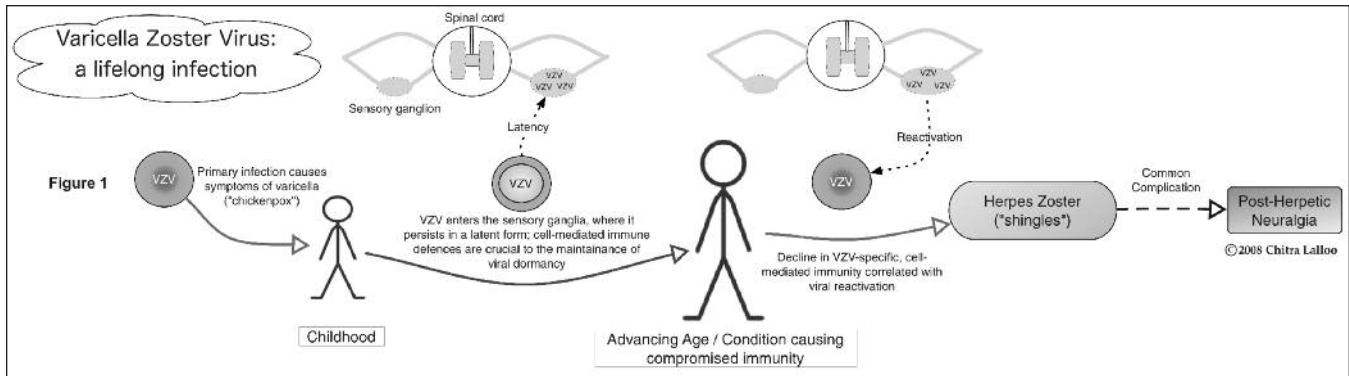


Figure 1. Varicella zoster virus (VZV) is the causative agent of both varicella (“chickenpox”) and herpes zoster (“shingles”). Primary exposure to the virus, resulting in varicella, is followed by a prolonged asymptomatic period wherein VZV persists in a latent form within the sensory ganglia. Depletion of cell-mediated immunity, particularly with advancing age, is correlated with an increased risk of VZV reactivation causing herpes zoster. A common complication of herpes zoster is a chronic pain condition called post-herpetic neuralgia, which affects an estimated 25% of zoster patients.

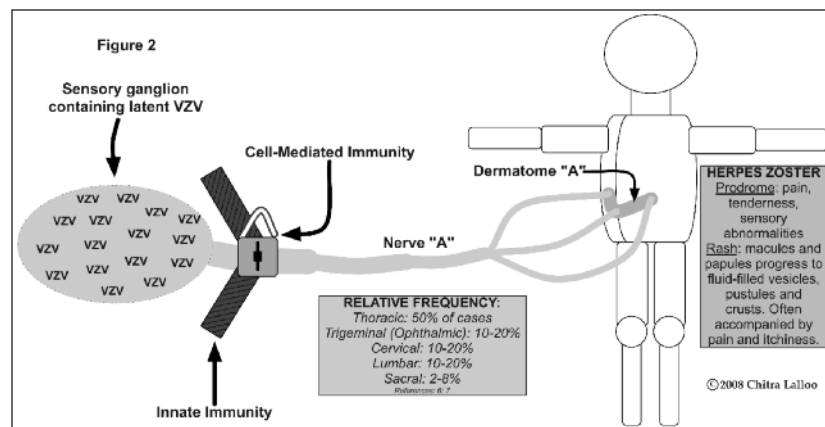


Figure 2. Following resolution of varicella, VZV enters the sensory ganglia, where it will persist throughout the host's life. Reinfection of VZV is prevented through two mechanisms: 1) Innate immunity: non-specific response to a pathogen; typically cannot independently prevent VZV reactivation. 2) Cell-mediated immunity: the most powerful and targeted defensive mechanism. VZV-specific T cells are critical to the maintenance of viral latency within the sensory ganglia. In this conceptual diagram, innate immunity is portrayed as a set of “floodgates” between the VZV-containing sensory ganglion and peripheral nerve. Cell-mediated immunity is the “lock” that maintains the security of the floodgates. The age-related decline in cell-mediated immunity may be conceived as a “rusting” of the lock. If the lock becomes sufficiently frail, VZV may burst through the floodgates, travel along the nerve, and manifest as sensory abnormalities and a painful rash within the corresponding dermatome(s). This constellation of symptoms is known as herpes zoster.

reactivation through declining cell-mediated immunity and renewed reliance on innate immune defenses.

Although the mechanisms of reactivation remain unclear, the pathological progression of the reawakened virus has been well-documented. No longer inhibited by the defenses of an immunocompetent host, the virus is liberated from the sensory ganglia. Recall that these specialized neurons carry sensory information such as temperature and touch from collection points along the periphery to the central nervous system for processing. Each ganglion transmits sensory data from specific bands of skin, called dermatomes, to the brain. As VZV spreads down the infected ganglia, symptoms begin to appear within corresponding dermatomes.⁴ Often, this outbreak occurs in one dermatome, which presumably cor-

responds with a ganglion where VZV is particularly populous.¹ For example, if a ganglion of the lumbar region becomes infected, symptoms will appear in a predictable band around the lower midriff. The most commonly affected sites include the thoracic dermatomes (up to 50% of cases); ophthalmic division of the trigeminal nerve (10 to 20%); and cervical (10 to 20%), lumbar (10 to 20%) and sacral dermatomes (2 to 8%).^{6,7}

The Second Hit: Herpes Zoster

Although the natural history of herpes zoster is variable, most patients present with a prodrome of abnormal sensations across one or more dermatomes on one half of the body.⁸ These localized sensory dysfunctions may include

pain, burning, tingling, itching, numbness or extreme sensitivity to stimuli, and could be accompanied by flu-like symptoms. Due to the non-specific nature of these initial symptoms, herpes zoster may be misdiagnosed as herpes simplex, cardiac disease, appendicitis, herniated disc, or some other pain-related disorder.⁹⁻¹¹ According to Schmader,¹¹ the presence of tender or hyperesthetic (hypersensitive) skin in the affected dermatome may be used to differentiate herpes zoster from phenotypically similar conditions.

Only when the virus has reached the epidermal nerve terminals, typically within 4 to 5 days of the prodrome, does the recognizable zoster rash appear. This rash typically presents as a series of macules (distinct spots) and papules (raised pimples or swelling) on an erythematous base, which soon develop into a band of clustered vesicles. These fluid-filled blisters progress to pustules and crusts within ten days in the normal host.⁴ In contrast to the ubiquitous distribution of varicella, the zoster rash is localized to the dermatomal regions of infected sensory ganglia and generates more pain than itchiness. As the vesicles progress to crusts, this zoster-related nerve pain may gradually fade away.

The Determinants and Distribution of Herpes Zoster

Varicella zoster virus is an exceedingly common and highly infectious pathogen. In temperate climates, almost 90% of primary varicella cases occur by 10 to 14 years of age, and virtually all persons have been exposed to the virus by adulthood.¹² Since exposure to VZV is a requirement for development of herpes zoster, nearly all adults living in temperate climates are susceptible. The incidence of herpes zoster in Canada is currently estimated at 130,000 new cases per year.¹³ The lifetime risk for herpes zoster development is approximately 20% to 30%.¹⁴

The most common risk factor for herpes zoster, correlating with a decline in VZV-specific cell-mediated immunity, is advancing age.¹⁵ The Hope-Simpson prospective study reports an annual zoster incidence of 0.74 per 1,000 in children under ten years of age; 2.5 per 1,000 in adults aged 20 to 50 years; and 7.5 per 1,000 in adults older than sixty years of age.⁶ As well, nearly 50% of persons aged 85 years and older are likely to experience one or more zoster episodes.

Other sources of depressed cell-mediated immunity that could precipitate an episode of herpes zoster include neoplastic disease, immunosuppressive therapy, immune-mediated disease and HIV/AIDS.¹⁶⁻¹⁹

A Chronic Complication: Post-Herpetic Neuralgia (PHN)

Ideally, the healing of residual crusts marks the end of a herpes zoster episode. For a growing proportion of the population, however, the fading of a zoster rash merely ushers in a new wave of illness. The most common, and most feared, complication of herpes zoster in immunocompetent patients

is a chronic pain condition called post-herpetic neuralgia (PHN).²⁰ Affecting nearly 50% of shingles patients over age fifty, PHN is a pain that persists after the rash of zoster has resolved.²¹ Patients commonly describe this pain as “sharp and jabbing,” “burning,” or “deep and aching.” PHN may also produce abnormal sensations such as extreme sensitivity to touch and temperature, unbearable itching, numbness and headaches. Although the precise mechanisms of PHN pathogenesis remain uncertain, it is likely that the renewed activity of VZV injures specific sensory nerves, which is interpreted by the brain as persisting pain and/or abnormal sensation.

Risk of PHN Development

Advancing age is the most significant risk factor for PHN. Patients who are eighty years old, for instance, have almost five times the risk of experiencing pain one year after the zoster rash has resolved than patients younger than eighty.²¹ The incidence of PHN in Canada is currently estimated at 17,000 new cases per year.¹³ Overall, approximately 25% of herpes zoster patients eventually develop PHN.

Brisson and colleagues estimate that herpes zoster and PHN are responsible for 252,000 physician consultations and 2,000 hospitalizations in Canada each year. Furthermore, diagnosis and treatment of herpes zoster and its complications are estimated to cost the Canadian health-care system \$68 million annually.¹³

Other risk factors for development of PHN include: greater severity of initial pain and rash, presence of symptoms prior to rash onset, sensory disturbances during the zoster episode, psychosocial distress and compromised immunity.^{22,23}

It is projected that the global population aged 65 years and older will double from 15% today to almost 30% in 2050.²⁴ Given the clear association between herpes zoster/PHN and advancing age, it can be predicted that the human and financial burden of these diseases will increase exponentially in the foreseeable future.

MANAGEMENT OF HERPES ZOSTER AND PHN

Although herpes zoster is by definition a self-limiting disease, medical intervention is usually important and is based on factors such as disease severity and risk of complication. High-risk patients (e.g., those with compromised immune systems) are recommended to commence anti-viral medication as early as possible, but certainly within seventy-two hours of rash onset. By inhibiting the replication of VZV, anti-virals ultimately diminish the impact and duration of symptoms such as zoster rash and acute pain. Depending on the severity of zoster symptoms, physicians may also recommend corticosteroids to reduce inflammation and analgesics for zoster-associated pain.²⁵

The presentation, severity, and duration of PHN are highly variable. While some patients may experience only a dull,

uncomfortable pain, others can develop unbearable pain and itching as well as extreme sensitivity to harmless stimuli such as light brushing on the skin. Therefore, approaches to treating PHN are dependent on the unique needs of the patient. For the individual who experiences mild PHN symptoms, analgesics such as acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) may be adequate. Patients with greater disease severity are likely to have sustained serious nerve damage and will require more potent therapies. According to Moulin and colleagues,²⁶ PHN treatment should be prescribed in a step-wise pattern, depending on patient need, as follows:

- **First Line:**
 - Tricyclic antidepressants (amitriptyline, nortriptyline)
 - Anticonvulsants (gabapentin, pregabalin)
- **Second Line:**
 - Topical lidocaine
- **Third Line:**
 - Opioids (oxycodone, fentanyl, morphine)

Preventive Measures

Although a chicken pox vaccine has been available for children since 1995, development of a shingles vaccine for adult populations has been slower to reach fruition. Zostavax® [Zoster Vaccine Live (Oka/Merck)], the first and only herpes zoster vaccine, received approval for use in the United States in May 2006. This live, attenuated strain of VZV provides a boost in cell-mediated immunity for older adults, which reduces the subsequent risk of viral reactivation and herpes zoster development.

The largest clinical trial of Zostavax® [Zoster Vaccine Live (Oka/Merck)] conducted to date involved a study population of 38,546 adults over age sixty years.²⁷ Criteria for inclusion were: a positive history of varicella or residence in the United States for at least thirty years, and informed consent. Exclusion criteria included, but were not limited to: immunosuppression resulting from disease or therapy, history of herpes zoster, prior receipt of varicella vaccine, and presence of a condition that could interfere with full participation in the study.²⁸ Randomization of subjects to the intervention or control group was stratified by study site and age group (60 to 69 years and 70 years and older). Subjects received a single subcutaneous injection of either vaccine (containing live virus, neomycin and stabilizers) or placebo, which lacked the virus and neomycin. Both patients and outcome assessors (individuals who determined the presence and severity of subsequent disease) were blinded to the randomization pattern.

The primary outcome measure was burden of illness due to herpes zoster, which took into account the severity and duration of disease-associated pain and discomfort. The pri-

mary assessment tool, the Zoster Brief Pain Inventory, was developed and validated as a subject-completed questionnaire for this study. The secondary outcome measure was incidence of PHN, defined as "...pain associated with herpes zoster that was rated as 3 or more on a scale ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine"), persisting or appearing more than 90 days after the onset of rash" (p.2274).^{28,29}

Patients were monitored for a median of 3.12 years and less than 5% of subjects dropped out prior to study completion. The investigators report that the vaccine lightened the burden of illness due to herpes zoster by 61.1% (95% confidence interval [95% CI]: 51.1 – 69.1) and reduced the incidence of herpes zoster and PHN by 51.3% (95% CI: 44.2 – 57.6) and 66.5% (95% CI: 47.5 – 79.2), respectively. All of these results met the a priori criteria for "success". Common adverse effects at the injection site included mild redness (35.8% of vaccine recipients versus 7% of placebo group), pain or tenderness (34.5% vs. 8.5%), swelling (26.2% vs. 4.5%), and pruritus (7.1% vs. 1%).

Zostavax® [Zoster Vaccine Live (Oka/Merck)] has been recommended by the U.S. Food and Drug Administration for the prevention of shingles disease in adults 60 years of age and older.³⁰ It is not recommended for the treatment of herpes zoster or PHN. The vaccine is contraindicated in patients with a history of allergic reaction to any of the vaccine components, states of immunodeficiency or immunosuppression, active tuberculosis and pregnancy. The vaccine was approved by Health Canada in August 2008; recommendation by Canada's National Advisory Committee on Immunization is currently pending.

VIRAL REFLECTION

Varicella zoster virus is thus a menace with two lives. After materializing during childhood it sinks beneath the surface, often not reemerging until the sixth decade of life or later. Just as the patient's appearance has been dramatically altered by the intervening years, so has that of VZV. The entity that originally presented as a widespread rash of itchy red pox has morphed into a remarkably defined band of painful vesicles and accompanying sensory disturbances. This secondary VZV infection also carries a significant risk of PHN, a chronic and debilitating pain syndrome.

The dual infections of VZV occur during periods of pronounced immune vulnerability. Underdevelopment of acquired defenses correlates with primary viral infection, while a decreasingly effective immune system permits a secondary outbreak in advancing age. Only through preventive measures such as early treatment or vaccines for varicella and herpes zoster can we expect to forestall the influx of VZV and PHN cases predicted to transpire in the near future. †

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Author Biographies

James L. Henry, a neurophysiologist who has worked throughout his career to understand the underlying mechanisms of chronic pain, is the inaugural scientific director of the Michael G. DeGroot Institute for Pain Research and Care at McMaster University. He also holds an endowed chair in central pain. Dr. Henry joined McMaster in January 2005 as a professor in the departments of Psychiatry and Behavioural Neurosciences and Anesthesia.

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Chitra Laloo is a first year graduate student in the Medical Sciences program at McMaster University, working under the supervision of Dr. James Henry. She completed her undergraduate studies in the Bachelor of Health Sciences Program at McMaster in May 2008. Her research involves the assessment and validation of an iconic pain assessment tool in a population of neuropathic pain patients.