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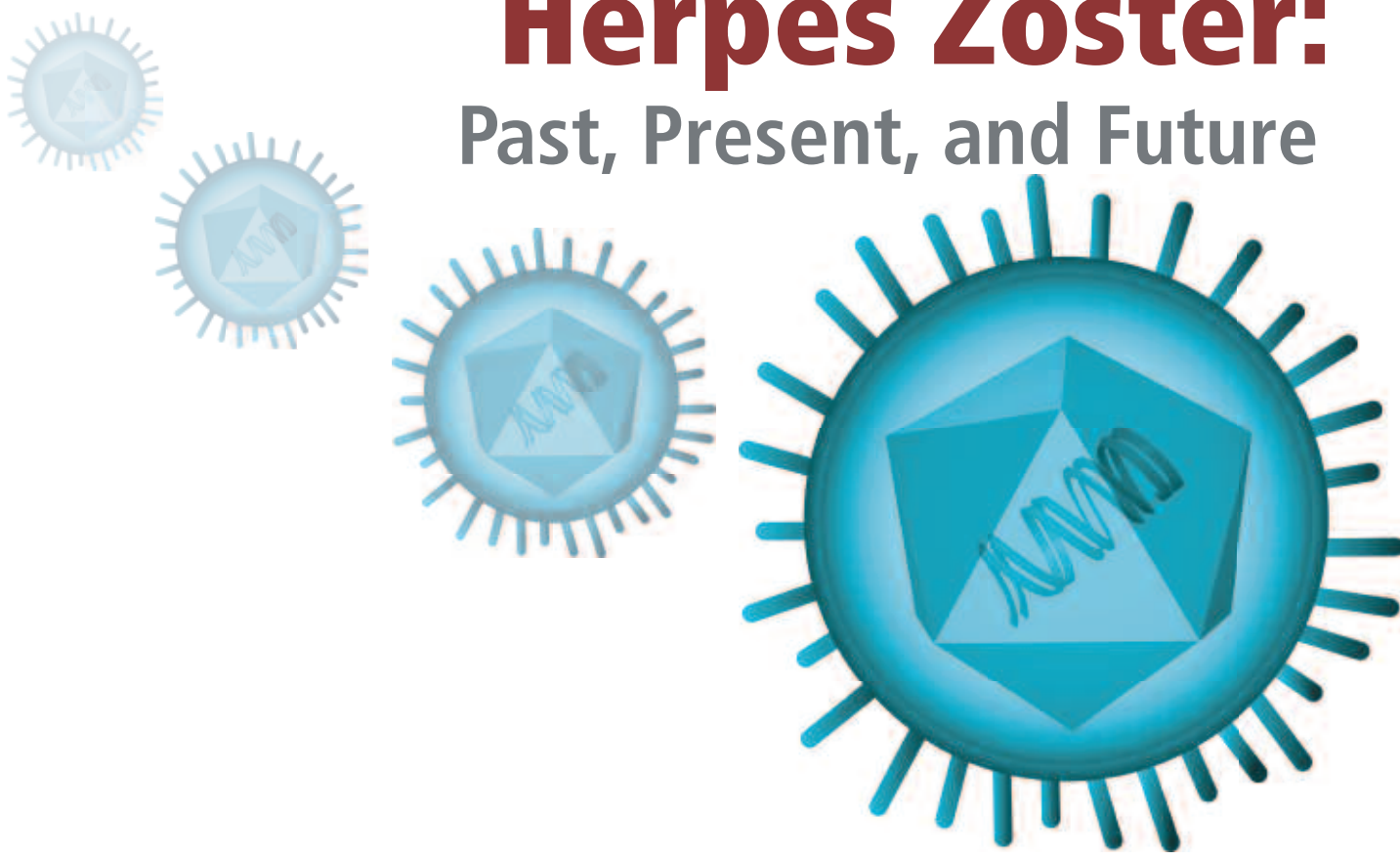
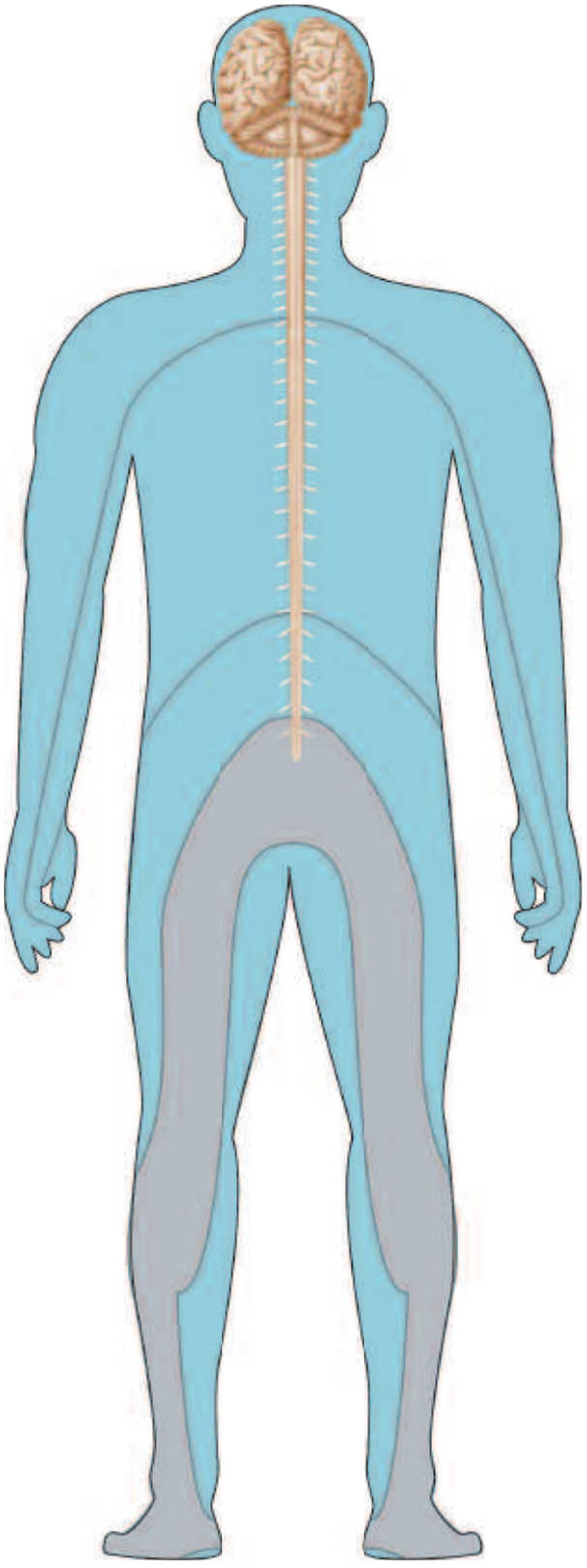
Herpes Zoster:
Past, Present, and Future



Supplement

Herpes Zoster

November/december 2006



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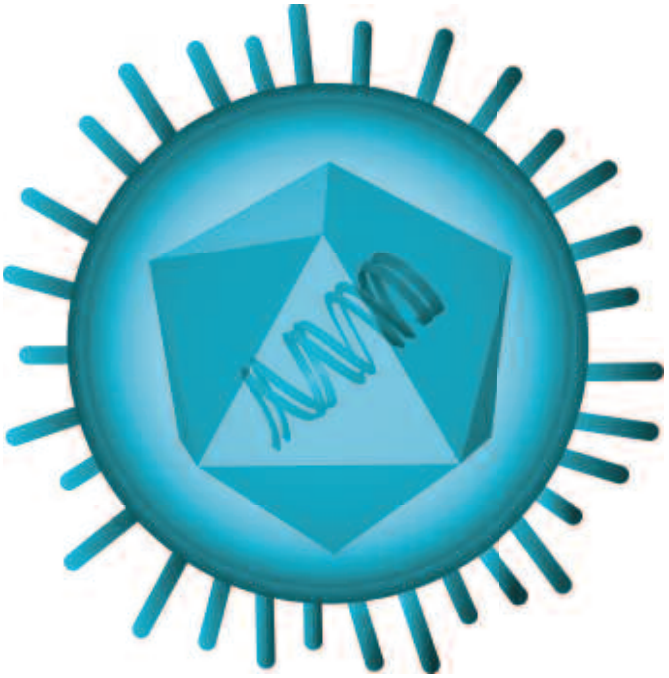

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Herpes Zoster and its Complications in the Older Adult Population

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As I watched the U.S. Open tennis tournament in early September, I was surprised to learn that the then number one–ranked American tennis player, James Blake, had developed a condition that many people regard as a disease of the old and infirm. At the age of 24, Blake severely injured his neck, resulting in a lengthy hospitalization. During this time he developed herpes zoster (HZ). Blake described HZ as being "more painful than his broken neck," and the debilitating consequences from the virus alone sidelined his career for several months. If zoster can be this detrimental to a young, healthy athlete, it is no surprise that treating HZ in older individuals poses a therapeutic challenge. During medical school and my internal medicine residency, I learned that HZ could be deadly in the immunocompromised and that postherpetic neuralgia (PHN) could be very painful. It wasn't until my geriatrics fellowship that I realized how distressing HZ and zoster-related pain could be for an older adult—that it could lead to or exacerbate depression, curtail an individual's independence, and ultimately lead to institutionalization was a revelation to me. Zoster is a condition that I, and any physician who cares for a primarily older patient population, look for vigilantly. We all appreciate that it is essential that the diagnosis be made in a timely manner so that antiviral therapy can be instituted quickly and effectively. However, early diagnosis is not always achieved in this patient population. Persons with cognitive impairment may not complain of a rash or of pain. Often, older adults and their caregivers may assume that the rash is inconsequential or untreatable, and not complain to their physicians. Even when therapy is appropriately started, it is often impossible to tell which individuals will develop the agonizing consequences of the reactivated virus.

We are all aware of the growing population of older adults and the emerging increase in prevalence of many chronic illnesses. What role do varicella and resulting zoster have in the growing population of older adults? Are they conditions worth preventing? In this supplement to Geriatrics & Aging, I follow this commentary on the burden of zoster and of PHN with an article on HZ epidemiology and challenges in pain management. Drs. Stuart Skinner and Fred Aoki describe the background and current situation of varicella zoster virus (VZV) and present a scenario of what the future of older adults may look like with respect to VZV. Dr. Ian Landells describes the challenges with differential diagnosis of the HZ rash, and the difficulties in management, while Dr. Peter Watson discusses the best methods of managing the pain of HZ and the chronic pain of PHN. As with many aspects of pain management in older adults, there are several confounding factors, such as medication interactions and chronic pain from more than one source.

Dr. David Patrick delves into what the future of zoster holds, explaining the shingles prevention study (SPS) and discussing the newly available preventative vaccine. The varicella vaccine has been shown to be cost-effective when used in children to protect against chicken pox.[1] Rapidly escalating health care costs shadow over health care systems worldwide, and policy makers must ensure that new treatments are cost-effective. Although vaccination programs are costly to implement, their outcomes compare favourably with many medical therapies.[2]

As physicians, we must be vigilant for atypical presentations of HZ among older adults because it is crucial that diagnosis be made judiciously and quickly. Perhaps with the advent of a zoster vaccine, this disease will someday be a rarity. Until then, all physicians, particularly those that treat older adults, must be well educated on the signs, symptoms, and management of HZ.

No competing financial interests declared.

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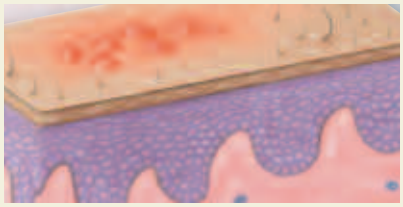
abstract



Ninety percent of adults have had prior infection with the varicella zoster virus. There is no way to predict when the virus will reactivate and who will develop herpes zoster. The lifetime incidence of herpes zoster is approximately 25% and increases to ~50% by age 85 years. Pain is the major feature of herpes zoster. Treatment of postherpetic neuralgia is challenging as the condition can be refractory and frequently requires a multipronged approach (multiple medications and alternative therapies). Many older persons (>65 years) with postherpetic neuralgia experience long-standing severe, debilitating pain and poor quality of life; levels of dissatisfaction with treatment are high.

Key words: *epidemiology, herpes zoster, older adult, postherpetic neuralgia, pain*

Herpes Zoster: Epidemiology, Burden of Illness, and Challenges in Pain Management

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Case Study

Mrs. R.W. is a 75-year-old woman in long-term care who complains of low back pain for two days. She has mild cognitive impairment. She is unable to describe the character of the pain but states that it does not radiate. On physical exam, vital signs are stable. There is some tenderness on the right lower flank and some pain with movement. There is no skin abnormality. Urine is sent to rule out urinary tract infection. The most likely diagnosis is thought to be muscular, and the patient is prescribed acetaminophen with codeine. Her pain improves slightly after taking the acetaminophen with codeine regularly for two days. Urinalysis comes back negative. However, Mrs. R.W. becomes confused, unsteady, and falls. On physical exam, there is some bruising over the right hip due to the fall, and a vesicular rash is now noted over the right flank.

Introduction

Canadian Epidemiology Data

Ninety percent of adults have had prior infection with the varicella zoster virus (VZV).[1] The VZV remains latent after the initial, acute infection, and herpes zoster (HZ) is the reactivation of this latent viral infection at the dorsal root ganglion.[2–5] There is no way to predict when the virus will reactivate and who will develop HZ. The frequency and severity of herpes zoster in older people is likely the result of an age-related decline in VZV-specific T-cell mediated immunity.[6–8]

One consequence of virus reactivation is sensory neural injury and resultant chronic neuropathic pain.[9] In Canada, the estimated average lifetime risk of at least one VZV reactivation was 28% between 1990 and 1997. Routine varicella vaccination programs are now implemented across Canada. It is still uncertain what impact, if any, this program will have on the incidence and severity of HZ.[10,11]

The lifetime incidence of herpes zoster (HZ) is approximately 25%, and this figure increases with age, particularly after the age of 50 years. The lifetime incidence is approximately 50% by age 85 years.[4,12–15] The annual incidence of HZ in Canada is 130,000, with about 20,000 of these progressing to postherpetic neuralgia (PHN).[14]

There are over 4,000 hospitalizations a year in Canada due to HZ, with an estimated cost up to $82 million annually (drug costs, infection control measures, and PHN management costs are not included). Between 1979 and 1997, hospitalization in the 65+ age group was 86 per 100,000 individuals, with an average length of stay of 20 days.[14–16]

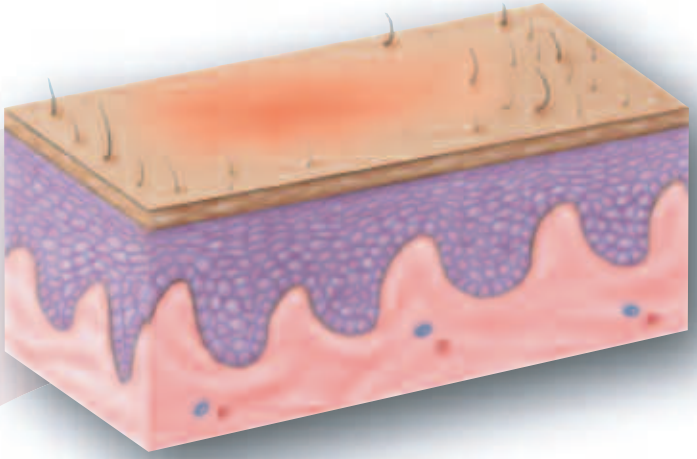
Symptoms and Complications

Pain is the major feature of HZ. There is a continuum of pain from onset to resolution, known as zoster-associated pain (ZAP) (Figure 1). The Zoster Brief Pain Inventory (ZBPI) should be used in order to assess the efficacy of treatment and to evaluate the impact of HZ pain on quality

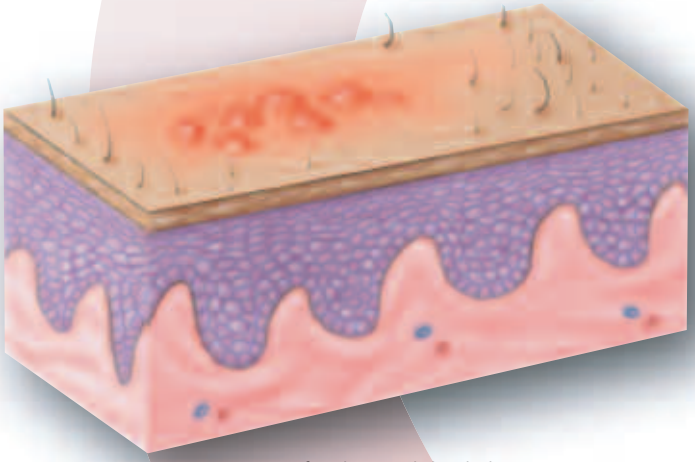
Figure 1: Development and Progression of Zoster-Associated Pain (ZAP)

Prodromal pain

Burning or aching in nature, with superimposed shooting or stabbing pains plus associated itching and other sensory disturbances. Symptoms may simulate the pain of myocardial infarction, pleurisy, duodenal ulcer, cholecystitis, renal colic, appendicitis, prolapsed intervertebral disc, or early glaucoma, which may lead to serious misdiagnosis.



Before rash onset (1–5 days)
(Zoster sine herpete)



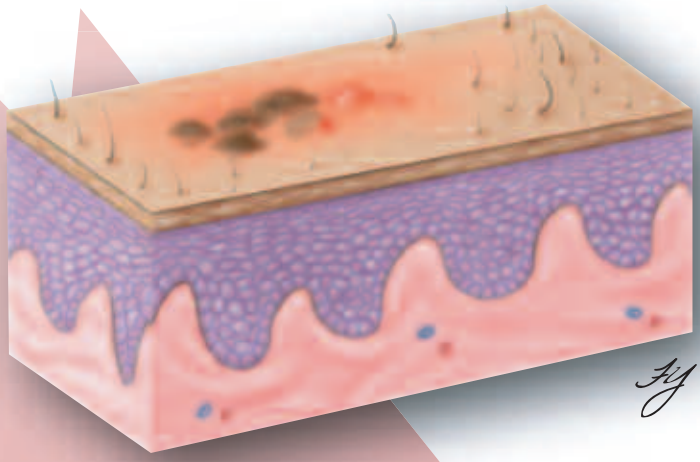
Acute pain

Burning or aching in nature, with superimposed shooting or stabbing pains plus associated itching and other sensory disturbances. Allodynia and hyperalgesia may be present, making the wearing of clothes over the affected area difficult.

Onset of rash to rash healed

Postherpetic neuralgia (PHN)

Patients with postherpetic neuralgia (PHN) may experience constant pain (described as burning, aching, or throbbing), intermittent pain (described as stabbing or shooting) and stimulus-evoked pain such as allodynia (described as tender). Allodynia is the most distressing and debilitating type of pain in patients with PHN and affects 90% of these patients. These subtypes of pain may produce chronic fatigue, sleep disorders, depression, anorexia, weight loss, and social isolation. Between 25–50% of adults older than 50 years develop PHN, depending on early antiviral therapy for HZ.



Pain persisting 1–4 months after rash onset or after the crusting over of the skin lesions

Source: Text modified from references 9,12,33,40–43.

of life.[17] The ZBPI is an HZ-specific and validated questionnaire that assesses not only pain but also evaluates allodynia and pruritis.

The underlying cause of pain associated with HZ is damage to neural tissue due to VZ virus replication. The anatomic and functional changes responsible for PHN appear to be established early in the course of HZ, perhaps in the prodromal phase.[9,18] Postherpetic neuralgia is the most common and debilitating complication of HZ; the risk factors associated with its development are shown in Table 1. Older patients whose ZAP is moderate or severe have up to a 60% self-reported rate of depression.[19] The impact of acute HZ on quality of life is at least as significant as with other chronic diseases such as congestive heart failure, diabetes, myocardial infarction, and major depression.[20] Increased HZ pain correlates with decreased ability to perform activities of daily living or to engage in social activities, and also contributes to increased emotional distress.[21,22] The total number of quality-adjusted life-years (QALYs) lost annually in Canada is estimated to be 7,682, and most of the pain and suffering is attributed to PHN (81% of total QALYs lost).[14,19]

In addition to pain, HZ can result in other complications, including neurological, ophthalmic, and cutaneous sequelae (Table 2).

Table 2: Complications of Herpes Zoster

Neurologic	Segmental motor paralysis (15%), Ramsey Hunt syndrome, peripheral sensory neuritis, aseptic meningitis
Ophthalmic	Conjunctivitis (most commonly), keratitis, uveitis, and optic neuritis If these latter disorders are not diagnosed and treated adequately, the patient's eyesight may become permanently affected. *Opthalmic HZ represents 10–20% of all zoster cases, meaning that one out of every 100 individuals will develop ophthalmic zoster during his/her lifetime.*
Cutaneous	Cutaneous dissemination and bacterial superinfection (2%) that can lead to cellulitis and scarring

Source: Modified from references 9,30,37,38.

Misdiagnosis

The prodromal (pre-rash eruption) pain of HZ may be misdiagnosed as myocardial infarction, pleurisy, duodenal ulcer, cholecystitis, renal colic, appendicitis, prolapsed intervertebral disc, or early glaucoma.[9]

Sometimes VZV can be reactivated and pain develops without a rash, a condition known as *zoster sine herpete*.[23] This usually occurs in older patients. An accurate early diagnosis of shingles in such cases is often difficult. Some evidence suggests that some cases of Bell's palsy might actually be an indication of *zoster sine herpete*. Other than the apparent tendency for pain of *zoster sine herpete* to recur, there is no other feature of the pain that distinguishes it from typical PHN. Virological evidence is necessary to confirm *zoster sine herpete*.[24]

Challenges of Managing ZAP in the Older Adult

The risk of PHN is very high in older adults and may persist for years. Treatment of PHN is challenging, can be refractory, and frequently requires a multipronged approach (multiple medications and alternative therapies). No treatment has been shown to prevent PHN; however, some treatments may shorten the duration or lessen the severity of symptoms. Although antivirals are effective in reducing the duration and intensity of HZ, they have limitations (Table 3).

Many older persons (>65 years) with PHN experience long-standing severe, debilitating pain and poor health-related quality of life; levels of dissatisfaction with treatment are high (Table 4).[19,25–30]

Older adults may have more pre-existing medical problems and may be taking more prescription drugs than younger adults.[31] Patients receiving pharmacological treatment for HZ and PHN are at higher risk, therefore, of drug

Table 1: Risk Factors for Postherpetic Neuralgia

Age >50 years
More severe acute zoster pain
Greater rash severity
Greater neurological damage during acute zoster (sensory abnormalities)
Prodromal pain

Source: Modified from references 33–36.

Table 3: Limitations of Antivirals for Treatment of Herpes Zoster

1. Treatment must be given within 24–72 hours of onset of rash. Valacyclovir and famciclovir are equivalent in terms of both the rate of cutaneous healing and pain resolution.
2. Treatment does not reliably prevent postherpetic neuralgia: 20% of treated patients aged >50 years continue to have pain six months after onset (acyclovir: 25.7%; valacyclovir: 19.3%; and famcyclovir: 19%).
3. Antiviral treatments do not prevent the clinical manifestations of HZ. Resolution of pain vs. placebo are as follows: acyclovir: 41 vs. 101 days; valacyclovir: 38 vs. 51 days; and famciclovir: 63 vs. 163 days.

Source: Modified from references 2,28,39.

Table 4: Effectiveness of Treatment for Postherpetic Neuralgia

Gabapentin	26%
Amitriptyline	Moderate relief (any change in Visual Analog Scale [VAS] score): 47–67% Complete relief: 13%
Morphine	38–50% reduction of VAS
Gabapentin and morphine combination	Mean daily pain (on a scale from 0 to 10, with higher numbers indicating more severe pain): 5.72 at baseline, 4.49 with placebo, 4.15 with gabapentin, 3.70 with morphine, and 3.06 with the gabapentin-morphine combination ($P<0.05$ for the combination vs. placebo, gabapentin, and morphine)

Source: Modified from references 26–28.

interactions with potentially serious side effects. Cognitive impairment may hamper medication adherence. Fear of side effects and of disapproval by regulatory bodies may result in undertreatment with opioids.[32]

Only half of older adults with zoster report having spoken to their physician about their zoster pain.[19] Because of this underreporting of pain by older adults, it is crucial that the physician ask about pain even if the patient does not initiate this discussion. It is important, too, to realize that older adults, even with moderate cognitive impairment, are able to give a reliable pain history.[44]

The nonopioids most commonly used to treat ZAP include tricyclic antidepressants (e.g., amitriptyline, nortryptiline) and antiepileptics (e.g., gabapentin). Both groups of drugs can result in sedation, confusion, and falls if dosed too high or increased too quickly. Treatments require close monitoring and slow dose titration to reduce adverse events and side effects, especially in the older adult. On the opposite end of the spectrum, many older adults with PHN may be suboptimally treated because physicians may have fears of overmedicating. This holds particularly true for opioids, where fear of overmedicating, particularly in older adults, is common.

It is crucial for physicians to ask about pain when zoster is diagnosed, even in patients with cognitive impairment. It is important for caregivers to be involved in this process. Medications should be started at low doses but increased as needed to obtain maximum pain relief.

Key Points

People with cognitive impairment can still give a good pain history.

A high degree of suspicion for zoster is required in older adults because of the need to treat early and avert the high cost of suffering/pain associated with delayed diagnosis.

Neuropathic pain is difficult to manage in older adults and may manifest as falls or confusion.

The development and deployment of a vaccine for herpes zoster is important because pain can start prior to the rash; also, individuals with severe dementia may not be able to give a thorough history.

Widespread vaccination will ultimately reduce the incidence of postherpetic neuralgia, which can be debilitating and in some cases refractory to treatment.

Case Study: Follow-up

Mrs. R.W.'s pain is diagnosed as PHN and continues for two years. She is treated with a fentanyl patch and gabapentin, which her physician closely monitors. She has good pain relief and needs breakthrough oral morphine sulfate 5 mg once every couple of days.

No competing financial interests declared.

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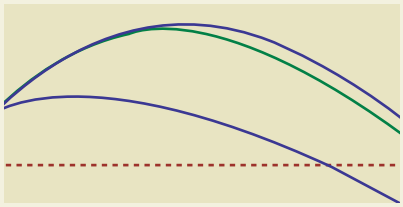
abstract



The incidence of herpes zoster (HZ) increases with age due to varicella zoster virus (VZV)-specific immunosenescence. Exposure to varicella in children mitigates the effect of aging on VZV immunity. Universal childhood varicella vaccination may abrogate this booster effect and thereby increase the incidence of zoster in adults. Broad application of an HZ vaccine in adults over 50 years may in part counteract this loss of natural varicella boosting. The impact of these vaccines on the future of HZ is unclear and requires further research.

Key words: *zoster, varicella vaccine, zoster vaccine, cell-mediated immunity, immunosenescence*

The Future of Herpes Zoster

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Introduction

In 1954, Weller and Coons demonstrated that varicella and zoster were due to the same virus.[1] In 1965, Hope-Simpson presented persuasive evidence that herpes zoster (HZ) was due to the reactivation of varicella, following a prolonged period of latency based on observation of varicella and HZ from his clinical practice.[2] These two studies provided us with the essential framework for our understanding of varicella zoster virus (VZV).

Herpes Zoster Risk Factors

Increasing age is the major risk factor for zoster, making it predominantly a geriatric condition, with dramatic increases occurring in individuals over the age of 50.[2,3] Hope-Simpson postulated that this epidemiologic pattern reflected an age-related decline in specific immunity that permits reactivation of VZV.[2] He also hypothesized that through regular exposure to varicella in the community, previously infected individuals received a boost to their immunity against VZV, and these exposures were pivotal to the prevention of reactivation resulting in zoster. These prescient hypotheses have been borne out by studies that have confirmed that VZV immunity declines in older adults and can be boosted throughout life. Both humoral and cell-mediated immune responses have been shown to increase in response to natural exposure to varicella (and via vaccination).

Cell-mediated Immunity

Cell-mediated immunity (CMI) is essential to the prevention of zoster, and VZV–specific CMI declines progressively with age. Numerous studies have shown age-related reductions in the number and activity of lymphocytes that recognize VZV.[4–6] On the other hand, VZV antibody levels do not decline among older adults[7,8] and patients with isolated immunoglobulin defects are at no increased risk of zoster. The importance of CMI is also seen indirectly in patients with lymphoma, allogeneic bone marrow transplant, and HIV, in whom T-cell function is compromised and associated with an increased risk of zoster.[9,10]

A Vaccine for the Prevention of Herpes Zoster

The development of attenuated, live vaccines to prevent varicella in children, and, at a higher dose, to prevent HZ in older adults, may affect the epidemiology of HZ.[11] The Oka virus strain used in both vaccines was developed by attenuation through multiple passages in human and nonhuman fibroblasts. It is uncertain precisely which mutations are responsible for attenuation among commercial suppliers although most mutations lie in open reading frame 62.[12,13] A live, attenuated vaccine has been licensed in Canada since 1999 for the prevention of varicella in children. A higher dose vaccine that prevents zoster in older adults is not licensed in Canada.

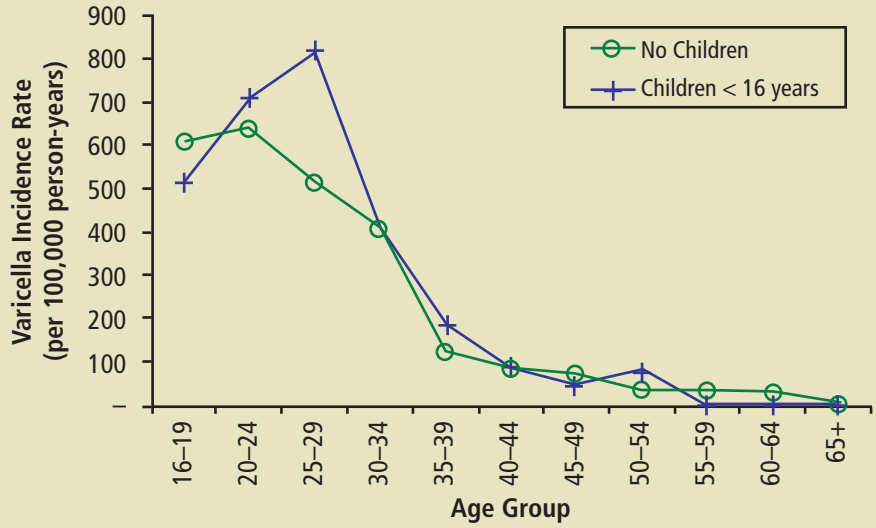
Widespread use of varicella vaccine may increase the incidence of HZ.[14,15] The constant circulation of wild-type varicella in the community has been shown to increase immunity throughout one's life and decrease the risk of developing zoster. This was observed in an

epidemiological study of adults living with or without children in the household.[14] Adults' exposure to varicella in the children was associated with an increased incidence of varicella in those individuals 16 to 34 years of age (Figure 1a) and a decreased incidence of zoster (Figure 1b) in adults in the household aged 35 and older. A similar conclusion was reached in a population-based case-control study showing that individuals exposed to wild-type varicella via contact with children had a graded reduction in the incidence of zoster.[15] Adults with the closest contact with children have up to one-fifth the rate of zoster compared to those with minimal contact.[15] With universal vaccination programs in effect, a reduction of circulating varicella is expected that may result in a future "epidemic" of zoster in the older population. One mathematical model has estimated a greater than 50% increase in the peak incidence of zoster compared to prevaccination numbers, with the largest effect in those in the 10–44 age group, this group having the most contact with young children now vaccinated (Figure 2).[14] Concurrently, the increase in zoster incidence in those previously infected with wild-type virus is projected to continue to increase in all age groups for the first 30–50 years before decreasing. However, the high-risk older adult population generally has much more limited exposure to children, and the two age groups are less likely to live under the same roof. Hence, the protection provided by exposure to wild-type VZV is therefore more limited in older adults. Consequently, the impact of universal varicella vaccination programs in children regarding the risk in the geriatric population may have been overstated.

Close monitoring of the incidence of zoster will be necessary to determine if the varicella vaccine causes an increase of zoster in excess of what would be expected due to an increasing aging population alone. Studies of the effectiveness of varicella vaccine in children show that effectiveness drops from 97% at one year to 84% from two to eight years following immunization.[16] Epidemiologic surveillance in parts of the U.S. has not identified increasing cases thus far.[17] One study monitoring varicella and zoster incidence seven years since the introduction of vaccination programs found that varicella incidence has decreased 65%. Although crude rates of zoster increased from 3.92 cases per 1,000 person-years during 1996 to 4.48 cases per 1,000 person-years during 2002, this increase disappeared once rates were adjusted for age, indicating the difference was due to an increase in the older adult population.[18] As zoster incidence does not follow the seasonal patterns seen with varicella, protection against zoster afforded by contact with wild-type varicella is not influenced immediately but rather over a prolonged time period.[2,16] Thus, it is still too early to be certain of varicella vaccination program effects on zoster incidence.

The widespread use of a vaccine to

Figure 1a: Varicella Incidence Rate for Adults Age 16 and Over



Source: Brisson M et al., 2002.[14] Reprinted with permission of Elsevier.

Figure 1b: Herpes Zoster Incidence Rate for Adults Age 16 and Over

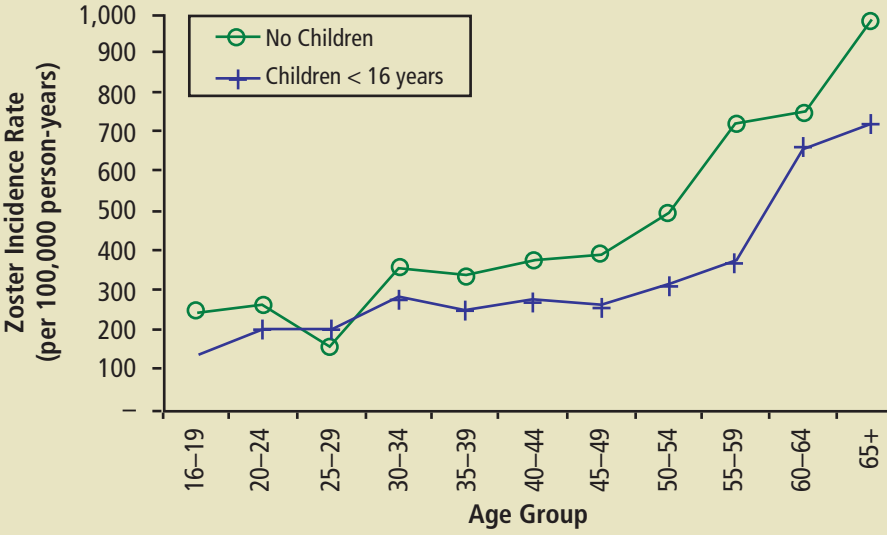


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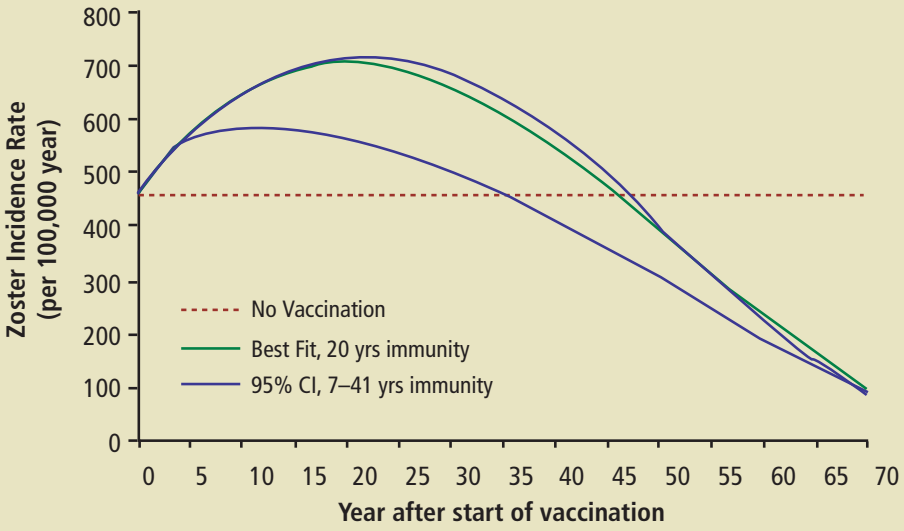
Figure 2: Effects of Varicella Vaccination on Zoster Incidence



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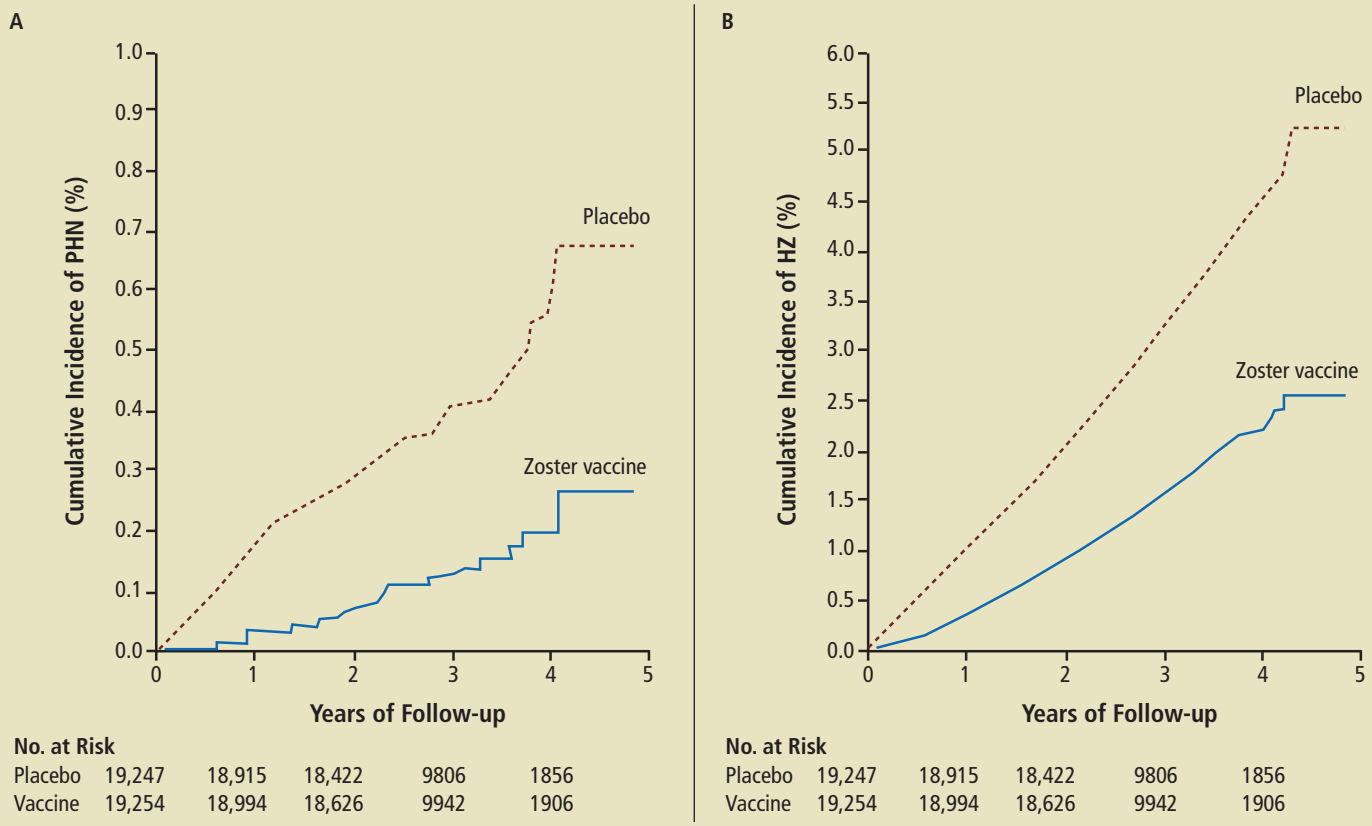
prevent herpes zoster in older adults can be expected to reduce the incidence of zoster. The concept of using VZV vaccination to boost CMI to prevent zoster has been looked at for years in adults. A number of small clinical studies demonstrated that boosting CMI in older individuals resulted in a reduced risk of zoster in this population.[7] This led to the recent large, randomized, double-blind, placebo-controlled trial by Oxman *et al.* of the Oka/Merck vaccine.[18] Of the 39,000 patients over the age of 60 enrolled, half were immunized with high-dose vaccine and in just over three years follow-up, the incidence of zoster was reduced from 11.12 to 5.42 cases per 1,000 person-years (51% reduction), PHN was reduced by 66%, and the burden of illness decreased by 61% (Figure 3a & 3b, Figure 4).

Future Impact of the Herpes Zoster Vaccine

Varicella zoster virus vaccination to prevent zoster would increase individual quality-adjusted life-years and may be cost-effective depending on the age the individual were vaccinated and the duration of immunity.[19] Although the available data are robust, many questions still remain such as the duration of immunity and the possible need for additional

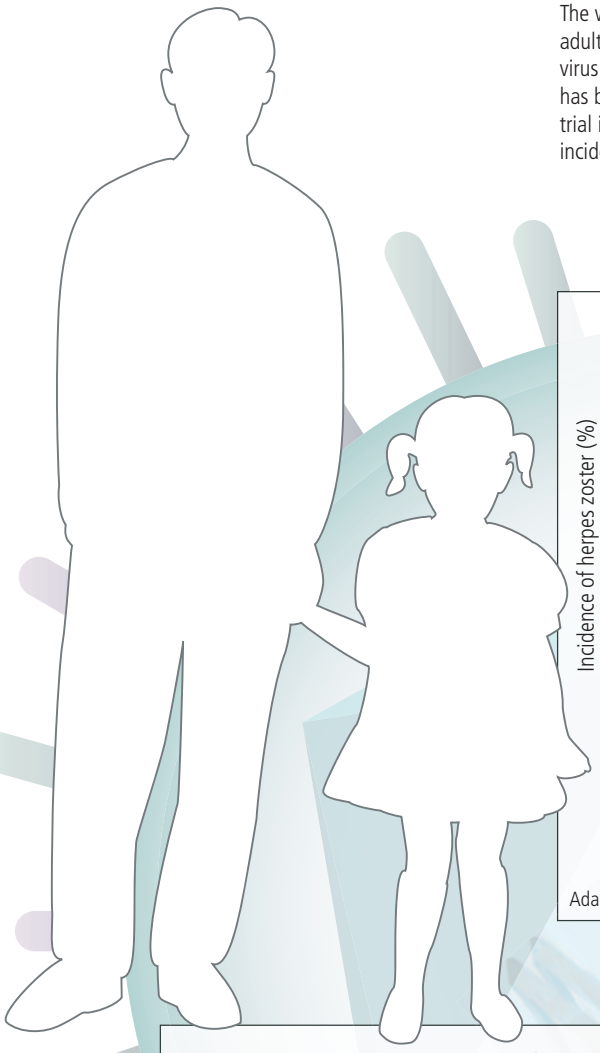
Figure 3: Incidence of Herpes Zoster and Postherpetic Neuralgia Postvaccination

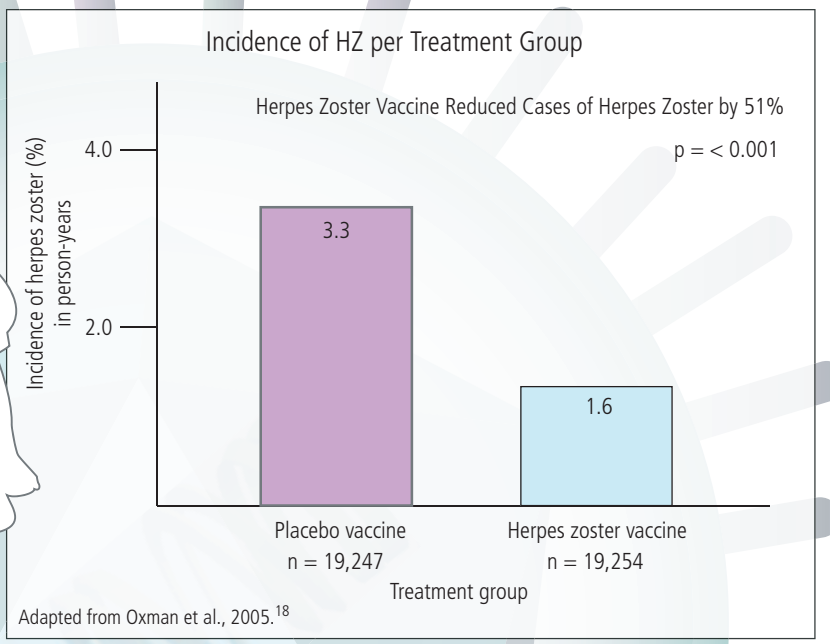


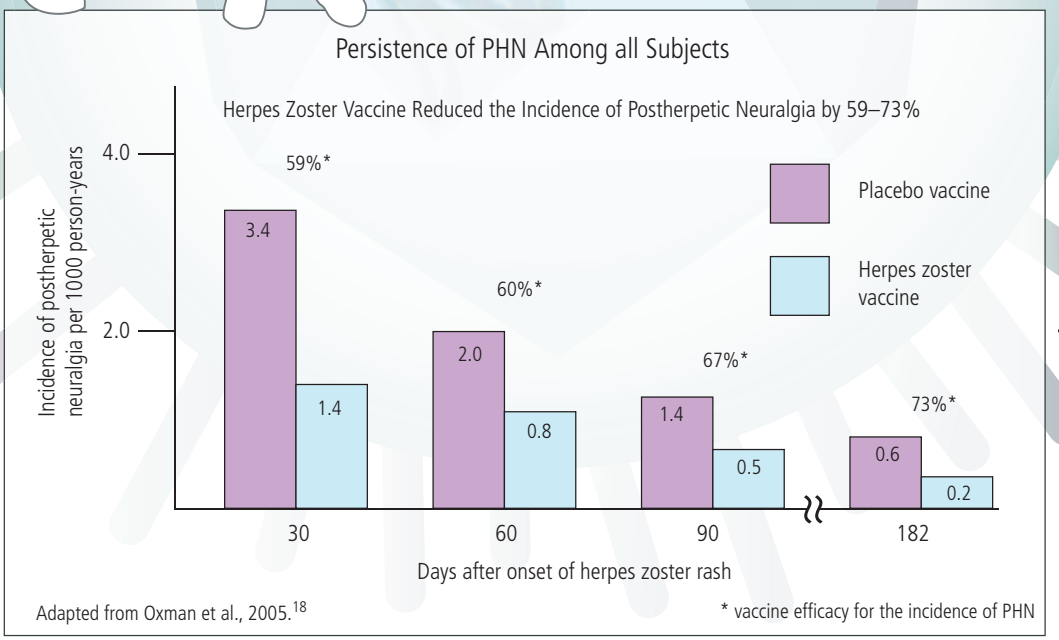
Source: Oxman MN et al., 2005.[18] Reprinted with the permission of the New England Journal of Medicine.

Figure 4: Herpes Zoster Vaccine Has Reduced the Cases of Herpes Zoster and Postherpetic Neuralgia

The widespread use of a vaccine to prevent herpes zoster (HZ) in older adults should reduce the incidence of zoster. The concept of using varicella zoster virus (VZV) vaccination to boost cell-mediated immunity (CMI) to prevent zoster has been looked at for years in adults. In a large randomized double-blind clinical trial in adults more than 60 years of age, a herpes zoster vaccine reduced the incidence of shingles and postherpetic neuralgia.







vaccine doses. Significant, although waning, protection against zoster lasting six years has been observed with high-dose VZV vaccine.[20] The median period of follow-up in the study by Oxman *et al.* was just over three years.[18] Moreover, the older adult population, particularly those over the age of 70, has diminished immune responses to vaccination. Collectively, these issues highlight the uncertainty of the impact of the herpes zoster vaccine on zoster epidemiology in the future.

Although the impact of childhood vaccination against varicella and of vaccinating older adults against zoster on the epidemiology of zoster is uncertain, the safety of vaccination has not been an issue. Generally, the vaccines have been well tolerated. There have been four reports of transmission of vaccine virus from healthy recipients of the varicella vaccine and no reports of reversion to clinical virulence among children vaccinated.[21] The zoster vaccine uses a much higher dose of virus and caused more injection site reactions than the placebo vaccine. Varicella-like rashes occurred more frequently at the injection site in vaccine recipients (0.1%) than in placebo recipients (0.04%). There were no differences in the frequency of serious adverse events in the two groups. The theoretical possibility of reversion exists. As an alpha-herpes double-stranded DNA virus, VZV has a large, relatively stable genome with a lower mutation rate than RNA viruses, such as HIV. A lack of knowledge regarding which mutations are responsible for attenuation, combined with a high inoculum of virus used to enhance immunity and an older population with reduced immune competence, results in an increased risk for disseminated infection among vaccines. This is a possibility that must be studied carefully.

Conclusion

It is not certain what the epidemiology of herpes zoster will look like in the future. The complex interplay of universal childhood vaccination against varicella, the possible widespread use of a herpes zoster vaccine in older adults to prevent herpes zoster, and the emergence of an increasingly aged population with perhaps more marked immune suppression due to age, disease, and pharmacotherapies make it difficult to predict how the future of herpes zoster will look.

Dr. Aoki has been an investigator in trials of antiviral drugs for the treatment of herpes zoster and/or the prevention of postherpetic neuralgia. Trials were sponsored by GlaxoSmithKline.
Dr. Skinner declares no competing financial interests.

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abstract

Herpes zoster often presents as a painful rash and is caused by reactivation of the varicella zoster virus. It is common among aging patients. The rash can usually be diagnosed clinically by its characteristic appearance and dermatomal distribution. Postherpetic neuralgia is the most common complication of zoster infection and can severely impair quality of life. Prompt antiviral treatment reduces the risk of developing postherpetic neuralgia. A vaccine for adults aged 60 years and older has been shown to effectively reduce the incidence of both herpes zoster and postherpetic neuralgia.

Key words: *herpes zoster, shingles, postherpetic neuralgia, older patients, vaccine*

Herpes Zoster and Postherpetic Neuralgia in Older Patients: Challenges in Diagnosis and Treatment

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Case Study

A 67-year-old man presents with a three-day history of intensifying pain of the left (L) anterior chest wall, extending to the L upper back and L neck. He has a history of angina, but describes this as more intense and as keeping him awake. An ECG is found to be normal and he is given analgesics.

Twenty-four hours later a vesicular eruption on an erythematous base develops over the area of pain (Figures 1a and 1b). It corresponds to the distribution of C3–C4 on the left. A swab taken from the base of a vesicle after the roof is removed is sent for direct fluorescent antibody testing. This test is positive for varicella zoster virus (VZV). As the diagnosis was made within 72 hours of the onset of the rash, antiviral therapy is initiated, the affected area is cleansed daily with normal saline, and an antibiotic cream and a nonadherent dressing are applied. Acetaminophen is prescribed regularly around the clock for analgesia, and codeine is prescribed p.r.n.

Healing occurs after one week, yet after another week he is still feeling significant pain and having difficulty sleeping. The movement of his clothing over the now-healed area causes significant discomfort. The analgesics are not controlling this discomfort and he is given a topical anesthetic. After two more weeks, nortryptiline is added. Two weeks later he is still very uncomfortable and the dose of nortryptiline is increased.

He returns two weeks later and is still experiencing significant pain. He complains of significant sleep deprivation and feelings of depression. Low-dose gabapentin is added and slowly titrated over two weeks, and some improvement is seen in the pain; however, significant drowsiness and dizziness are troubling him, and he is unable to take more than a moderate dose. Opioids are added, also starting with a low dose but titrating upward.

One year after the onset of the rash, ongoing gabapentin is required as well as opioid use. Although his sleep patterns are much better, the patient reports symptoms of continuing depression.

Introduction

Herpes zoster (HZ), commonly known as "shingles," is a neurocutaneous disease caused by reactivation of the varicella zoster virus (VZV). A painful unilateral vesicular rash, which usually resolves over a two-to-three week period, is the key characteristic of the disease. After a primary infection with VZV, the virus remains dormant in the dorsal root ganglia and the sensory ganglia of the cranial or spinal nerves, usually for several decades.[1] Reactivation of VZV is typically associated with declining VZV-specific immunity, and therefore occurs primarily in older patients and in the immunocompromised.

Herpes zoster is usually a self-limiting disease; however, complications may arise. The most common complication of HZ is chronic pain in the form of postherpetic neuralgia (PHN), which can have a significant impact on patient

Figure 1a: Herpes Zoster

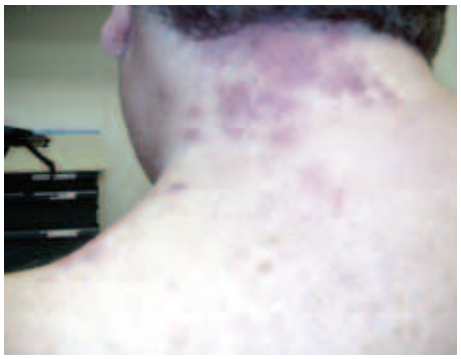


Figure 1b: Herpes Zoster

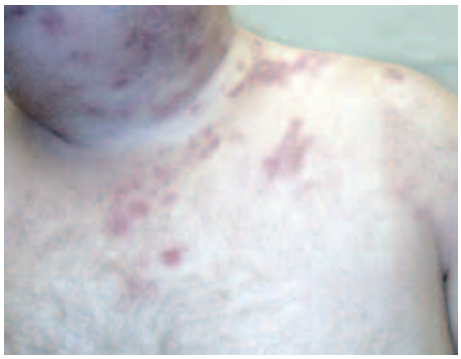
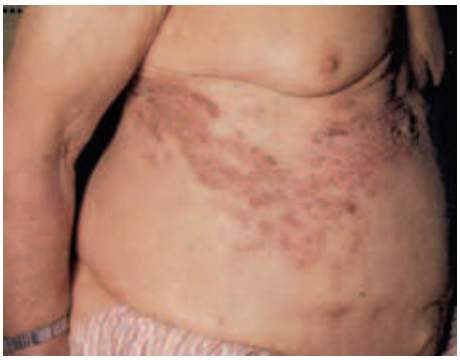


Figure 2: Thoracic Zoster



Note the dermatomal distribution.

quality of life. This complication is thought to result from inflammatory injury to sensory nerves, ganglia, and nerve roots. Other factors likely to be involved in PHN include disturbances in pain signaling responses and the failure of pain receptors to return to normal after the inflammation subsides.[3] Age is also the major risk factor for developing PHN, with approximately half of patients over age 60 who have HZ developing the condition, and approximately 75% of those aged 70 and over.[4] This review will focus on the diagnosis and treatment of HZ and its most common complication, PHN.

Clinical Presentation of Herpes Zoster

As mentioned in Dr. Madhuri Reddy's review, the cutaneous manifestation of HZ is often preceded by a prodromal phase lasting from one to four days. Pain associated with this phase may be misdiagnosed.

Initially, the HZ rash consists of erythematous macules and papules, which progress to vesicles within 24 hours. Three to four days later, pustules develop, followed by the formation of crusts after seven to 10 days. These usually fall off after two to three weeks; however, they may leave scarring or changes in skin pigmentation.

The rash is almost always limited unilaterally to a single dermatome or two dermatomes closely grouped together. Dermatomes most commonly affected, in descending order, are the thoracic (Figure 2), cranial (Figure 3), cervical (Figure 4), and lumbar (Figure 5) dermatomes. Herpes zoster may also affect the maxillary region and the eyes; ophthalmic zoster is considered a medical emergency since it can potentially lead to blindness.[4] Involvement of the V1 distribution of the trigeminal nerve, including the tip of the nose, warrants close observation for eye involvement (Figure 6).

Postherpetic Neuralgia

Postherpetic neuralgia is the most common complication of HZ. Pain that persists for more than 30 days after the rash heals or that arises 30 days after a pain-free interval indicates PHN. Women, as well as male patients with ophthalmic involvement, are at high risk of PHN. As noted, older adults are at the greatest risk of this complication, which can vary widely in extent and duration. Studies suggest that the incidence of PHN in HZ patients aged over 55, 60, and 70 years is 27%, 47%, and 73%, respectively.[2] Pain symptoms persist for eight weeks in almost half of patients with PHN, and less than a year in 78% of cases. For the remaining 22%, PHN may continue for a year or longer and there have been reported cases lasting as long as 20 years.[6] PHN has a considerable impact on quality of life, and the chronic pain associated with the condition can be considered to be as detrimental as that associated with other chronic diseases.

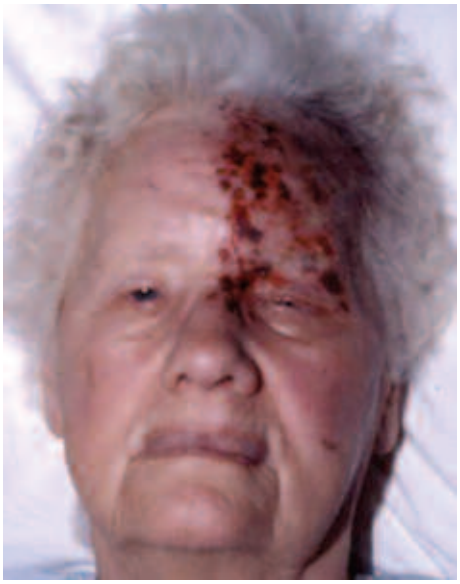
Diagnosis of Herpes Zoster

Diagnosis of HZ is usually made on clinical examination. The dermatomal distribution of the rash and characteristic pain and appearance of grouped vesicles are very distinctive. If the clinical presentation is not clearly indicative of HZ, or if herpes zoster is suspected in the absence of a cutaneous eruption in the prodromal phase, laboratory confirmation using polymerase chain reaction (PCR) is the most specific and sensitive diagnostic test.[2,3,5] Alternatively, or if PCR is not available, direct immunofluorescent antigen staining of skin lesion material is highly sensitive and is more rapid than viral culture. Serology is of limited use because the test has crossreactivity for herpes simplex virus; similarly, there is crossreactivity with herpes simplex using Tzanck tests.

Differential Diagnosis

In cases where the clinical presentation is atypical, HZ may be mistaken for other

Figure 3: V1 (Cranial) Distribution



Note the sharp cut-off at midline.

Figure 4: Cervical Zoster

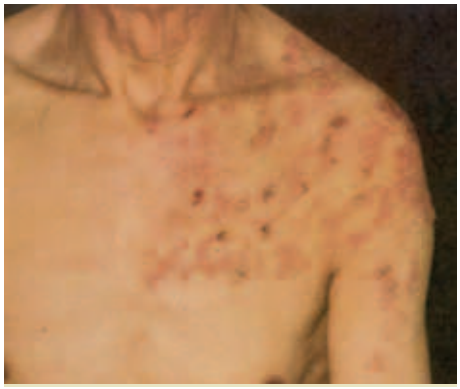


Figure 5: Lumbar Zoster

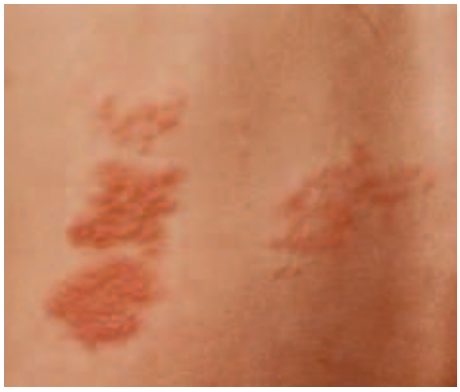
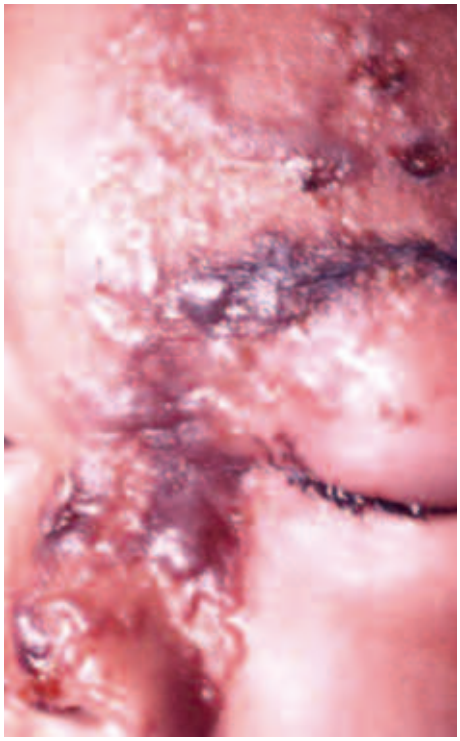


Figure 6: Involvement of the V1 Distribution of the Trigeminal Nerve



Location of eruption on V1 distribution along nose.

cutaneous conditions (Table 1). Laboratory confirmation using PCR or direct immunofluorescence of HZ should be undertaken when the diagnosis is not clear.

Treatment of HZ and PHN

Acute HZ is typically self-limiting. The primary goals of treatment are to relieve pain, limit the spread and duration of the rash and associated inflammation, and prevent or minimize the development of complications such as PHN. As previously stated, ophthalmic involvement constitutes a medical emergency, and patients should be immediately referred to a specialist for management.

Symptomatic treatment of HZ includes local treatment using topical agents and antisepsis. Nonstick dressings and topical lotions may provide some relief. Anesthetic creams may help alleviate pain. Acute pain associated with the rash can usually be managed with analgesics such as acetaminophen or, if this is inadequate, opiates.

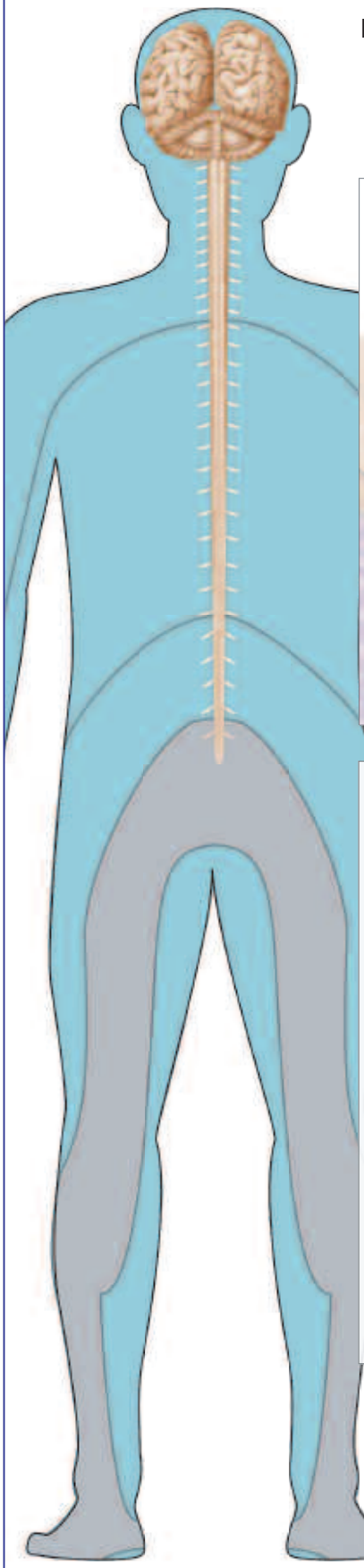
Antiviral therapy is particularly important for patients with more severe rash, with immunodeficiencies, or malignant primary disease, as well as for patients over age 50, who are at high risk of developing PHN.[2,3] Patients with cranial or ophthalmic involvement should promptly receive antiviral therapy. In general, the earlier antiviral treatment is initiated, the better the prognosis. Treatment initiation within 48 to 72 hours after the onset of the rash reduces the severity and duration of acute symptoms, and may help prevent or minimize the extent of PHN. The "50-50-50 rule" may be helpful as a general treatment guide: initiate antiviral treatment 50 hours or less after the appearance of skin lesions, in patients 50 years and older, or in those with 50 or more lesions.[5]

The most common antiviral treatments for acute HZ include oral acyclovir, famciclovir, or valacyclovir for seven days. All three medications have been shown to effectively alleviate pain endpoints and reduce the duration of symptoms, particularly in older patients, and are generally safe and well-tolerated.[2,3,7] Acyclovir is available in an oral and parenteral form. Valacyclovir and famciclovir are dosed three times daily, while acyclovir is dosed five times daily. Table 2 summarizes the antiviral therapies for the treatment of HZ. Therapeutic

Table 1: Differential Diagnosis of Herpes Zoster

Condition	Clinical Features
Herpes simplex virus	Vesicles on an erythematous background
Erysipelas Hemorrhagic Bullous	Orange-peel appearance, well-delineated advancing margins
Impetigo	Features of generalized pustular psoriasis with symmetry and grouping of areas of pustulation
Folliculitis	Asymptomatic eruption of chronic follicular papules occurring mainly on the limbs with one or more perforations into the dermis
Contact dermatitis	Localized vesicles and bullae on erythematous skin (acute); erythematous lichenified plaques (chronic)
Insect bites	Often firm papules or nodules surrounded by an erythematous area
Drug eruptions	Various morphologic patterns and lesions; exanthematic reactions are the most frequent

Figure 7: Preventive and Antiviral Treatments for Herpes Zoster

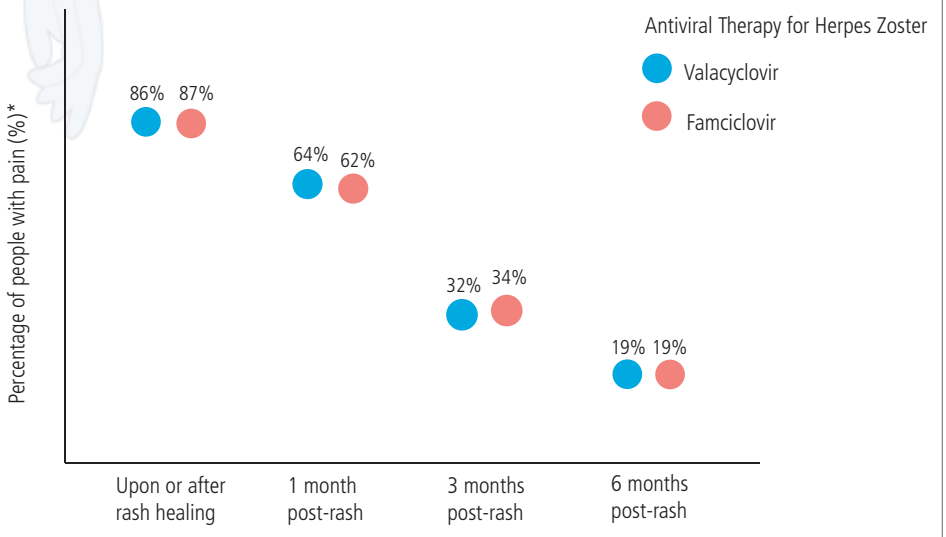


Prevention: Herpes Zoster Vaccine

- Reduces herpes zoster pain/burden of illness by 61%
- Reduces herpes zoster by 51%
- Reduces postherpetic neuralgia by 67%
- Increases varicella zoster virus–specific CMI response
- Has an excellent safety profile
- Efficacy for herpes zoster and postherpetic neuralgia endpoints was demonstrated through 48 months of follow-up

Oxman M et al., 2005.[10]

Proportion of Patients with Pain



Tyring SK et al., 2000.[11]

*total number of people = 597

Common areas of herpes zoster distribution: thoracic, cranial, cervical, and lumbar dermatomes

Table 2: Antiviral Treatment for Herpes Zoster

Antiviral Medication	Dosage
Acyclovir	800 mg 5 times daily for 7 days
Famciclovir	500 mg 3 times daily for 7 days
Valacyclovir	1000 mg 3 times daily for 7 days

value agent-to-agent is similar and costs are equal; however, t.i.d. dosing is seen as preferable.

There is contradictory evidence to support the use of corticosteroid therapy for the management of HZ. When added to antiviral treatment with acyclovir, corticosteroids may shorten the duration of acute HZ pain, but there has been no beneficial effect noted for the chronic pain of PHN.[8,9] The side effect profile and risks associated with corticosteroids may outweigh the potential benefits in patients with comorbidities such as diabetes, renal insufficiency, and hypertension.

Once PHN is established, simple analgesics may not adequately relieve pain, and oral medications may be required, as Dr. C. Peter N. Watson notes in his discussion. Simple measures that patients can adopt to alleviate discomfort include wearing loose clothing or using cling film to shield sensitive skin from irritation.[4] These interventions may be particularly relevant for patients with allodynia.

Given the high incidence of PHN in the older population with HZ, treatment should be individualized based on comorbid conditions and concomitant medications, as well as underlying renal dysfunction and its effects on drug metabolism.

Figure 7 depicts preventive and antiviral treatments for herpes zoster.

Prevention of HZ

Vaccination against VZV in children is likely to reduce the incidence of HZ over time but will not benefit the large population of people who currently have a latent infection with the virus. For high-risk groups such as people who are immunocompromised, varicella zoster immune-globulin may reduce the risk of development of HZ by approximately 50%.[6]

Adults in the general population may also benefit from vaccination against VZV. A recent study evaluated the effectiveness of a vaccine against VZV to reduce the incidence and severity of HZ and PHN in more than 38,000 adults aged 60 years and older.[10] Vaccination significantly reduced the incidence of HZ by 51% and of PHN by 66%. Importantly, the vaccine was effective across the different age strata, with similar efficacy across different dermatomal regions, including the ophthalmic branch of the trigeminal nerve.

Acute HZ can be transmitted to people who have not had prior exposure to VZV. Therefore, patients in institutional settings should be isolated to prevent dissemination to susceptible individuals.

Conclusion

Shingles, or herpes zoster, is a common condition among older patients, with incidence rates rising markedly with advancing age. It can usually be diagnosed on clinical grounds, based on the characteristic appearance and dermatomal distribution of the rash. The major complication of HZ is a postherpetic neuralgia, which can seriously impair quality of life. While HZ is self-limiting condition and can be treated with simple analgesics, older patients should be promptly treated with antiviral medication as they are at increased risk of developing PHN. Once PHN is established, management should be individualized. The prospect of a vaccine that can prevent HZ or reduce the risk of PHN for those over 60 is extremely exciting.

Dr. Landells has acted as a consultant on advisory boards for GlaxoSmithKline, Novartis and Merck and done clinical trials as an investigator for Novartis and GlaxoSmithKline.

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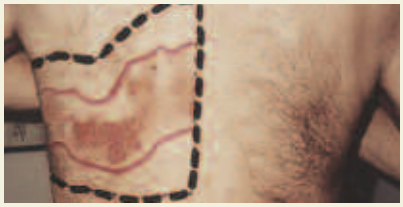
abstract



Herpes zoster (HZ) affects more than 130,000 individuals per year in Canada, and about 20,000 will have postherpetic neuralgia (PHN) at one month after the rash. As many as half of these individuals will experience insufficient pain relief, and many suffer indefinitely. The most established risk factor is age, and as many as 75% at age 70 and above will develop PHN. With the expected upward shift in age demographics we can expect an increased incidence of both HZ and PHN. Despite the availability of antivirals to treat HZ the effect of these and other therapeutic measures is limited and difficult to initiate promptly. Once established, PHN is challenging to treat. For all these reasons the advent of an effective vaccine to prevent herpes zoster holds great promise.

Key words: *herpes zoster, postherpetic neuralgia, antivirals, vaccine, pain*

Managing the Pain of Herpes Zoster and Postherpetic Neuralgia in the Older Adult Population

C. Peter N. Watson, MD, FRCPC, Assistant Professor, Department of Medicine, University of Toronto, Toronto, ON.

Case Report

An 80-year-old female with lung cancer metastatic to the brain developed severe herpes zoster (HZ), treated in 24 hours with valacyclovir, and subsequent postherpetic neuralgia (PHN) in the left breast area. She had already suffered severe pain for eight months when first seen. All treatments failed to provide good relief, including gabapentin, various antidepressants, and opioids. She continued to suffer severe pain until her death six months later.

Introduction

The above vignette illustrates the difficulty in managing HZ and PHN, even with early antiviral treatment of HZ and the best drugs for neuropathic pain titrated to maximum effect. Herpes zoster is common and PHN is its most frequent and feared complication. The incidence of both disorders is directly related to age so that with an aging population we can expect a further increase in both conditions. This article will review the definition, epidemiology, pathology, putative pathogenesis, clinical features, and prevention and treatment of PHN, focussing on the older adult population.

Antiviral drugs are limited in their ability to prevent PHN and other complications of HZ. Established PHN is difficult to treat, and as many as 50% of patients find inadequate pain relief despite our best measures, including opioids. The prospect of the effective prophylaxis of many cases of HZ by vaccination of the older population is a critical development. I will discuss the findings of high-quality randomized controlled trials (RCTs) of treatment approaches based on a systematic review (Medline, Pubmed) and the quality assessment tool of Jadad *et al.*[1]

General Considerations

Definition

Postherpetic neuralgia is pain along the course of a nerve following the characteristic rash of HZ (Figure 1). A commonly used and more specific definition of PHN is pain persisting after the rash has healed (usually one month). Because of the tendency for pain to diminish with time after one month by reason of the natural history, some investigators studying therapeutic approaches have chosen a longer period of three months after disease onset.

Incidence, Natural History, and Demographics of PHN

The incidence of PHN (defined as pain persisting for more than one month) has been variously estimated from 9–14%.[2] Despite this overall low incidence and marked early tendency for PHN to improve with time, the incidence is directly related to age. About 50% of adults at age 60 and nearly 75% at age 70 with HZ progress to PHN one month or more following the rash.[2] With childhood varicella vaccination the lack of natural boosts of immunity brought about by contact between older adults and children with chicken pox may also result in more HZ.

Pathology and Pathogenesis

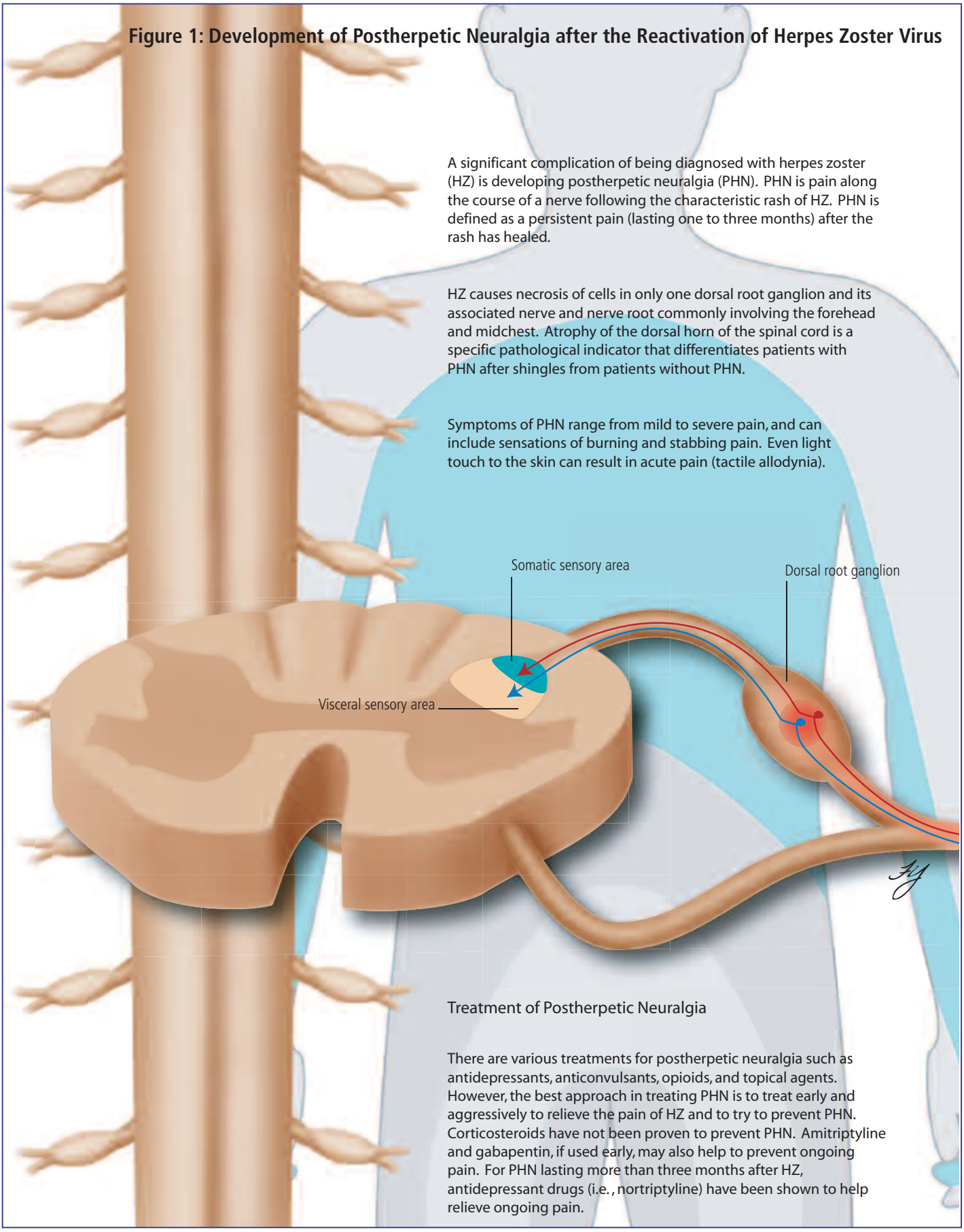
Zoster is caused by the reactivation of the varicella virus that lay dormant in

Figure 1: Development of Postherpetic Neuralgia after the Reactivation of Herpes Zoster Virus

A significant complication of being diagnosed with herpes zoster (HZ) is developing postherpetic neuralgia (PHN). PHN is pain along the course of a nerve following the characteristic rash of HZ. PHN is defined as a persistent pain (lasting one to three months) after the rash has healed.

HZ causes necrosis of cells in only one dorsal root ganglion and its associated nerve and nerve root commonly involving the forehead and midchest. Atrophy of the dorsal horn of the spinal cord is a specific pathological indicator that differentiates patients with PHN after shingles from patients without PHN.

Symptoms of PHN range from mild to severe pain, and can include sensations of burning and stabbing pain. Even light touch to the skin can result in acute pain (tactile allodynia).



Treatment of Postherpetic Neuralgia

There are various treatments for postherpetic neuralgia such as antidepressants, anticonvulsants, opioids, and topical agents. However, the best approach in treating PHN is to treat early and aggressively to relieve the pain of HZ and to try to prevent PHN. Corticosteroids have not been proven to prevent PHN. Amitriptyline and gabapentin, if used early, may also help to prevent ongoing pain. For PHN lasting more than three months after HZ, antidepressant drugs (i.e., nortriptyline) have been shown to help relieve ongoing pain.

sensory nerves subsequent to a bout of primary varicella. A search for an underlying condition causing immunosuppression such as malignancy is not warranted in the usual patient. Herpes zoster causes necrosis of cells in only one dorsal root ganglion and associated nerve and nerve root most commonly involving the forehead and midchest. Atrophy of the dorsal horn of the spinal cord is a specific pathological finding that differentiates patients with PHN after shingles from those without.[2]

Clinical Considerations

Clinical Features

When the acute rash has healed, the affected skin often exhibits a reddish discolouration (Figure 2) that subsides and leaves pale scarring. Occasionally, severe pain with no residual scar may occur and in very long duration cases the scars are barely perceptible. The scarred areas are usually at least hypoesthetic and often anesthetic, and yet the skin often exhibits marked pain on tactile stimulation (allodynia). A steady burning sensation may occur and also jabbing pain. Both may occur spontaneously and are often aggravated by light touch such as friction from even the lightest clothing.

The examination of the scarred skin usually reveals a loss of sensation to pinprick, temperature, and localized touch over a wider area than the scars with paradoxically sensitive or painful skin-to-skin stroking (dynamic allodynia) in this anesthetic area and a more extensive area.

Prevention

Results of a large trial of vaccination (with a live attenuated varicella vaccine 14 times as potent as the childhood varicella vaccine) indicate a protective effect against HZ in vaccinated older age groups with 50% reduction in HZ in those over 60 and a reduction in PHN by 66%.[3] The other preventive avenue is to treat herpes zoster early and aggressively. This would require education of the general population so that patients would recognize the symptoms of zoster, contact a physician, and make arrangements to be seen and treated promptly. Physicians' secretaries, nurses, and physicians also need to realize the importance of scheduling the patient on the day of the call for immediate treatment. There are several possible approaches for the early therapy of herpes zoster. First, it is important that antiviral therapy with valacyclovir or famciclovir be initiated within 72 hours of the onset of pain or rash in order to inhibit viral replication. There is a modest reduction in PHN with this approach (less than 30%).[2] A second scientifically unproven but reasonable measure is the early, aggressive use of analgesics (including opioids if necessary in severe instances) to prevent the development of sensitization of the nervous system. Third, there is some uncontrolled evidence[2] that nerve blocks may help to resolve severe acute pain and to prevent PHN, although further studies are needed. It has been suggested that early therapy with amitriptyline[4] (10–20 mg at bedtime) and gabapentin (900 mg) at the stage of herpes zoster may help to prevent ongoing pain. The dose of amitriptyline can be titrated every few days by similar increments until relief occurs or side effects supervene.

The Treatment of Established Postherpetic Neuralgia

There are four main categories of drugs for treating PHN. These are specific antidepressants, anticonvulsants (gabapentin and pregabalin), opioids, and topical agents (especially the lidocaine patch).

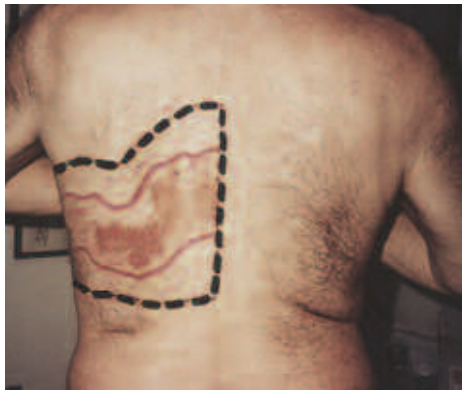
Antidepressants

RCTs

A double-blind, placebo-controlled, crossover trial of amitriptyline found good results in 67% of patients treated.[5] Most patients were not depressed, and relief of steady burning as well as jabbing occurred without a change in depression ratings in most patients, indicating that the drug appeared to result in pain relief independently of an antidepressant effect. This analgesia occurred at lower doses than usually used to treat depression (median 75 mg). A subsequent trial has corroborated these results.[6] Amitriptyline has limitations in the long term because of side effects; additionally, relief is rarely complete and occurs in only about one-half to two-thirds of patients. One of the effects of this drug is to potentiate both serotonin and noradrenaline in the central nervous system. Subsequent research has explored whether selective serotonergic or noradrenergic antidepressants might be more effective. Experience with serotonergic agents (such as fluoxetine) in PHN has been disappointing. The evidence supporting the use of noradrenergic agents is more compelling.[7–9]

Desipramine, a selective norepinephrine reuptake inhibitor, has been shown by randomized controlled trials (RCT) to be more effective than placebo in PHN and pain relief with this drug as well was found not to be mediated by mood elevation.[7] An RCT comparing maprotiline (noradrenergic) with amitriptyline found that both were effective.[8] A comparison of nortriptyline (more noradrenergic) with amitriptyline by RCT showed about equal efficacy for both drugs but fewer side effects with nortriptyline.[9] We recommend nortriptyline as a first-line agent because of this. Raja *et al.*[10] conducted an RCT comparing desipramine and nortriptyline with morphine and methadone. Both antidepressants were found to be effective, but they found a trend favouring opioids.

Figure 2: A Case of Postherpetic Neuralgia



The dotted line demarcates a wide area of touch-evoked pain and pigmented scarring.

Anticonvulsants

Quality RCTs

Gabapentin has been proven superior to treatment with placebo for individuals with PHN in a double-blind, randomized, multicentre trial; 43% of the patients reported at least moderate improvement (versus 12% with placebo).[11] A dose of 3,600 mg/d was aimed for in this trial and many patients achieved that.

A second successful trial of gabapentin[12] (Rice *et al.*) utilized doses of 1,800 mg/d versus 2,400 mg/d versus placebo. Dworkin *et al.*[13] studied pregabalin in a placebo-controlled trial in PHN. These authors found that 50% of patients had 50% or greater improvement versus 20% on placebo.

Opioids

RCTs

An RCT of sustained-release oxycodone demonstrated that 58% of patients experienced at least moderate improvement in pain versus 18% on placebo.[14] Raja *et al.*[10] conducted a comparative RCT in PHN and found a trend for morphine and methadone to be more effective than the antidepressants nortriptyline and desipramine. Boureau *et al.*[15] reported a modest but favourable effect in a placebo-controlled RCT of tramadol, which has opioid and monoaminergic effects. Although percent pain relief was higher with tramadol, there was no difference in pain intensity or quality of life; thus, the effect did not appear to be a strong one. A variety of sustained-release oral opioid preparations are now available and may be of advantage, including codeine, morphine, oxycodone, and hydromorphone, as well as a transdermal preparation of fentanyl.

Topical Agents

Topical therapies for PHN fall into three main categories: capsaicin preparations, acetylsalicylic acid (ASA) and other nonsteroidal anti-inflammatory preparations, and local anesthetics. The reader is referred to a more comprehensive review,[2] but this article will limit discussion to capsaicin and local anesthetics.

Capsaicin remains controversial. Several hundred patients have now participated in controlled and uncontrolled clinical trials, yet reported results diverge widely, with some investigators reporting no benefit in well-designed, controlled studies.[2] Other have reported success rates for capsaicin that seem extraordinarily high for a condition long thought to be among the most intractable of chronic pain syndromes.[2] Crushed ASA can be mixed with petroleum jelly, lotion, chloroform, or ethyl ether and is internationally available, but the latter two vehicles have their obvious problems in the aged.

The specific analgesic mechanism of action of topical local anesthetics applied for the pain of PHN is unknown. Damaged and regenerating nerve endings express changes in number and location of sodium channels, the target of local anesthetic drugs.

Lidocaine has been formulated into adhesive patches (Lidoderm®) with a soft, woven backing that can be applied to cover the area of pain. A randomized, placebo-controlled trial has demonstrated the benefit of lidocaine patches.[16] The majority of subjects reported partial pain relief with 10 of 35 noting moderate or better relief. This patch is not yet available in Canada.

Surgical Therapy

Surgical procedures for postherpetic neuralgia have been much studied and are not useful for most patients with PHN.[2]

A Summary of Practical Guidelines for Prevention and Treatment of Postherpetic Neuralgia

Most of the putative preventive approaches (except antivirals) to PHN can be regarded as not conclusively established by more than one controlled trial with adequate numbers of patients. Pending final proof, it is reasonable to treat patients early and aggressively to relieve the pain of HZ and to try to prevent PHN if the therapy is safe and well tolerated. It is important to recognize that the population at highest risk for PHN is older adults 60 years of age and over, who may have a risk of 50% or more of developing this complication.

There is no good evidence supporting the use of corticosteroids to prevent PHN. As noted, valacyclovir and famciclovir, which exert a modest effect at preventing PHN, should be given within the first 72 hours. Amitriptyline[4] and gabapentin, if used early, may also help to prevent ongoing pain. Although no controlled trial has ever been done of nerve blocks to treat HZ pain or prevent PHN, they are reasonable and safe in experienced hands for severe pain and may be repeated, if effective, as symptoms dictate. The use of nonsteroidal anti-inflammatory drugs and opioids are justified to relieve severe pain with the acute illness. Whether better control of acute pain will reduce the occurrence of PHN needs to be evaluated. There are significant problems, though, in starting these therapies within 72 hours of onset of rash and pain. The future will likely include the routine vaccination of older adults to prevent HZ and hence PHN, and may be the best way of dealing with these often intractable disorders.

For established PHN (persisting more than three months after HZ) the most consistently effective agents appear to be the older antidepressant drugs. Several RCTs indicate that pain may be taken from moderate or severe to mild in about one-half of two-thirds of patients. We tend to commence with nortriptyline (fewer side effects than amitriptyline) in a dose of 10 mg before bedtime in those over 65 years and with 25 mg in those 65 or under. The dose is increased by similar increments in a single bedtime dose every 7–10 days until relief is obtained or side effects supervene. If those fail, we then usually try amitriptyline or imipramine and then a noradrenergic agent, such as desipramine. Antidepressants proven useful in other neuropathic pain states by RCT may be worth trying (bupropion, venlafaxine, or topical doxepin). We routinely prescribe a stool softener and mouth spray to counter anticholinergic effects. In patients with contraindications to the analgesic antidepressants, such as those with prostatism or cardiac arrhythmia, or in those with sedation, an alternative approach is to

Key Points

Herpes zoster is difficult to treat; treatment must be instituted early after the onset of the rash and pain in order to prevent complications such as postherpetic neuralgia.

Postherpetic neuralgia is often poorly relieved or intractable.

The population at highest risk for PHN is the age group 60 years and over, who may have a risk of 50% or more of developing this complication.

Currently available therapies for HZ and PHN include analgesic antidepressants, anticonvulsants such as gabapentin, and a variety of short- and long-acting opioids; available topical agents are simple and free of systemic effects but are probably best as adjuvant agents.

Vaccination of the older adult population is likely to be crucial in the prevention of herpes zoster and postherpetic neuralgia.

use the anticonvulsants, i.e., gabapentin increased to as much as 3,600 mg/d in divided doses or pregabalin up to 300 mg twice daily.

It is our common practice with resistant cases to prescribe analgesics, including opioids, on an as-needed and/or round-the-clock basis. A variety of short- and long-acting opioids are available. The dose can be increased to satisfactory relief or unacceptable side effects. The use of topical agents is attractive as it is simple and free of systemic effects. These can be used as sole therapy but are probably best as adjuvant agents. These include capsaicin, acetylsalicylic acid, and local anesthetic agents. Transcutaneous electrical nerve stimulation (TENS) may be worth trying. Electrode placement, frequency, intensity, and duration of stimulation are a matter of trial and error. Some patients may benefit from nerve blocks which, if efficacious, may be repeated at appropriate intervals; however, scientifically based data regarding the efficacy of nerve blocks for either prevention or long-term treatment of PHN are not available. Approximately 50% of patients, including even those with long-standing pain, improve slowly over the years with one-half of these eventually being on no treatment,[2] but this leaves many poorly relieved or intractable.

The incipient advent of vaccination of the older adult with a live attenuated vaccine 14 times as potent as the childhood varicella vaccine is, in the author's view, a major advance in preventing these frequently intractable disorders.[3]

Dr. Watson has been a speaker for Purdue Pharma Canada and is currently working with Merck Canada as a speaker and in preparing educational material prior to the launch of a zoster vaccine.

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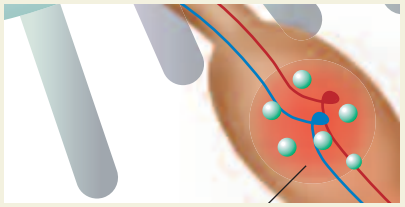
abstract



New tools are at our disposal for the prevention and management of herpes zoster. A preventive vaccine is under development that could reduce the incidence of zoster and its complications in older adults. Antiviral treatment with valacyclovir or famciclovir reduces the duration of an acute episode and shows a small benefit in reducing the risk of postherpetic neuralgia. Postherpetic neuralgia, once established, may be a therapeutic challenge. However, topical analgesia (lidocaine patch or gel), gabapentin, pregabalin, tricyclic antidepressants (TCAs), opiates, and pain clinic referral may constitute components of a graded treatment approach. Caution is required with TCAs and opiates in older adults.

Key words: *herpes zoster, postherpetic neuralgia, valacyclovir, famciclovir, immunization*

Prevention and Management of Herpes Zoster in Older Adults

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Case Study

A 72-year-old man presents with a painful unilateral rash in the distribution of the ophthalmic branch of the trigeminal nerve (Figure 1). How would this problem best be managed? Could it have been prevented?

Introduction

Clinical Course and Diagnosis of Herpes Zoster

Herpes zoster is a common problem among older adults and is expected to increase in incidence with an aging population in Canada. As previous articles have described, the natural history of varicella zoster virus (VZV) infection begins with varicella (chicken pox).[1] When reactivation does occur, VZV begins replication in the sensory nerve ganglion (Figure 2). This process, together with inflammation directed against newly expressed antigens, is responsible for the dermatologic features and neuropathic pain so typical of an episode of zoster. Acute neuritis may be accompanied by a painful prodrome three or more days before presentation of a dermatomal rash.

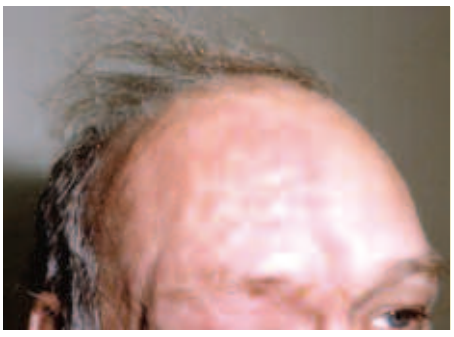
Antegrade transport of VZV down the sensory nerve leads to viral replication in the skin and the characteristic dermatomally distributed rash; characteristic lesions at progressive stages of evolution are displayed in Figures 3a–d. As noted, zoster may occur in any dermatome but is most common in a thoracic distribution (50–55% of cases) followed by cranial, lumbar, cervical, and sacral distributions.[2] Laboratory confirmation of the clinical diagnosis of zoster is not necessary for diagnosis in most cases.

Following acute zoster, many individuals will suffer from prolonged zoster-associated pain. As noted by the previous authors, significant pain persisting after three months is commonly referred to as postherpetic neuralgia (PHN) and signals that axons and peripheral nerves have been damaged by VZV. This, coupled with altered signal processing in the central nervous system (CNS), not only causes pain but may also induce hyperactive pain responses to normally non-noxious stimuli, termed allodynia.

The Linked Epidemiology of Chicken pox and Zoster

Chicken pox (varicella) has been a universal infection of childhood. In temperate and northern climes, infection has generally taken place by the age of ten. Chicken pox is seldom serious in young patients but can be complicated by neurological

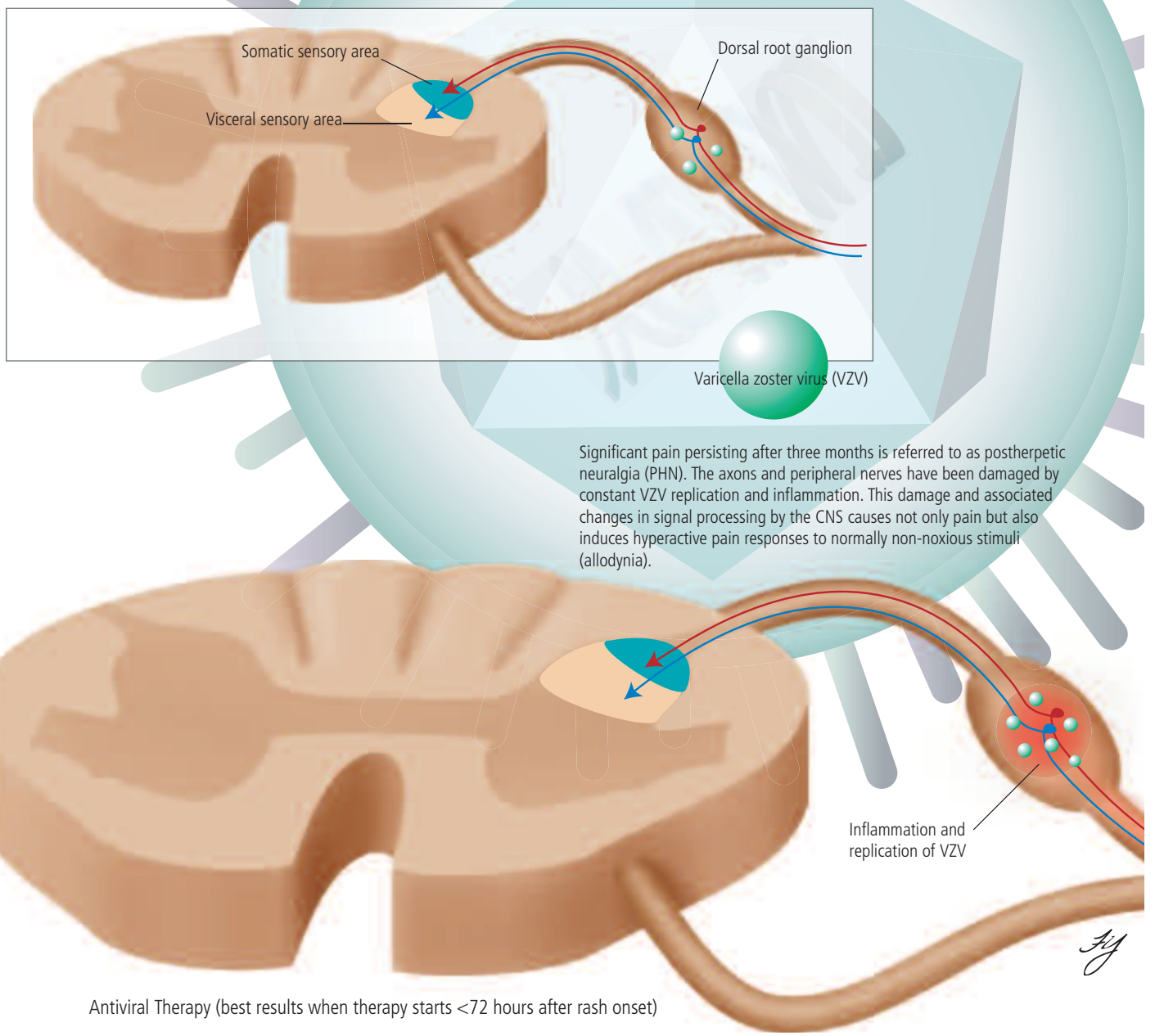
Figure 1: Herpes Zoster



Distribution is along the opthalmic branch of the trigeminal nerve.
All photos courtesy of Dr. Hank Balfour

Figure 2: Reactivation of Varicella Zoster Virus and Antiviral Therapy after Diagnosis

The origin of varicella zoster virus (VZV) begins with varicella (chicken pox). Reactivation and replication of VZV takes place in the sensory nerve ganglion within the dorsal root. As the body tries to fight off the virus, inflammation results, leading to the dermatologic features and neuropathic pain typical of an episode of zoster. Antegrade transport of VZV down the sensory nerve leads to viral replication in the skin and results in rash along the associated dermatome. The most common dermatome affected by VZV is the thoracic region followed by cranial, lumbar, cervical, and sacral distributions.



Significant pain persisting after three months is referred to as postherpetic neuralgia (PHN). The axons and peripheral nerves have been damaged by constant VZV replication and inflammation. This damage and associated changes in signal processing by the CNS causes not only pain but also induces hyperactive pain responses to normally non-noxious stimuli (allodynia).

Antiviral Therapy (best results when therapy starts <72 hours after rash onset)

Oral valacyclovir (1000 mg) or famciclovir (500 mg) can be provided to patients who are immunocompetent and are demonstrating signs of moderate to severe pain or eye involvement. Acyclovir (10 mg/kg) can be prescribed to patients who are immunocompromised or with disseminated cutaneous or visceral herpes zoster.

complications, severe skin infections, dissemination, and, uncommonly, death. The average age of infection is older in the tropics.[3] This can be a concern because there is a higher rate of dissemination and complication among adults who get varicella when compared with children.

Varicella immunization of children with live attenuated Oka strain vaccine has been a boon for the immunized cohort.[4,5] Death and hospitalization rates from varicella have plummeted where uptake has been high, and there are sound early observations to suggest that the risk of zoster is lower in this cohort than in those who have been infected by wild-type varicella.[6,7]

The Effect of Immunization on Future Disease Expression

Varicella immunization could lead to two principle effects that may affect those not protected by vaccine. First, as was observed with rubella immunization, immunization campaigns achieving only low rates of coverage could result in an increase in the mean age of infection. If this meant that more people were infected with chicken pox at an older age, there could be an increase in the rate of complications. However, mathematical models indicate that if immunization programs were to achieve a high level of uptake and were accompanied by some efforts to catch up older susceptible people, this would not lead to an increase in incidence and morbidity of varicella disease in older individuals.[8]

A second concern linked to varicella immunization is that less circulating VZV might lead to a loss in immunological "boosting" of those who have already had chicken pox and a possible increase in the rate of zoster among them. To understand this issue, it is worthwhile revisiting the foundational hypotheses of the late Dr. Edgar Hope-Simpson.[9,10] Hope-Simpson postulated and proved that zoster was a consequence of reactivating VZV. He also suggested that a decline in immunity with aging accounted for the increasing incidence of disease among older adults and that exposure to VZV boosted immunity. Several cohort studies, including Hope-Simpson's own, showed a great increase in incidence of zoster with age, particularly after the age of 65 (Figure 4).[11] Incidence in these studies increased from 50 cases per 100,000 per year in those under 14 to over 400 per 100,000 in those over 75. If Hope-Simpson was correct, there is the possibility that zoster incidence will transiently increase among present-day adults. Early observations do not allow us to draw firm conclusions. Some studies have demonstrated the possibility of an early effect while others have been negative.[12,13] Continued surveillance of the age-adjusted incidence of zoster is warranted in order to ascertain if an increase in zoster incidence will be real and sustained.

Complications of Zoster

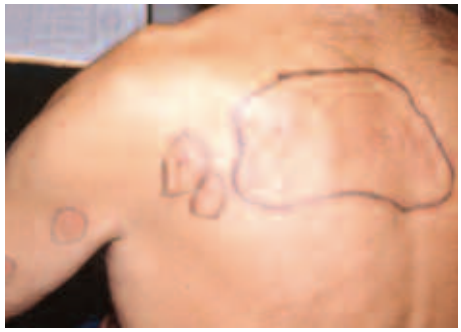
As noted, PHN is by far the major complication in otherwise healthy adults. Other problems include ocular complications of trigeminal nerve involvement, visceral dissemination in immunocompromised patients (for example, pneumonia or hepatitis), central nervous system complications, and complicated cutaneous presentations.[2]

Zoster-Associated Pain

Any pain associated with zoster has been termed zoster-associated pain. People generally distinguish between prodromal pain experienced before the rash is evident, acute pain experienced with the rash, and pain continuing long after the rash has healed or PHN. Most rigorous definitions of PHN allow for approximately three months of persistence after the acute episode and some indication of the sensation being more than trivial. Discomfort due to zoster is not always characterized as pain per se. Allodynia and pruritus can be very disruptive.

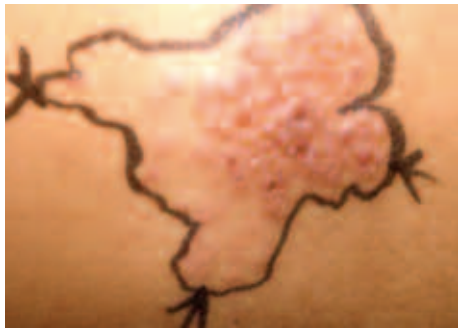
There are some well-established risk factors associated with developing PHN. Not only does the risk of zoster increase with age, but so also does the risk of getting PHN after an episode. PHN occurs in approximately 70% of untreated adults over age 70 years. The risk of PHN is also increased in those who note severe pain during the prodrome or during the rash phase of the illness.[2,11,14]

Figure 3a: Herpes Zoster



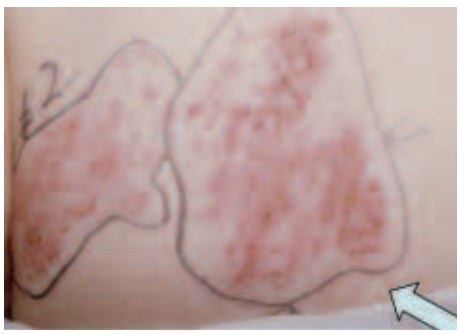
Evolution, day 2.

Figure 3b: Herpes Zoster



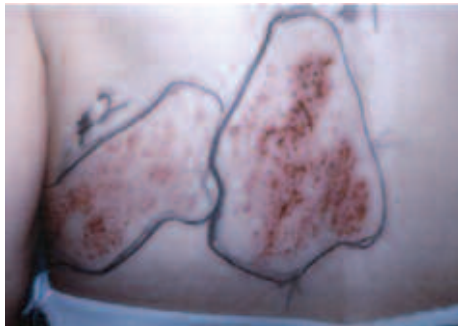
Evolution, day 3.

Figure 3c: Herpes Zoster



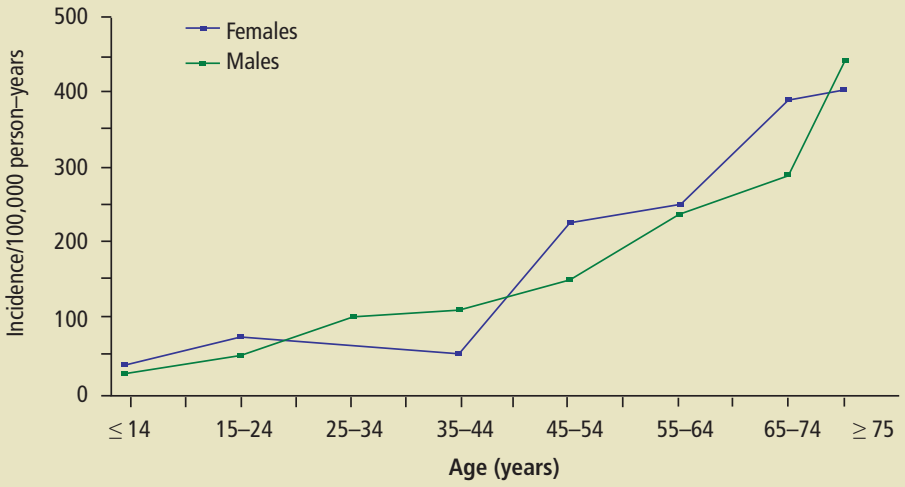
Evolution, day 6.

Figure 3d: Herpes Zoster



Evolution, day 8.

Figure 4: Increasing Incidence of Zoster with Age



Source: Ragozzino MW et al., 1982.[11] Reprinted with permission of Lippincott, Williams & Wilkins.

Therapy for Acute Herpes Zoster

Treatment of Complications other than PHN

While therapy for acute herpes zoster and PHN have been discussed by the previous authors, the clinician should be aware of treatment options for complications of HZ other than PHN. Herpes zoster ophthalmicus (zoster in the distribution of the ophthalmic branch of the trigeminal nerve) can be complicated by pathology of virtually any structure in the eye. Acyclovir has proved to be effective in the treatment of acute herpes zoster ophthalmicus and in reducing the incidence of these complications in two placebo-controlled trials. Oral valacyclovir and famciclovir have been shown to be as effective as acyclovir in preventing ocular complications, and treatments have similar tolerability (Table 1).[14,15–17] Early initiation of antiviral therapy is important, and it is recommended to refer to an ophthalmologist who can monitor for signs of specific ocular complications that may require further treatment.

Other serious complications of zoster can affect many body systems and may be varied in presentation. These may include neurological syndromes such as encephalitis, myelitis, polyradiculitis, and nerve palsies, as well as dissemination to virtually any organ system in the compromised host. Dissemination is especially likely in any condition characterized by a deficit of cell-mediated immunity. Those at high risk of dissemination for this reason include patients with lymphoproliferative malignancies (especially T-cell dysplasias), those having received bone marrow or solid organ transplant within the previous 12 months, HIV-positive individuals with fewer than 200 x 10^9 CD4 cells/l, and those taking a high doses of corticosteroids or cytotoxic chemotherapy. For all such serious complications and for apparently uncomplicated zoster occurring in the above high-risk groups, IV acyclovir is the hallmark of therapy.[18,19]

Regular suppressive doses of oral antiviral therapy should be considered for prevention of zoster and its complications among certain transplant patients, especially bone marrow transplant recipients.[20]

Immunization to Prevent Herpes Zoster

Declining Cell-mediated Immunity

As discussed above, almost all older adults have been infected with wild-type VZV and are at increasing risk of zoster as they age. This is thought to be a function of declining cell-mediated immunity with time since the original varicella (chicken pox) infection. It is also postulated that older adults are less likely than younger ones to come into contact with children with chicken pox and, as a result, do not have the opportunity for exogenous boosting of immunity, which might make zoster less likely. Therefore, there is a concern that

Table 1: Antiviral Treatment for Herpes Zoster

Patient Group	Antiviral Therapy	Pain Management	Comments
Immunocompetent, <50 years, moderate to severe pain or eye involvement	Oral valacyclovir 1000 mg or famciclovir 500 mg	Consider single-dose gabapentin and/or oral analgesia	Best results are achieved if antiviral therapy is started <72 h after rash onset, but therapy is also useful if new lesions are forming
Immunocompetent, >50 years Immunocompromised or with disseminated cutaneous or visceral herpes zoster	3 x daily for 7 days i.v. acyclovir 10 mg/kg every 8 hours for 7–10 days		Refer patients with eye involvement to an ophthalmologist

the age-related risk for zoster may potentially increase over time as a result of the advent of childhood varicella immunization. Recently, data from a large, randomized, controlled trial of zoster vaccine have shown some promise.[21] The zoster vaccine is composed of a significantly higher dose of live, attenuated Oka-strain varicella than is required for the childhood vaccine.

The Shingles Prevention Study

The Shingles Prevention Study trial involved approximately 38,000 people randomized to receive vaccine or placebo.[21] The primary endpoint was derived from the zoster brief pain inventory (BPI), which measures both severity and duration of zoster-associated pain, pruritus, or allodynia. An important secondary endpoint was the actual incidence of PHN (PHN in this case was rigorously defined as pain score greater than three out of 10 occurring more than 90 days after rash).

Remarkably, 95% of more than 38,000 subjects completed the study. Vaccine recipients experienced a 51.3% reduction in the incidence of zoster (315 vs. 642 cases). Severity of illness was also lower in vaccine recipients who experienced shingles so that the reduction in zoster BPI was greater (61% reduction from mean score of 250 to 97). Of note, those under 70 years of age benefited by a larger decline in incidence, whereas subjects 70 years and older continued to benefit by a decline in severity of PHN. This trial shows that it is possible to reduce the burden of a common cause of chronic pain in older adults using a simple protective vaccine. Indeed, reduction of incidence and severity of zoster would be expected to prevent much of the loss in quality of life associated with PHN. Should the benefits of the vaccine prove to be of long duration, its use may grow to be a routine part of care for older adults.

Conclusion

Any patient with herpes zoster ophthalmicus and all patients with shingles presenting over the age of 60 should be offered antiviral therapy within 72 hours of rash onset to reduce the duration of zoster-associated pain. High-risk patients (those with herpes zoster ophthalmicus or severe pain) should not be denied therapy after this point, particularly if there is new lesion formation.

However, each case of clinical zoster should give us pause to consider if we have done everything possible to prevent it in the first place.

Zoster has been a feared and debilitating condition among older adults. By making use of the full range of preventive and therapeutic tools at our disposal, we can go a long way toward mitigating this risk.

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Notes