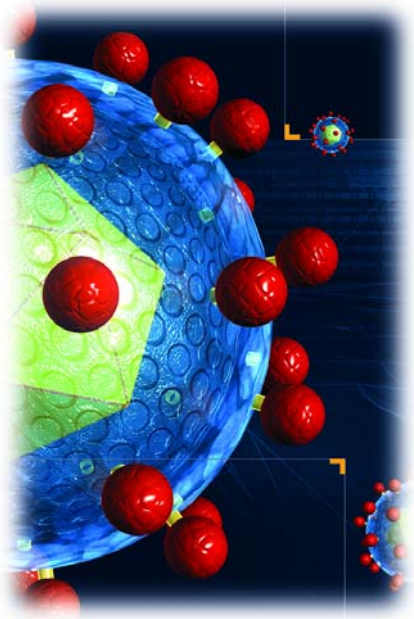

The Burden of Herpes Zoster and Postherpetic Neuralgia in the United States

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Herpes zoster (shingles), a painful and disabling disease, affects an estimated 1 million individuals in the United States annually and results in significant morbidity, lost productivity, and diminished quality of life. Herpes zoster constitutes the reactivation of varicella-zoster virus (VZV), the same virus that causes chickenpox. After resolution of chickenpox, VZV remains dormant in dorsal root ganglia. Varicella-zoster–specific cell-mediated immunity wanes naturally with advancing age or earlier in the setting of an altered immune status, which can result in the reactivation of VZV as herpes zoster.

The pain associated with the rash caused by herpes zoster is often described as burning, stabbing, itching, or aching. Postherpetic neuralgia, the most common complication of herpes zoster, occurs after the zoster rash has resolved, affecting up to a third of patients. Herpes zoster is associated with significant morbidity, especially in the elderly. Herpes zoster is both more common and more severe among older adults. In both acute herpes zoster and postherpetic neuralgia, pain is the primary cause of morbidity.

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An estimated 1 million or more new herpes zoster cases, characterized by a painful rash that results from the reactivation of latent varicella-zoster virus (VZV) infection, occur each year in the United States. Affected individuals typically have severe acute pain and distress, and as many as a third of them continue to have pain long after the zoster rash has healed. This neuropathic pain syndrome is known as postherpetic neuralgia (PHN) and is difficult to treat. The pain interferes with activities of daily living, dampens mood, and undermines the well-being of those affected.

Until recently, nothing could be done to prevent herpes zoster or PHN.

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In 2006, however, a herpes zoster vaccine was approved by the US Food and Drug Administration (May 25, 2006) and recommended by the Advisory Committee on Immunization Practices (October 25-26, 2006) for the prevention of herpes zoster in individuals aged 60 years or older. This new vaccine provides a boost to waning cell-mediated immunity (CMI) against herpes zoster, thus reducing the incidence of the disease and its severity in those in whom shingles develops despite vaccination.

Incidence and Epidemiology of Herpes Zoster

Herpes zoster, or shingles, is the result of reactivation of a latent VZV infection, the precise mechanism of which is poorly understood. However, it is known that after a primary VZV infection, or chickenpox, whereby the virus becomes latent in the dorsal root ganglia, CMI keeps the virus under control.[1] It is also known that this immunity may be boosted by periodic exposure to external sources of VZV, such as children infected with chickenpox and by periodic minor reactivation of internal virus.[2] It is believed that when the CMI to VZV is insufficient to keep it under control, the virus reemerges from the dorsal root ganglia, usually causing acute herpes zoster rash and severe pain. Factors that compromise the CMI to VZV increase an individual's chance of herpes zoster developing. Chief among these factors are advancing age and accompanying immunosenescence[1]; disease states such as HIV infection or treatment regimens that impair CMI may achieve similar results in any age group.

Stress and physical trauma also appear to play a role in determining the timing and, possibly, location of herpes zoster. In a case-control study of patients with herpes zoster who were matched by age, sex, and race with herpes zoster–free control subjects, individuals with herpes zoster were significantly more likely to have had negative life events in the 2, 3, or 6 months before the onset of zoster and to have had significantly more total life events in the 6 months before the onset of the rash.[3]

The role of physical trauma in onset of herpes zoster was investigated in a similar case-controlled study of individuals with and without herpes zoster matched for timing and trauma site. Individuals with herpes zoster were more likely to report trauma at their rash site, but were just as likely as subjects without herpes zoster to report trauma at other sites during the preceding 6 months.[4] Thus, evidence suggests that both mental and physical stress may play a role in precipitating an outbreak of herpes zoster.

Recent data suggest that herpes zoster develops in approximately 1 million Americans each year. This frequency is based on an incidence of 11.12 cases per 1000 patient-years in a sample of individuals aged 60 years or older.[5] The incidence is low among individuals younger than 40 years, ranging from 0.9 to 1.9 cases per 1000 patient-years, but it begins to climb thereafter: herpes zoster occurs in 2.5 per 1000 patient-years among individuals aged 40 to 49 years; 3.8 cases per 1000 patient-years among those aged 50 to 59 years; 6.1 cases per 1000 patient-years among those aged 60 to 69 years; 8.5 cases per 1000 patient-years among those aged 70 to 79 years; and 9.4 cases per 1000 patient-years among individuals aged 80 years or older. Sixty percent of cases occur in individuals aged 50 years or older.[6]

Recurrence of a herpes zoster episode is rare in immunocompetent patients, estimated at 1% to 6%.[2,7,8] The likely reason for this low recurrence rate is that patients with competent immune systems have a boost in CMI after an episode of herpes zoster. These estimates of the incidence of both a first and subsequent episode of shingles are based primarily on reported office visits. Undoubtedly, mild outbreaks occur but go undiagnosed because all patients with a rash do not seek medical attention, particularly if the rash is not extremely painful, if they do not have access to medical care, or if they are unaware of the rash because of an altered mental status. Also, patients with subsequent episodes of shingles may not seek care if the recurrence is mild and they are familiar with the clinical course.

Herpes zoster poses a significant healthcare burden to the US population. Herpes zoster results in 2.1 hospitalizations per 100,000 patient-years; this number encompasses hospitalization for zoster across all age groups, but hospitalization is far more common among older adults—9.3 per 100,000 patient-years for those aged 60 years or older—than for younger adults (1.5 per 100,000 patient-years for those aged 25 through 59 years).[9]

The numbers in the study by Coplan et al,[9] generated from a survey of the Kaiser Permanente database in Northern California, reflect the incidence of hospitalizations for herpes zoster after the advent of the varicella vaccine. These hospitalizations are expensive. In a separate study before the availability of the varicella vaccine, Lin and Hadler[10] found that the average cost per herpes zoster–related hospitalization in 1995 was $15,583.

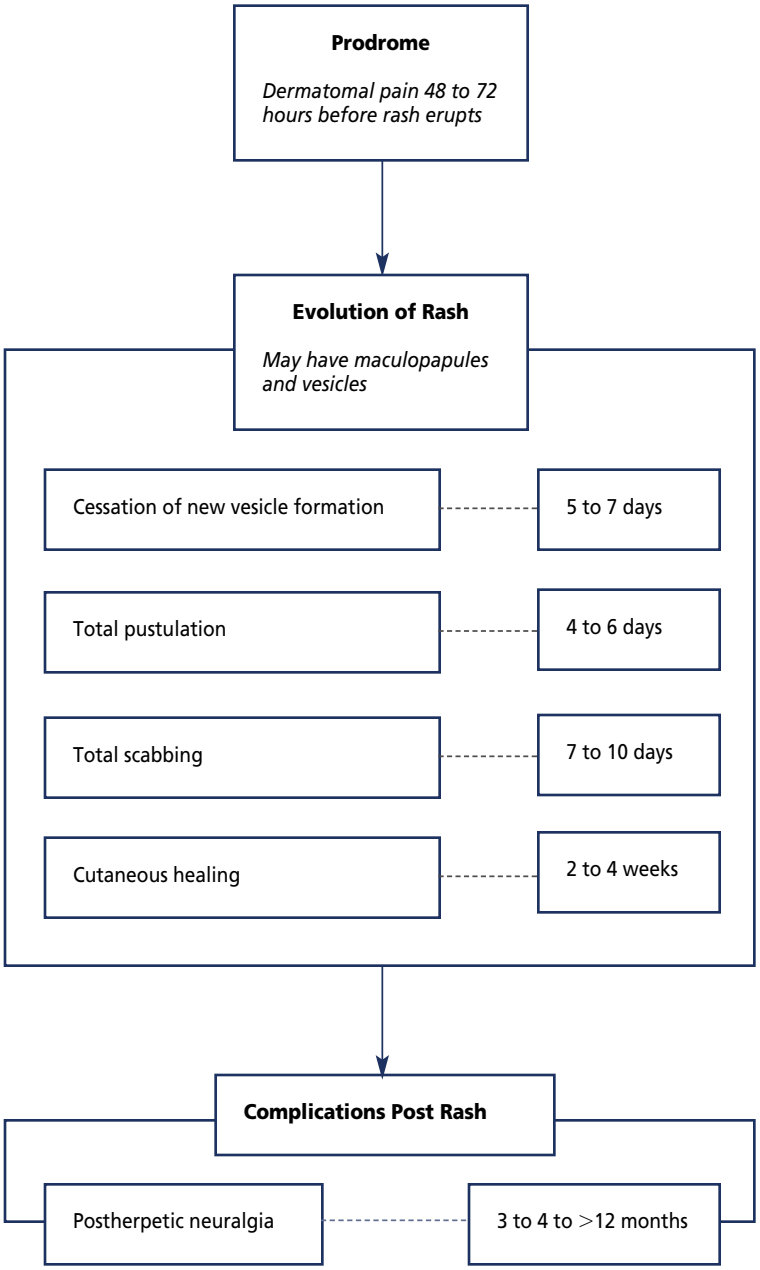
A slightly earlier survey of statewide data in Connecticut from the pre–varicella vaccine era suggests a much higher incidence of hospitalization: 16.1 per 100,000 patient-years.[10] Coplan et al[9] hypothesize that the difference in the prevalence of HIV infection between the Kaiser Permanente sample and the 1986-1995 Connecticut sample may explain some of the discrepancy. In the Connecticut study, HIV infection was coded as an underlying condition in 8% of all herpes zoster–related hospitalizations.[10]

The Kaiser Permanente study was also conducted during a year (1994) when antiviral medications were more available to patients and providers than during much of the time frame of the Connecticut study. If administered within the first 72 hours of onset of the rash, these medications decrease the duration and severity of the rash.

Acute Herpes Zoster

Acute herpes zoster typically first appears as a rash that is unilaterally localized in a region affecting up to three adjacent dermatomes, but most often is isolated to one dermatome. The rash cycles through lesions primarily in the first 96 hours of rash, though 10% to 15% of patients may have a longer period of lesion formation. The lesions,

Figure 1. *Clinical manifestation of herpes zoster. (Source: Wood MJ, Easterbrook P. Shingles, scourge of the elderly: the acute illness. In: Sacks SL, Straus SE, Whitley RJ, Griffiths PD, eds.* Clinical Management of Herpes Zoster. *Amsterdam, Netherlands: IOS Press; 1995:193-209.)*



in turn, develop into erythematous maculopapules, vesicles, and pustules, in varying stages (*Figure 1*).

The pustules generally crust within 10 days. The crusted lesions may last an additional 1 to 2 weeks. On average, older individuals have a rash of longer duration.[11] Rarely, herpes zoster may occur without a rash but with pain, a condition known as *zoster sine herpete*.[12]

More than half of the time, the rash appears on the trunk; however, the trigeminal nerve is most often affected (10% to 15% of cases) when zoster involves an individual dermatome. Many individuals so affected have involvement of the ophthalmic nerve, which puts them at risk of ophthalmic complications (*Figure 2*), including lid ulceration, conjunctivitis, stromal keratitis, uveitis, optic neuritis, retinal necrosis, secondary glaucoma, and, in severe cases, blindness.

Postherpetic neuralgia is the most common complication of herpes zoster. Other complications include bacterial superinfection, motor paralysis, meningoencephalitis, transverse myelitis, cerebral vasculitis, pneumonitis, myocarditis, pancreatitis, and esophagitis.[11]

The rash of herpes zoster often is preceded by and accompanied by throbbing, stabbing, burning, or lancinating pain; the pain is not a direct result of the rash, but instead is thought to be a result of viral inflammation of the nerves. Older individuals and immunocompromised patients are more likely to have more severe acute herpes zoster pain[11] that can have increased consequences for their quality of life and ability to perform daily activities.

Katz et al[13] assessed the incidence and quality of pain and the relation of pain to physical, role, social, and emotional functioning in 110 patients with herpes zoster who were receiving care at a dermatology clinic. Although variability existed among patients, pain seemed to be the rule rather than the exception—only 4% of patients reported no pain. Reported pain could be quite severe: 42% of patients referred to their worst pain as "horrible" or "excruciating." Most patients (58.9%) reported pain most days (14%) or every day (44.9%); individual pain episodes lasted from a few minutes for 25.6% of patients to all day for 22.9% of patients. The remainder had pain episodes ranging from several minutes to several hours.

In the study by Katz et al,[13] pain was significantly correlated with impairment in physical functioning (Pearson $r=0.47$; $P<.001$), role functioning (Pearson $r=0.52$; $P<.001$), social functioning (Pearson $r=0.57$; $P<.001$); and with depressive symptoms (Pearson $r=0.26$; $P<.01$). This pain, in addition to being associated with clinically significant morbidity of its own, is positively correlated with the development of PHN, in that patients who have more severe pain during acute herpes zoster may be at increased risk of more prolonged PHN.[11]

Postherpetic Neuralgia

Postherpetic neuralgia has been defined as pain that lasts after the acute herpes zoster rash has healed. Different studies, however, have recast the meaning in varying ways, sometimes defining PHN as pain lasting a specified time after rash healing, as well as lasting various times after rash onset.[12] The pain of PHN takes many forms, including dysesthesia, an unpleasant abnormal sensation, spontaneous or evoked; allodynia, pain evoked by a normally innocuous stimulus; and hyperalgesia, pain of exaggerated severity in response to normally painful stimulation.[14,15] The pain itself has been described as "tender," "hot-burning," "stabbing," "throbbing," "shooting," and "sharp."[16] The pain is generally least severe in the morning and progresses in severity throughout the day; this pattern is maintained even when medication is used to manage the pain and may contribute to problems sleeping.[17]

Postherpetic neuralgia is the third most common cause of neuropathic pain in the United States, behind neuropathic low back pain and diabetic neuropathy.[18] Postherpetic neuralgia is of varying duration and develops in 9% to 34% of individuals with herpes zoster, depending on the definition used and population studied.[12]

In a longitudinal study of 94 patients with herpes zoster judged to be at elevated risk for PHN because of the presence of acute herpes zoster pain more than 2 weeks after rash onset, 50% had PHN, defined as any pain at 3-month follow-up, whereas only 3% had pain judged to be "clinically meaningful" (score ≤30/100 on the pain visual analog scale).[16] At 6-month follow-up, 32% had PHN and 2% had "clinically meaningful" PHN.[16] Thus, for many individuals, PHN persists for at least 6 months after cessation of rash. In author's professional experience, postherpetic neuralgia has been noted to last years or for the duration of an affected individual's lifetime.

Postherpetic neuralgia is thought to result from permanent changes in the affected neurons and to be pathophysiologically distinct from the shorter-term pain of acute herpes zoster. At post-mortem study of subjects who had had PHN, dorsal horn atrophy and changes in the sensory ganglion were found. The role of these changes in PHN is supported by their absence on the contralateral side of a patient's body (PHN being, like herpes zoster, unilateral) and in patients with acute herpes zoster pain but not PHN.[12]

Complications

- **Neurologic**
  - Postherpetic neuralgia
  - Motor neuropathy
  - Cranial palsy
  - Encephalitis
  - Transverse myelitis
- **Cutaneous**
  - Bacterial superinfection
  - Disfigurement
- **Ophthalmic**
  - Stromal keratitis
  - Iritis
  - Visual impairment
  - Retinitis
  - Episcleritis
  - Keratopathy
- **Visceral**
  - Pneumonitis
  - Hepatitis
  - Encephalitis

Figure 2. *Complications of herpes zoster. (Source: Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster.* N Engl J Med. *2002;347:340-346.)*

Risk Factors for Postherpetic Neuralgia

Risk factors for PHN—determined by comparing patients with herpes zoster in whom PHN developed with those in whom it did not while controlling for rash duration—include advanced age, female gender, having had a prodrome, severe acute pain, and severe rash.[19] The location and number of affected dermatomes of the rash and involvement of the trigeminal nerve were not found to be risk factors.[19] However, other studies have found an increased risk of PHN among individuals with ophthalmic zoster, which affects the first division of the trigeminal nerve.[20]

Individually, the identified factors have limited ability to predict PHN, but a clear elevation in risk existed in patients with multiple risk factors. For example, PHN developed in almost half of all female patients older than 60 years who had a prodrome, severe rash, and acute herpes zoster pain. In addition, PHN was unlikely to develop in patients who did not have any of these risk factors: PHN developed in only 5% to 10% of patients who had none of these risk factors.[19]

Frequency and Duration of Postherpetic Neuralgia

Both the frequency and duration of PHN increase with age (*Figure 3*). Among patients with acute herpes zoster, PHN develops in 73% of adults aged 70 years or older versus only 27% of those older than 55 years, and almost half of patients aged 70 years or older (48%) have PHN of greater than a year's duration. Postherpetic neuralgia develops in 47% of adults with acute herpes zoster who are older than 60 years.[21]

Postherpetic neuralgia, like other chronic pain syndromes, erodes the health and well-being of those affected. Older individuals, who are most susceptible to PHN, may be at greater risk for complications such as fatigue, anorexia, weight loss, insomnia, depression, difficulty concentrating, and difficulty performing activities of daily living, such as bathing or housework.[22]

In a survey of 385 individuals aged 65 years or older with PHN, 40% of individuals reported moderate to severe impairment of general activities, 45% reported a moderate to severe impairment in mood, and 48% reported moderate to severe impairment of their enjoyment of life as a result of PHN. More than half (54%) had problems performing their usual activities, while 5% were completely unable to do so.[23]

Treatment of Patients With Postherpetic Neuralgia

Medications are available to ease the pain of PHN, but evidence suggests that they are limited in their capacity to alleviate the pain of PHN. In the population discussed in the preceding paragraph,

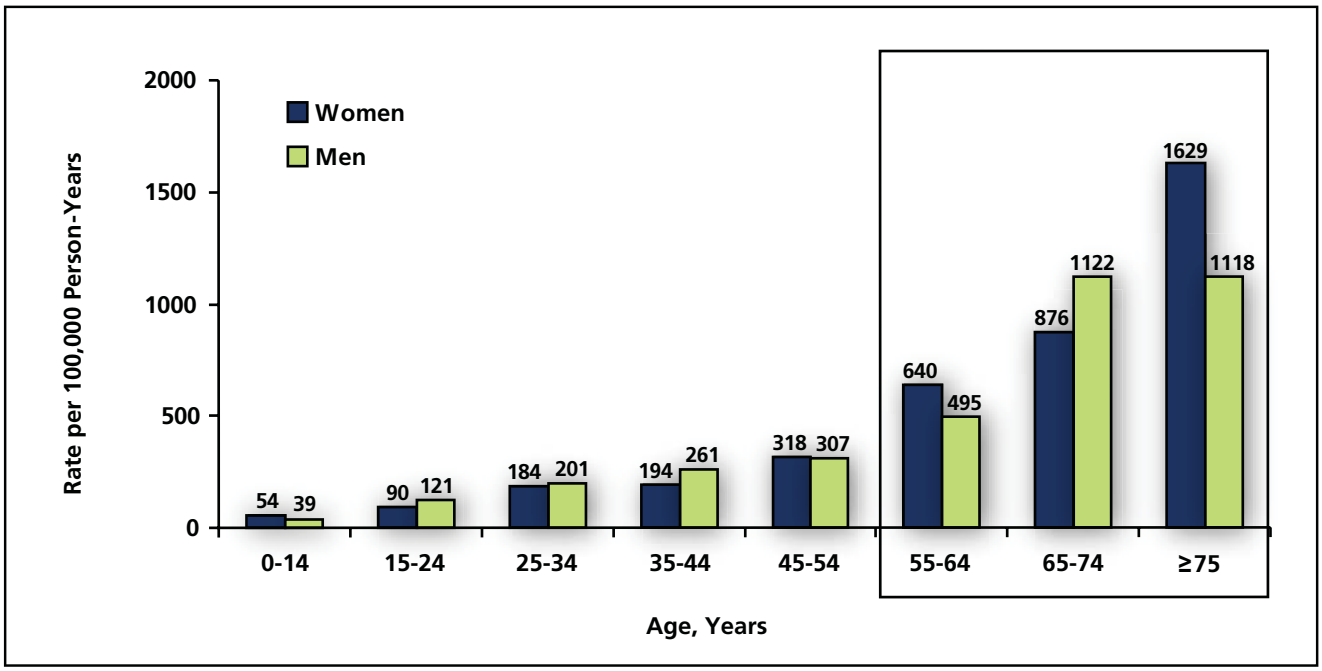


Figure 3. *Increasing incidence of herpes zoster with age. (Adapted from Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster.* Arch Intern Med. *1995;155: 1605-1609.)*

Oster et al[23] found that 84% of study participants had taken prescription medication for their PHN at some point, whereas 50% had done so in the week before the study. Of those who had taken prescription pain medication in the previous week, 58% had taken opioids; 46%, antiepileptics; and 35%, psychotherapeutic agents.

All the medication classes cited by the patients in the survey by Oster et al[23] have some efficacy in alleviating the pain of PHN. In addition, 18% of these survey respondents had used nonsteroidal anti-inflammatory drugs, and 15% had used sedatives and hypnotics. Few patients were satisfied with the level of pain relief they attained with these regimens: 14% of respondents were satisfied "a lot" or "quite a bit," whereas 31% were "not at all" or "a little" satisfied. In addition, about 10% were bothered "a lot" or "quite a bit" by side effects of their medications.[23]

Comment

Herpes zoster and PHN are relatively common diseases associated with significant morbidity. Herpes zoster is most common in older adults, as is PHN. Other factors such as increasing age, severe herpes zoster pain, prodromal pain, and severe zoster rash further increase the likelihood that PHN will develop.

Both herpes zoster and PHN are associated with clinically significant pain, but though the pain of herpes zoster is generally short-lived, the pain of PHN can continue for months or even years. In both instances, the pain has a significant negative impact on an individual's mood and ability to conduct activities of daily living.

Medications are available to ameliorate the pain of PHN, but data suggest that these agents provide incomplete pain relief and their use is often accompanied by troubling side effects, especially in the population with whom they are most often used. Although the zoster vaccine reduces the incidence of herpes zoster and PHN among vaccinated individuals, further research is needed to develop new treatment modalities and to optimize existing modes of treatment to provide adequate pain control, particularly for those patients who are not eligible for vaccination and in whom the pain of acute herpes zoster and PHN develop.

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