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Prevention of herpes zoster and its painful and debilitating complications

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Summary
Background: Reactivation of latent varicella-zoster virus in sensory neurons to cause herpes zoster (shingles) is common in adults 50 years of age and older; half of adults experience an episode by age 85 years. Herpes zoster is attributable to the progressive decline in the VZV-specific cell-mediated immunity that occurs with aging or other conditions that cause immune compromise. Herpes zoster and complications, such as postherpetic neuralgia (PHN), can have a substantial negative impact on quality of life.
Discussion: The incidence of herpes zoster and its associated morbidity is increasing worldwide as the population ages. Nevertheless, the severity and impact of this condition, and its painful sequelae, are often unrecognized. Many patients delay seeking medical attention, complicating both diagnosis and treatment. Prevention appears to be the best option. A new herpes zoster vaccine significantly reduced the burden of illness (61.1%), the incidence of PHN (66.5%), and the incidence of herpes zoster (51.3%) ($p < 0.001$). Vaccine tolerability was good, with minor local injection site reactions the most common adverse event.
Conclusions: Herpes zoster and PHN represent a substantial burden in terms of suffering and associated costs. Immunization of older adults is a good option to prevent herpes zoster and PHN.

Introduction

The vast majority of adults are likely to have been infected with the varicella-zoster virus (VZV). The initial infection causes chicken pox, usually in childhood.[1] Subsequently, VZV remains latent in sensory ganglia for life. Symptomatic reactivation of VZV as herpes zoster, also called shingles, is a common age-related disease, affecting up to half of all adults who live to 85 years of age.[2,3] Reactivation is attributed to the natural immunosenescence that occurs with aging, as well as to other conditions that cause immunocompromise.[4–8]

Studies worldwide document that the incidence, severity, and complications of herpes zoster all increase with age.[3,9–13] Historic data show a consistent upward trend in the incidence of herpes zoster.[5,10] As the elderly population increases, the number of people affected by herpes zoster

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will increase.[2,14] This is important because the management of herpes zoster and its complications is associated with a large economic burden. A U.K. study exemplified the high costs involved in both acute care and treatment of complications, with the highest medical costs for patients 65 years of age and older.[15]

Despite the widespread nature of this disease, rapid, early diagnosis is sometimes problematic because it relies primarily on the appearance of the typical rash.[3,9] Differential diagnosis during the prodromal phase involves ruling out other causes of localized pain, such as trauma, myocardial ischemia, renal colic, gallbladder disease, dental pain, and pleurisy.[9] The nature of the symptoms is such that acute treatment is often delayed because patients either wait to seek treatment or remain undiagnosed while other conditions are ruled out.[8,9] Antiviral agents are partially effective in reducing acute pain, hastening rash resolution and shortening the duration of pain. These are well tolerated and most effective when offered early, but the diagnosis is often delayed beyond the 72-hour window of opportunity for optimal treatment effect.[9]

Following the acute disease phase, herpes zoster can be associated with severe complications and morbidities that reduce functioning and quality of life. Complications occur in at least half of all older patients affected by herpes zoster.[5,7] Postherpetic neuralgia (PHN) is the most common and most feared of these complications, and can cause an otherwise high functioning elderly patient to become debilitated.[1,8,16,17] Treating PHN is difficult because no therapy is predictably effective, treatment is time consuming, and side effects and drug interactions are especially common in older patients receiving multiple medications.[9,14]

We review the epidemiology and natural history of herpes zoster, emphasizing its impact on patients and the difficulties involved in case management. Given the difficulties with rapidly diagnosing herpes zoster and treating its painful, debilitating sequelae, prevention through vaccination is discussed as the most promising option currently available.

Epidemiology

Herpes zoster

Primary infection with VZV causes varicella, which usually occurs in children in temperate climates, but also in adolescents and adults in tropical areas. Following this infection, VZV remains latent in sensory ganglia. Latent virus can reactivate, often 4 to 5 decades later, to produce herpes zoster.[8] The mechanism of latency is poorly understood, but it is clear that some minimal level of VZV-specific immunity is required to maintain VZV in its latent state. A decline in this immunity, such as occurs in patients with immunosuppressive illnesses or therapies, is associated with a large increase in the incidence of herpes zoster.[3,18] Moreover, a significant decrease in VZV-specific cellular immunity (but not in VZV antibody), which is a natural consequence of aging, explains why VZV reactivation and the resulting herpes zoster is associated with aging. Although reactivation also occurs in younger people who do not have immunocompromising conditions, their risk for complications of shingles is diminished.[4,9]

The incidence of herpes zoster increases significantly with age, with 67% of cases occurring in persons over 50 years of age.[12] This was shown in a U.K. study (1947–62) in which the annual incidence of herpes zoster was 7.8 per 1000 persons in patients over 60 years of age compared with an overall annual incidence of 3.4 per 1000 persons.[10] A more recent study demonstrated a correlation between increasing herpes zoster incidence and age, where incidence rates of 1.9 to 3.1 per 1000 were observed in patients younger than 55 years of age, compared with 11.8 per 1000 person years in patients older than 65 years.[19] This translates to a large at-risk population[5,9,20] that is remarkably consistent worldwide (Figure 1).[10,20–24] Up to 800,000 cases of herpes zoster occur annually in the U.S.,[11] for a lifetime incidence of up to 20% in the general population.[3] The lifetime risk in Europe is between 23 and 30%.[13,21,25] Approximately 90% of adults in the European Union have had chickenpox, so that 1.8 million new cases

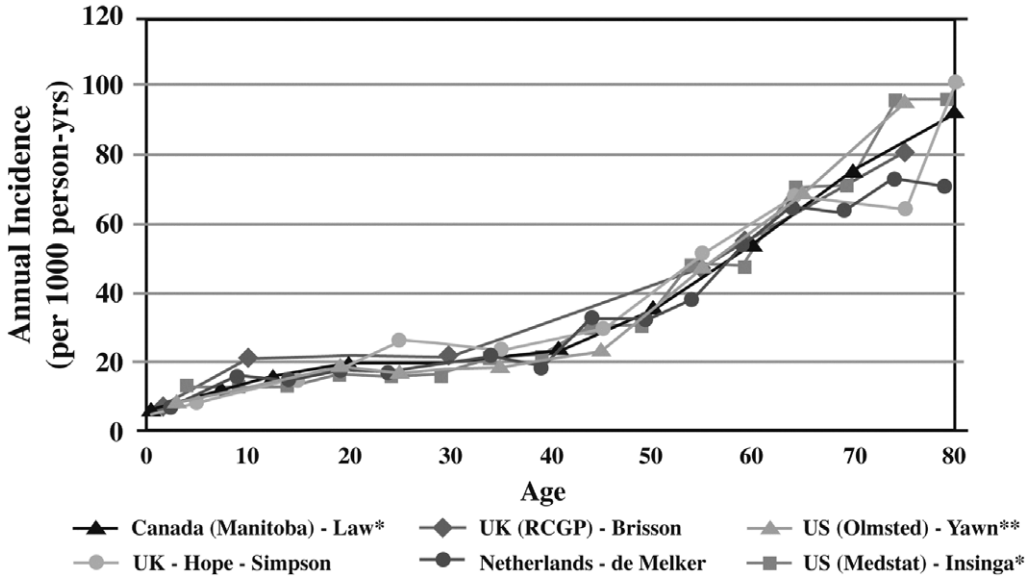

Figure 1 The incidence of herpes zoster is consistent, worldwide.[10,20–22,45–47]

of herpes zoster would be expected each year, assuming a population of 460 million.[10,26,27] Annual rates for patients of all ages in Europe have been reported as 4.14/1000 in Italy,[23] 4/1000 in France,[24] 3.56 in the United Kingdom,[22] 3.30 in the Netherlands,[20] and 2.26/1000 in Germany.[28]

PHN

An age-associated increase in the prevalence of PHN is characteristic of herpes zoster.[9] The proportion of patients with herpes zoster who develop PHN increases rapidly from age 50.[10] While there is no consensus on a definition for PHN, it is commonly defined as pain persisting at least 1 to 3 months after the onset of the herpes zoster rash.[14] Given this definition, 20% of all patients 50 years of age and older who have herpes zoster will develop PHN.[9,13,14,29]

The risk of PHN, as defined above, increases dramatically with age; 3% to 4% of adults 30 to 49 years old, 21% of those 60 to 69 years of age, 29% of those 70–79 years of age, and 34% in those over 80 years develop PHN.[10] This translates to a 14.7-fold higher prevalence of pain 30 days after rash onset and a 27.4-fold higher prevalence 60 days after rash onset in patients at least 50 years of age when compared with younger patients.[30]

Natural history

VZV-specific antibody, which does not decline with age, is the primary defense against the host developing chickenpox again after re-exposure to VZV. VZV-specific cell-mediated immunity, which declines with age and immune compromise, is the defense against herpes zoster. This immunity is boosted exogenously when a person is exposed to children with varicella, and endogenously by sub-clinical reactivation. The frequency of recurrent herpes zoster in immunocompetent individuals is low, 1.7% to 5.2%, probably because a single episode of herpes zoster results in a very strong boost in VZV-specific cell-mediated immunity.[1,31]

Clinical features of herpes zoster include pain and paresthesia, in a dermatomal distribution, that may precede the rash by up to 4 days, with a range of symptoms from itching to severe lancinating pain. Constitutional symptoms such as fever, headache, or malaise may also occur.[7,8,14,18,29,32] Herpes zoster most commonly localizes to the thoracic region (50–62%), followed by the cranial region – which includes ophthalmic zoster (12–21%) – the lumbar (10–14%), cervical regions (11–14%), and the sacral region (2–8%).[6,10,33,34]

Complications of herpes zoster

PHN is the most common complication of herpes zoster,[35] involving the peripheral and central nervous system.[36] Risk factors for PHN include greater age, severity of acute pain, extent of rash, presence of prodromal pain, and, possibly, concomitant disease such as diabetes, which could be due to preexisting neuropathy.[36] The PHN manifestations can be steady, throbbing or burning pain, spontaneous, constant or intermittent pain, that can be sharp or shooting, and allodynia (pain from stimuli that are not normally painful).[36] The duration and severity of zoster-associated pain increases with age (Figure 2).[37]

PHN treatment requires a multifaceted approach.[7,16] Treatment is difficult because the symptoms and mechanisms vary between patients, and medical management of chronic neuropathic pain is challenged by comorbidities and susceptibility to cognitive decline that increase the risk for drug adverse effects and drug-drug and drug-disease interactions. Psychosocial issues may also complicate pain management and often have functional and affective consequences.[38]

Impact on quality of life

World Health Organization data suggest that while medical advances have resulted in prolongation of life, the gap

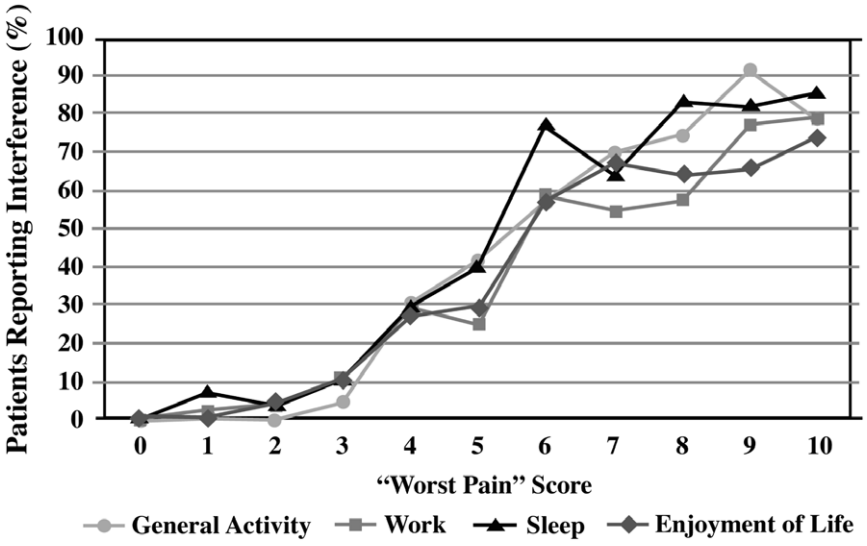

Figure 2 PHN has a substantial impact on quality of life. Greater pain burden has been associated with decreased physical, role, and social functioning, as well as increased emotional distress in the form of depression and psychological impairment.[37]

that still exists between morbidity and disability lowers the quality of life for older people. Instead of dying earlier, people are living longer with disability.[39,40] The development of herpes zoster and PHN in older adults is likely to lead to extended periods of restricted activity and bed rest, further complicating the disease and underlying disease process, and contributing to disability and functional decline.[41,42]

Much of the personal disability and reduced quality of life associated with herpes zoster and PHN may not be captured in studies that focus on work days lost or length of hospital stay due to the chronicity of the disease. Severe or longer-lasting pain continues to impair quality of life after the acute event.[16] Specifically, patients with a greater herpes zoster pain burden have poorer physical functioning, increased emotional distress, and decreased role and social functioning.[16] Approximately 30% of older patients with herpes zoster (mean age 70 years) reported interference with activities of daily living (general, work, sleep, enjoyment), and 70% noted interference at a pain level indicative of marked interference with activities of everyday living.[17]

Challenges in treating herpes zoster and PHN

Treatment of herpes zoster may be sub-optimal because of delayed or atypical presentation.[2,9] Antivirals can alleviate acute pain and the duration of long-term pain. It remains controversial as to whether antivirals reduce the incidence of persistent PHN.

Corticosteroids also have beneficial effects on acute pain, but no effect on preventing PHN.[30,35] Pain medications are difficult to use in an optimal fashion, especially in the elderly, in whom side effects or drug interactions may limit their utility.[2,9] Current management of PHN relies on oral medication from one of three groups of drugs either alone or in combination. The tricyclic antidepressant drugs (e.g. nortriptyline, amitriptyline, desipramine) have similar efficacy to both alpha-2 delta ligands (e.g. gabapentin, pregabalin) and strong opioids (e.g. morphine, oxycodone). The choice of first line drug will depend upon the status of an individual patient but there is no evidence to indicate that choice may be made according to pain mechanism as suggested by the patient's particular symptoms and signs. Topical lidocaine can be effective as adjunctive therapy and some patients tolerate and gain benefit from capsaicin cream. Probably less than half of patients gain 50% benefit from treatment. It should be remembered that response to pain has psychosocial as well as biological components and encouraging patients to remain as active as possible will limit the disabling complications of zoster and PHN. A single, non-replicated, study of intrathecal injection of methylprednisolone suggested significant benefit but there are concerns about long term safety.[43,44]

Prevention of herpes zoster

Prevention through vaccination is the most promising approach to the problem of herpes zoster and its severe complications.[3,8,35] The new herpes zoster vaccine is a live, attenuated cell-free preparation of the Oka/Merck strain of VZV.[26] Attenuated by passages in tissue culture, it contains whole live virus, viral antigens, and several inert ingredients. The rationale for developing a vaccine was to boost VZV-specific cell-mediated immunity and thereby prevent or attenuate both herpes zoster and PHN.

The Shingles Prevention Study

The Shingles Prevention Study was undertaken to determine whether immunization with this live, attenuated zoster vaccine would reduce the incidence or severity of herpes zoster and PHN in patients at least 60 years of age.[26] This double blind, placebo controlled trial randomized 38,546 patients at 22 U.S. sites, stratifying patients by medical center and age (60–69 years vs. $\geq$70 years). The primary efficacy endpoint was the herpes zoster "Burden of Illness" score and incidence of PHN was a secondary endpoint. The Burden of Illness score captures in one measurement the incidence, severity, and duration of herpes zoster in each treatment arm of the study. Herpes zoster incidence was an additional measurement. The average

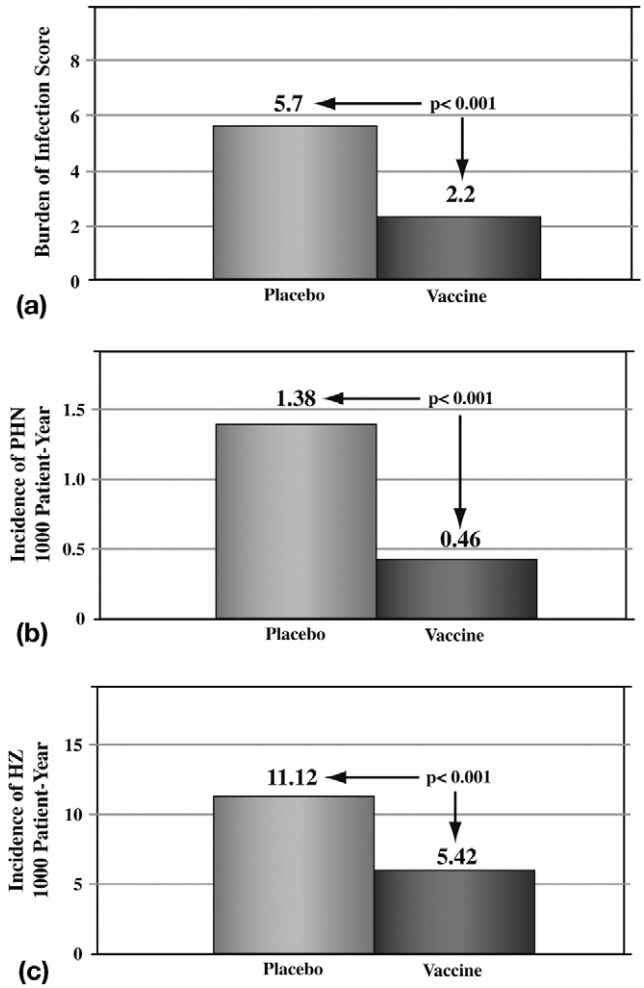

Figure 3 Immunization reduced: (a) herpes zoster burden of illness by 61.1% ($p < 0.001$ versus placebo), (b) incidence of PHN by 66.5%, and (c) incidence of herpes zoster by 51.3%.[26]

duration of surveillance was 3.1 years, with a maximum follow-up of 4.9 years.

A 61.1% reduction in Burden of Illness was observed ($p < 0.001$ vs. placebo; 95% CI 51.1−69.1) (Figure 3a). Greater decreases in the vaccinated subjects were observed with respect to the worst pain (Burden of Illness scores ≥ 600), so that the vaccine greatly reduced the number of patients with the most pain (11 versus 40). Significant reductions in the incidence of PHN (66.5%; 95% CI 47.5−79.2) and herpes zoster (51.3%; 95% CI 44.2−57.6) were also observed ($p < 0.001$ vs. placebo) (Figures 3b and c). Reduced efficacy was observed with regards to herpes zoster incidence among patients 70 years of age and older (37.5% reduction), but these patients still benefited significantly from lower Burden of Illness scores (55.4% reduction) and lower PHN incidence (66.8% reduction).

The safety of the vaccine was similar to that of the placebo in the overall population safety analysis. In the vaccine group 255 of 19,270 (1.37%) patients and 254 of 19,276 (1.36%) in the placebo group experienced serious adverse events. From these serious adverse events, only two were considered vaccine-related in the vaccine group and three in the placebo group. A safety sub-study provided detailed assessments of 6616 patients. In this sub-study, local injection-site adverse events were the most commonly reported (48.3% vaccine group versus 16.6% placebo group; $p < 0.05$), while a similar percentage of patients experienced a systemic adverse event (24.7% of patients in the vaccine group versus 23.6% in the placebo group). Vaccine-related systemic adverse events were experienced by 6.3% patients in the vaccine group and 4.9% in the placebo group ($p < 0.05$), headache being the most frequently reported (1.4% versus 0.9% respectively, $p < 0.05$).

Conclusions

Herpes zoster is a very common disease that can be severe. The impact of herpes zoster on older patients is not fully appreciated by some physicians. Herpes zoster can sometimes have devastating consequences on patient quality of life, particularly when PHN develops. Herpes zoster incidence has been remarkably consistent over time and throughout the world. Given the severity of disease and the considerable lifetime risk, more effective management of herpes zoster and PHN is essential. Over the past 20 years there has been progress in compressing morbidity to the very end of life through improved diet, exercise, and healthcare. The next challenge will be to postpone disabilities due to aging by using strategies such as vaccination to prevent diseases common in elderly patients. Prevention of herpes zoster and PHN should be one important goal for promoting healthy aging.

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Conflict of Interest statement

Dr. Robert W. Johnson has undertaken paid consultancy, lecturing and writing for Merck & Co., Inc., Sanofi Pasteur Merck, Merck Frosst, Astellas, Novartis and Menarini.

Dr. Janet McElhaney has received honoraria for speaking at Merck-sponsored symposia and fees for contributions to educational materials related to the impact of shingles and post-herpetic nauralgia.

Dr. Biagio Pedalino was employed at Sanofi Pasteur MSD from September 12, 2005 until March 11, 2007, during which period the article was prepared.

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