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# Postherpetic Neuralgia

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## Continuing Education Activity

Post-herpetic neuralgia (PHN) is the most common long-term complication of varicella-zoster virus (VZV) reactivation. This reactivation of the dormant VZV is known as herpes zoster or shingles. VZV is the pathogen that causes the once common childhood condition varicella, colloquially known as chickenpox. Before the advent of vaccination in the late 1990s and early 2000s, upward of 90% of American adults would test seropositive for VZV. Although this number and the percentage of adults who go on to develop herpes zoster and PHN may decrease in the coming generations, PHN is currently a topic of clinical importance. This activity will increase awareness amongst health professional teams in regards to appropriate vaccination and treatment.

**Objectives:**

- Review the risk factors for developing postherpetic neuralgia.
- Identify at-risk populations that would benefit from vaccination for postherpetic neuralgia.
- Describe the treatment options available for postherpetic neuralgia.
- Review the importance of improving care coordination amongst interprofessional team members to improve outcomes for patients affected by postherpetic neuralgia.

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## Introduction

Post-herpetic neuralgia (PHN) is the most common long-term complication of varicella-zoster virus (VZV) reactivation. [1] [2]This reactivation of the dormant VZV is known as herpes zoster or shingles. VZV is the pathogen that causes the once common childhood condition varicella, colloquially known as chickenpox. Before the advent of vaccination in the late 1990s and early 2000s, upward of 90% of American adults would test seropositive for VZV.[3] Although this number and the percentage of adults who go on to develop herpes zoster and PHN may decrease in the coming generations, PHN is currently a topic of clinical importance.

The hallmark of PHN is a lancinating/burning pain in a unilateral dermatomal pattern that persists for three or more months after the onset of a herpes zoster (HZ) outbreak.[4] Two universally accepted risk factors for HZ are increasing age and immunosuppression, and because HZ is a prerequisite for the development of PHN, the elderly and infirm are commonly afflicted. [2] The most successful treatments are multi-modal, with some researchers/clinicians focusing on prevention in high-risk populations rather than cure because of the debilitating and often refractory nature of PHN in already fragile patient populations. [5]

## Etiology

The VZV is a double-stranded DNA virus. It lays dormant in the ganglia of certain peripheral and central nerves after an episode of varicella resolves, generally in youth, with the immune system of the host eradicating the virus in most locations within the body. [2] Advancing age combined with a decrease in immunocompetence, usually accompanied by a psychological or physical stressor, may result in reactivation of the dormant/latent VZV as HZ. [2] The virus replicates and travels down axons until it reaches the skin, where blistering, erythema, and local inflammation occur. [1]

## Epidemiology

PHN occurs in a subset of the population suffering from an episode of acute HZ. A meta-analysis of the risk factors for the development of PHN published in 2016 noted that approximately 13% of patients older than or equal to 50 years of age with HZ would go on

to develop PHN. [3] The incidence increases with advancing age, which underscores the importance of immunocompetence, as a decrease in cell-mediated immunity is likely already present in those with HZ. Well-established risk factors for an acute HZ episode progressing to PHN include age, severe immunosuppression, the presence of a prodromal phase, severe pain during zoster outbreak, allodynia, ophthalmic involvement, and diabetes mellitus. [3]

## Pathophysiology

The exact physiology that separates a self-limited zoster outbreak from PHN is not fully understood. Histological examinations of relevant peripheral and central nervous tissue from sufferers of PHN reveal myelin and axon deficiency, as well as atrophy of the dorsal horn in certain instances. [6] One study compared the difference in epidermal axon densities between patients who suffered from PHN and those who had a self-limited occurrence of HZ. [7] Those afflicted with PHN had, in most instances, far fewer axons in the relevant dermatomes than non-sufferers. [7] Therefore, an anatomical derangement is likely at least partially responsible for the development of PHN. Some suggest that an unchecked inflammatory response at the neuronal level is the main culprit of the eventual development of PHN, specifically via the reduction of centrally-mediated inhibition of nociceptive input and the promotion of peripheral sensitization via damaged nociceptors. [8]

## History and Physical

Unlike other neuropathic conditions, the diagnosis of PHN is relatively straightforward and not one of exclusion.[8] As mentioned, an episode of HZ is a prerequisite for the development of PHN. Therefore, a history of unilateral rash with blisters in a dermatomal pattern should be established. Rarely, the characteristic rash will be absent.[9] Persistent (greater or equal to 3 months) lancinating/burning pain, allodynia, paresthesias, dysesthesias, pruritus, and/or hyperalgesia at or near the area of the rash is the hallmark of PHN. [8]

## Evaluation

PHN is almost universally diagnosed based on history and physical. However, laboratory tests and some targeted imaging may provide a degree of utility. They are of greater value in atypical presentations of PHN, such as zoster sine herpete or herpes zoster of the larynx. Serological testing for VZV IgG and IgM titers is available, although the sensitivity and specificity are less than ideal. Comparatively, immunofluorescence of vesicle scrapings detects VZV antigens in a highly specific and sensitive manner. Similarly, PCR is exquisitely sensitive for the detection of VZV DNA. [10] Small-scale studies suggest that magnetic resonance imaging (MRI) may hold promise for not only diagnosing challenging cases of PHN but also differentiating between PHN and HZ. Further studies are warranted.

## Treatment / Management

Three fundamental treatment approaches may be considered for PHN. The first is prevention, which focuses on identifying populations at risk for contracting HZ and administering a vaccine. The second is early recognition and treatment of an acute HZ infection, as delay may increase the chance of developing PHN. The third approach is symptom management of PHN via multimodal medication regimens and interventional procedures. The evidence regarding the efficacy of these methods is mixed but rapidly evolving, and certain approaches appear to be more successful than others. Prevention is advocated by many because PHN, once established, can be refractory to treatment, with a substantial number of sufferers achieving only a temporary and/or modest reduction in symptom severity despite multimodal therapy. [11]

PHN is notoriously difficult to treat for many reasons. Complete resolution of symptoms is rare. In fact, a 2014 study concluded that less than half of patients with PHN achieve significant symptom reduction. [5] The patient population is usually old and frail with multiple comorbidities, therefore side effect profiles of interventions take on greater importance.[4] Relevant studies comparing treatments and their outcomes are often suboptimally designed. There is no one clearly superior treatment regimen; however, expert consensus suggests that multimodal therapy is likely the best approach. Lastly, many of the advocated approaches are for the treatment of chronic neuropathic pain in general, and not specific to PHN.

Traditional non-invasive treatments include oral and topical medications. The American Academy of Neurology (AAN), Special Interest Group on Neuropathic Pain (NeuPSIG), and European Federation of Neurological Societies (EFNS) all recommend an oral tricyclic antidepressant (TCA), pregabalin, and the lidocaine 5% patch as first-line therapies. [12] The anticholinergic, antihistaminergic, and alpha receptor-blocking side effects of TCAs must be considered, as the elderly are more susceptible. [12] As a result, it is commonplace to initially prescribe and titrate a gabapentinoid, keeping in mind that patients with reduced renal function should be started at a lower dose and up-titrated more slowly. Some clinicians combine gabapentin and pregabalin despite a lack of compelling evidence that supports this tactic. The use of opioids to combat PHN is controversial because of the changing landscape regarding what constitutes appropriate use, and also renewed governmental interest in their administration given the epidemic of abuse, addiction, and mortality. That said, the above three medical societies recommend opioids as either first or second-line treatments, which underscores the pain-reducing capability of this medication class.

There are several other pharmacologic modalities to consider. Multiple studies have confirmed the short and long-term efficacy of the lidocaine 5% patch. [13] This patch also has the additional benefit of a small side effect profile that is mostly limited to application site reactions. Capsaicin preparations, in patch and cream formulations, are also available but not as well-studied as the lidocaine patch. [12] The leading cause of discontinuing capsaicin treatment is pain and irritation at the application site, suffered by almost all users in proportion to the capsaicin concentration. The cream has a low concentration of capsaicin, requiring multiple applications throughout the day to achieve a therapeutic effect. Conversely, the capsaicin patch is available in an 8% formulation, delivering a therapeutic dose in just one application. However, pre-treatment with oral analgesics and local anesthetic to the application site is often necessary to avoid painful irritation, and the degree of overall pain reduction is generally less than the lidocaine 5% patch. Nevertheless, encouraging case reports and other literature suggest the intervention warrants consideration and further study.

Other medication classes include non-TCA antidepressants and NMDA antagonists, but there is limited evidence supporting their usefulness. For example, larger studies involving SNRIs (serotonin-norepinephrine reuptake inhibitors) and SSRIs (selective serotonin reuptake inhibitors) have not shown better outcomes than TCAs, and both classes possess concerning side effect profiles, though typically less severe than TCAs. [12] The recent explosion of ketamine infusion clinics and related studies for the treatment of a wide range of ailments, from neuropathic pain to depression, has also resulted in renewed interest in the role of NMDA antagonism in the treatment of PHN. [14] There are anecdotal reports that ketamine may prove beneficial, and a few small studies support this finding, but long-term data and large-scale studies are non-existent. Lidocaine infusions have also been considered. One double-blind study in 1999 showed that an intravenous lidocaine infusion provided clinically significant short-term pain reduction in sufferers of PHN. In general, small studies and case reports have established that novel therapies may be useful in certain PHN sufferers when combined with other adjuncts. The pathophysiology of PHN is complex, and sometimes an individualized non-traditional approach may prove beneficial for a particular patient.

Invasive therapies include botulinum toxin injections, sympathetic blockade with local anesthetics, epidural/intrathecal injections, and spinal cord stimulation. Botox injections are simple to perform and have a limited side effect profile. However, more studies need to be conducted to evaluate their efficacy. The other invasive therapies mentioned carry the potential for significant peri-procedural risk and/or side effects. Epidural steroid injections and neuromodulation (both spinal cord and peripheral nerve stimulation) produce mixed results but are nevertheless intriguing, with the former resulting in limited short-term improvement at best and the latter sometimes resulting in complete long-term symptom resolution according to case reports. The recent development of the dorsal root ganglion stimulator to treat focal dermatomal neuropathic pain conditions is theoretically promising for PHN. One study originating from China in 2008 suggests that CT-guided radiofrequency ablation of the dorsal root ganglion may result in a significant reduction in symptomatology and sometimes complete resolution of PHN. However, the sample size was small, the technique may cause a pneumothorax, and repeat studies are lacking. Intrathecal medication administration also demonstrates promise. One 270-person study in 2000 investigated the use of intrathecal methylprednisolone with lidocaine for the treatment of PHN, resulting in significant analgesic effect in ninety percent of patients through two years of follow-up.[15]

## Differential Diagnosis

Neuropathic pain is an umbrella term that describes a type of pain common to many diseases and conditions. Nevertheless, unilateral neuropathic pain in a dermatomal pattern at or near the area of a previous HZ rash is highly specific for PHN. However, there are rare instances where other neuropathic conditions should be considered. For example, there is at least one case report of CRPS affecting dermatomes afflicted by HZ just 3 months prior. The location of neuropathic pain will assist in the development of a differential diagnosis. If present in the face, trigeminal neuralgia, and Bell's palsy may be considered. What appears to be PHN in the thoracic dermatomes may infrequently be appendicitis, cholelithiasis, or colitis. [15] In the exceptional case where the diagnosis of PHN is unclear, serological studies for the VZV may be beneficial.

## Prognosis

PHN is difficult to treat. Symptoms may continue for years, sometimes life. With the advent of adult vaccination and the newly developed non-live vaccine formulation, prevention looms as a realistic goal for most of the susceptible American population. [3] When prevention of HZ is not possible, timely treatment is advisable, as duration and severity of pain are considered risk factors for PHN. Unfortunately, once PHN is established, conservative first-line treatment rarely results in symptom resolution and does not offer long-lasting relief. Therefore, multimodal therapeutic approaches recommended by expert consensus should be considered. Limited but thought-provoking evidence suggests that certain unconventional techniques, both invasive and non-invasive, are promising and merit further investigation.

## Deterrence and Patient Education

The mainstay of prevention is the vaccination against HZV. [3] A large (n = 38,000) double-blind study published in the NEJM in 2005

showed that vaccination in the elderly reduced the incidence of HZ by 51% and PHN by 66%. Moreover, even among those who developed PHN, the burden of illness was reduced by approximately 61%. It must be noted that the immune-boosting effect of the vaccination is not long-lasting, and interval re-vaccination is necessary to maintain its efficacy. [3] Additionally, the current formulation of the vaccine is a live-attenuated virus, theoretically capable of causing infection in immunocompromised individuals, therefore limiting its use in this population.[3] However, in late 2017, the FDA Advisory Committee approved a subunit, non-live vaccine (Shingrix) for use in the United States for individuals over the age of 50. Shingrix may be used in immunocompromised individuals and may confer greater protection against HZ and PHN than the original live-attenuated virus in all patient populations. Preventative vaccination of at-risk populations may ultimately prove to be the safest and most efficacious approach in addressing the significant morbidity associated with PHN.

The other approach is to attempt to prevent the progression of HZ to PHN, with the understanding that the severity of an HZ episode is a risk factor for PHN. Unfortunately, the available evidence supporting this technique is by no means robust, and existing investigatory studies are suboptimally designed for the endpoint in question. Therefore, while antiviral drugs, glucocorticoid administration, and/or invasive procedures may reduce the severity of an HZ episode in certain instances, there is no clear evidence that these methods, alone or in combination, result in a reduced incidence of PHN. Simply stated, higher-quality studies are needed for a definitive stance.

## Enhancing Healthcare Team Outcomes

Considering that PHN is difficult to treat, and outcomes are variable, prevention is of paramount importance. Primary care physicians and geriatricians are therefore tasked with administering vaccinations to at-risk populations. When preventative measures fail or are never instituted, experts in the field of pain management who have experience with the condition and multimodal treatment techniques should be consulted.

## Review Questions

- Access free multiple choice questions on this topic.
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