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Zoster-Associated Pain and Post Herpetic Neuralgia

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1. Introduction

Herpes zoster (HZ, shingles) is a disease characterized by monolateral vesicular rash and pain, due to reactivation of VZV in the context of a waning specific anti-VZV cell-mediated immunity. Reactivation of VZV produces a new wave of viral replication within the dorsal root ganglia where latency was established after primary infection and its spread downwards to peripheral metameric fibers through the skin, all sensorial manifestations being the expression of VZV-related inflammatory response in sensory ganglia and nerve fibers. Systemic symptoms (fever, headache, malaise) are rare, being observed in some 20% of patients. Other manifestations as facial palsy can be observed in peculiar localizations as zoster oticus, or in particular categories of patients, such as vesicular dissemination in severely immunodepressed patients (Dworkin et al., 2007).

2. Epidemiology

HZ is a common disease, and HZ incidence was estimated in up to 1 million new cases every year in the United States (Schmader et al., 2008). The average lifetime risk was estimated as high as 30% in the general population; as a consequence, it affects almost half of the population aged over 65 during lifetime (Insinga et al., 2005; Yawn et al., 2007; Dworkin et al., 2007). Incidence all around the world was estimated in several studies, being calculated as 1.2-5.2 cases/person-years (Hope-Simpson, 1965; di Luzio Paparatti et al., 1999; Chidiac et al., 2001; Insinga et al., 2005; Yawn et al., 2007; Gauthier et al., 2009). Most of these studies were retrospective, based on health research or insurance databases. This may have possibly introduced selection biases, as some HZ cases, such as mild cases not ever seeking medical care, may have not been recorded or may have been incorrectly coded under the CDC ICD-9 or similar coding systems (Joesoef et al., 2011). Detailed information about pain, clinical aspects and therapy are not usually present in such databases, even though these studies usually include larger number of patients in comparison with prospective collections. In at least two cases, however, prospective evaluation of the incidence of HZ has been attempted in recent years (Oxman et al., 2005; Parruti et al., 2010). The Shingles

Prevention Study (Oxman et al., 2005) was a randomized double-blind placebo-controlled trial set up to demonstrate that vaccination against VZV can decrease the incidence and severity of HZ and post herpetic neuralgia (PHN), its more frequent complication. In this study 38,546 healthy subjects aged >60 years were randomly assigned to receive either a mock vaccine or an investigational live-attenuated VZV vaccine. In the large placebo arm (19,276 subjects) the incidence of HZ was 11.12 cases/1000 person-years (Oxman et al., 2005). An Italian cohort (Parruti et al., 2010) prospectively enrolled HZ patients of any age (mean age was 58 years, with 46% of patients aged <60 years) presenting to general practitioners, pediatricians or hospital specialists (dermatology, infectious diseases, pain management center) in a Local Health District. Incidence of HZ was prospectively calculated in a subset of that study, that is considering only cases consecutively enrolled by general practitioners, whose reference population is known. HZ incidence was 3.99 cases/person-years, over a total reference population of nearly 35,000 persons (Tontodonati, unpublished personal data). These data are largely congruent with those reported using different experimental models (di Luzio Paparatti et al., 1999; Chidiac et al., 2001; Insinga et al., 2005; Yawn et al., 2007; Gauthier et al., 2009). It is widely accepted that HZ incidence increases with age: even though HZ is not rare among young people, median age at presentation is around 64 years (Dworkin et al., 2007). Some decades ago, Hope-Simpson (Hope-Simpson, 1965) conducted a longitudinal study among his own outpatients, being a general practitioner, and estimated an increasing incidence of HZ from pediatric to older age: he estimated an incidence of 0.74 cases/person-years in children aged ≤10 years, 2.5 in patients aged 20-45 years, up to 7.8 cases/person-years in patients aged ≥65. HZ estimates in different countries (Iceland, France, Netherlands, United Kingdom, USA) and with different methodologies confirmed that HZ incidence rises with age (Hegalsson et al., 2000; Chidiac et al., 2001; Opstelten et al., 2002; Insinga et al., 2005; Yawn et al., 2007; Gauthier et al., 2009; Oxman et al., 2005). HZ incidence is known to increase in immunodepression, being more frequent and aggressive in transplant recipients, cancer patients, HIV-infected people, and in patients with autoimmune diseases (rheumatoid arthritis and lupus erythematosus sistemicus among others), diabetes, hypertension, renal failure and chronic obstructive pulmonary disease (Hata et al., 2011; Yi et al., 2010; Yang et al., 2011; Schmader et al., 2008). Notwithstanding this evidence, HZ can be considered a disease involving immunocompetent subjects in the vast majority of cases (Hegalsson et al., 2000; Oxman et al., 2005; Yawn et al., 2007; Parruti et al., 2010; Drolet et al., 2010). Contacts with patients with Varicella, more frequent for some professionals as pediatricians and teachers, turned out to be protective (Thomas et al., 2004), in line with the biological assumption that exposure to VZV may boost and strengthen natural cell-mediated immunity (Vossen et al., 2004). Recent studies investigated the role of Varicella vaccination programs in the epidemiology of HZ. Pediatric Varicella vaccination with a live attenuated vaccine was first introduced in the United States in 1995 and in many other countries in the following years. Universal Varicella vaccination programs will decrease the number of wild type Varicella cases (Jumaan et al., 2005; Schmader et al., 2008,; Reynolds et al., 2008). As contacts with patients with Varicella may be protective for HZ (Thomas & Hall, 2004), the decrease of Varicella in the general population will likely produce an increase in the incidence of HZ in the absence of parallel plans of population-wide HZ vaccination (Reynolds et al., 2008; van Hoek et al., 2011; n Schmader et al., 2008). Some other factors have been associated with an increased incidence of HZ. Trauma and surgical interventions have been suggested in

several case reports, case series and a single case-control study (Foye et al., 2000; Levy & Smyth, 2002; Evans & Lee, 2004; Thomas et al., 2004; Godfrey et al., 2006). Psychological stress was also associated with an increasing incidence of HZ (Thomas & Hall, 2004). Finally it is unclear whether a real difference exist in the incidence of HZ between sexes, female sex purportedly representing a predisposing factor in some studies (Thomas & Hall, 2004).

Post Herpetic Neuralgia (PHN) is the most common complication of HZ, ensuing in 10 to 20% of patients on average. Its prevalence has been estimated to range from 500,000 up to 1 million cases in United States (Schmader et al., 2008). Its incidence has been calculated in several studies in parallel with the incidence of HZ (Hope-Simpson, 1975; Hegalsson et al., 2000; Opstelten et al., 2002; Scott et al., 2003; Parruti et al, 2010). The first study deserving quotation is again by Hope-Simpson in 1975 (Hope-Simpson, 1975). Among his outpatients, he observed HZ and kept note of PHN during a period of over 25 years: he calculated the incidence of PHN as 14.3% and he observed an increase in PHN in older patients, with incidence raising up to 34.4% in patients aged >80. This observation was later confirmed in several studies. A large prospective population-based study was conducted in Iceland some years ago on local residents (Hegalsson et al., 2000). Lost to follow up were really few, and the study period was extraordinary long. They found a relatively low incidence of PHN in 421 HZ patients (6.95% in subjects aged >60), followed up to 7.6 years and gave formal evidence that PHN may last for as long as 5 to 7 years in a small proportion of patients (Hegalsson et al., 2000). A Dutch study estimated an incidence of 6.5% or 2.6% according to different definitions of PHN used (pain persisting at 1 and 3 months after HZ rash onset, respectively) (Opstelten et al., 2002). A significantly higher proportion of incident cases was reported in an English study, whereby PHN incidence was calculated in a prospective sample of patients referring to general practitioners in East London (Scott et al., 2003). The authors observed a 38% incidence at 6 weeks and 27% at 3 months after rash onset. Such differences may partly be due to different definitions of PHN (as discussed below), to a proactive search for pain persistence in some prospective studies, and to the lack of data on pain severity in most studies. All these methodological issues may have well hampered reporting of cases with less intense pain persistence, making comparisons difficult, as well as a meta-analytic evaluation of the incidence of PHN hardly obtainable. Finally, a wide array of factors influencing the incidence of PHN has been described in recent years (see below). A significant variation in the distribution of such factors in different populations may well contribute to the variability in the incidence of PHN in different studies.

3. Prodromal and acute pain in herpes zoster

Moving from the epidemiological to the clinical perspective, pain in HZ is the main element as it severely impacts patients' life in the acute phase, as well as within prodromic phases and possibly during persistence after rash healing. As the predominant HZ clinical feature, pain has been described as prodromal, acute and post herpetic; more recently, some authors proposed a new classification (Jung et al., 2004) as acute, subacute and post herpetic neuralgia (120 days after rash healing). More comprehensively, however, pain can be considered as a continuum from its prodromal phase to its latest presence in post herpetic neuralgia. The definition of post herpetic neuralgia has been questioned until recently, the most important matter of discussion being the time threshold to define its onset. Pain often begins in the same area as cutaneous lesions, even before rash appearance, being the only

clue possibly leading to the early diagnosis of HZ until rash appears: in this phase it is referred to as **prodromal pain**. Its characteristics are similar to that of acute pain during rash: it is described as sharping, burning, lancinating, shooting or throbbing, with a variable duration from 1-2 days up to one week (Volpi et al., 2007; Benbernou et al., 2011). It has been extensively investigated because of its important role in the diagnosis and of its predictive value for HZ severity and complications (see discussion below). A recent study (Benbernou et al., 2011) investigated prodromal pain and its burden of illness in a prospective sample of HZ patients referring to general practitioners and specialists: prodromal pain was common, occurring in almost 75% of patients aged ≥50 years, its mean duration before rash onset being 5 days and nearly half of patients rating their pain as severe. The authors clearly showed that the intensity of prodromal pain was related to the number of cutaneous lesions, as well as to the intensity of acute HZ pain. Prodromal pain is probably the clinical expression of the beginning of VZV reactivation and subsequent inflammatory responses in latently infected ganglia (Garry et al., 2005): its duration is likely to reflect the time necessary to VZV to replicate, run downwards along sensory nerve fibers, replicate in the skin and produce inflammatory damage and necrosis that is expressed in the appearance of the rash. Prodromal pain has also been associated with the risk of PHN: the higher its intensity and the longer its duration, the higher gets the probability that PHN may ensue after rash healing (Decroix et al., 2000; Jung et al., 2004; Katz et al., 2005; Volpi et al., 2008). This association may suggest that in patients destined to establish PHN replication of VZV in the ganglia and nerve fibers may be more long-lasting (Kleischmidt-Demasters & Gilden, 2001; Gilden et al., 2000). Pain accompanies the typical rash from onset to resolution. Typically, HZ appears as a monolateral dermatomeric papulo-vesicular rash, spreading proximal to distal in the involved regions (*see Figure 1*). First erythematous at its onset, rash rapidly evolves into papules and then vesicles, usually within 12-24 hours; vesicles tend to be confluent, clusters appearing more often where nerve fibers reach on skin surface (e.g. parasternal, median axillary, paravertebral; *see Figure 1.A*). They finally develop into ulcers and crusts. New waves of vesicles can ensue up to 3-7 days after rash onset in immunocompetent patients, so that lesions in different evolutive stages can be observed at the same time. Crusts detach in the following 3-4 weeks, leaving long-lasting scars and dischromic alterations in few cases. Pain has been reported as more intense when HZ is localized in the cranial dermatomes, that are involved in approximately 10 to 15 % of cases, whereas thoracic dermatomes are involved in over one half of cases (Dworkin et al., 2007). Pain can worsen into the rash phase, or it can appear for the first time in patients not experiencing prodromal pain. It has the same features as prodromal pain and may be accompanied by pruritus. The **acute phase** is dominated by a typical neuropathic pain, sharply confined along the involved dermatome(s) in the immunocompetent patient. Pain is often associated with neighboring allodynia and hyperalgesia, with an area of hypoalgesia surrounding all the involved areas. Patients often report that even a slight contact with clothes or with sheets can produce profound discomfort. Indeed in HZ this is the major cause of sleep disturbances and loss of working days. In a small proportion of patients, VZV-related pain can appear in the complete absence of cutaneous lesions, being then referred to as "zoster sine herpete": this entity has been supported by serological and molecular evidence of VZV reactivation in some acute pain syndromes, clinically very similar to HZ (Nagel et al., 2007; Dworkin et al., 2007).

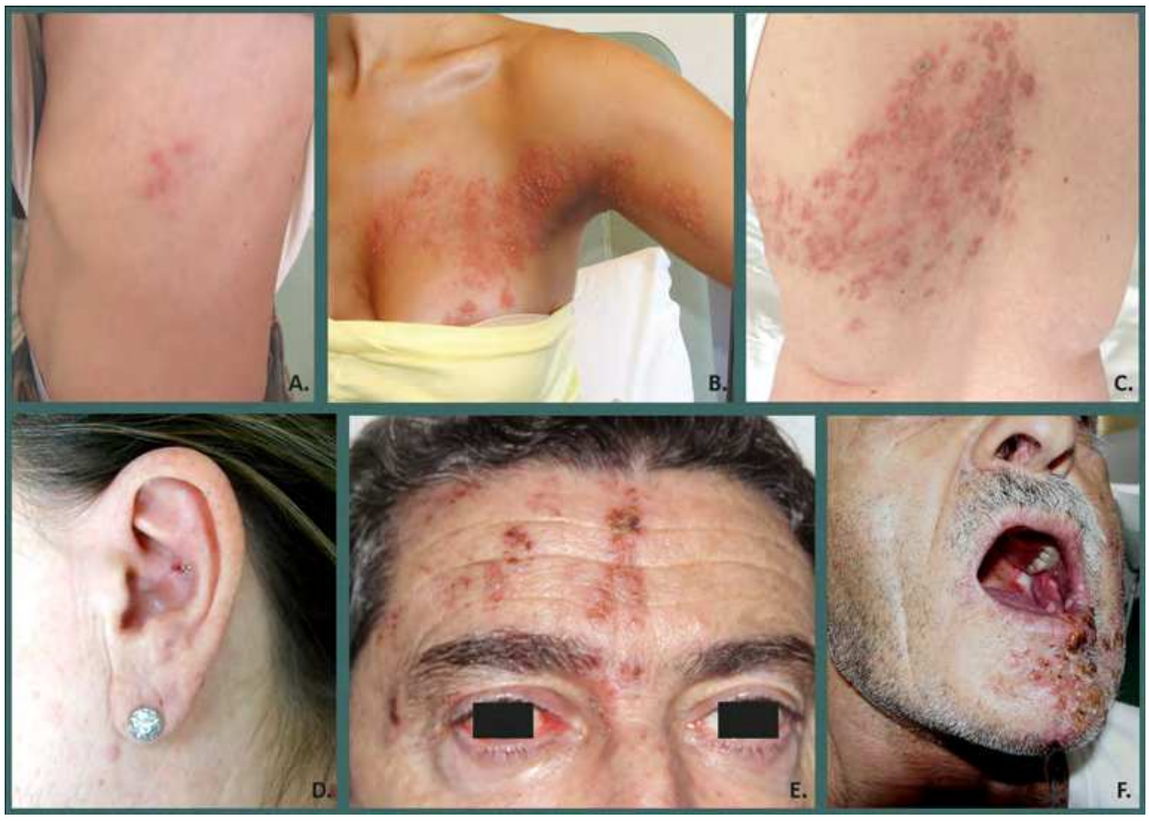


Fig. 1. Different clinical manifestations and localization of HZ rash. **A.** Minimally expressive rash, expressing in only few papules in the median axillary region. **B.** Typical dermatomeric rash, with a high number of lesions in the vesicular phase. Note that HZ rash never crosses the median line. **C.** Multidermatomeric rash, highly skin-destructing with a large number of lesions expressing in purulent vesicles; typical in immunodepressed patients. **D.** HZ oticus, vesicle within the ear. **E.** HZ ophtalmicus, involving the first branch of trigeminal nerve and the eye. **F.** Devastating maxillary HZ, involving with vesicles, crusts and ulcers the skin surface, the internal mucosa of the mouth and the tongue surface until the median line. Personal clinical experience.

4. Post herpetic neuralgia

HZ is usually a self limiting disease, with pain quenching at the end of vesicular eruptions. In a significant proportion of patients, however, it can persist or relapse months to years after rash healing, being then referred to as PHN. Pain in PHN is described as burning, throbbing or lancinating, similarly to that in acute HZ, or electric-shock-like, intermittent or continuous, sometimes associated with allodynia or hyperesthesia; it spreads along the interested dermatome(s) in the same way as during HZ. PHN has been variously defined as pain persisting or resuming 4, 6, 8, 12 weeks, and up to 6 months after rash healing. At the end of the 90's, Dworkin and Portenoy proposed a definition that was widely accepted: they set the time point for the diagnosis of PHN at 3 months after rash healing (Dworkin & Portenoy, 1996), referring to pain persisting at earlier time points as *Zoster-Associated Pain* (ZAP). More recently this definition has been revised, with a further distinction (Arani et al.,

2001; Jung et al., 2004, Niv & Maltsman-Tseikhin, 2005): pain present within 30 days from the onset of rash is defined as acute herpetic neuralgia; pain present between 30 and 120 days is defined as subacute herpetic neuralgia; pain persisting after 120 days from the onset of HZ is defined as PHN. Moreover other authors introduced the concept that only clinically relevant pain should be defined as PHN, to avoid overestimation of the problem: they proposed PHN to be defined as pain ≥3 on a 10-point VAS scale persisting 120 days after rash healing (Coplan et al., 2004; Oxman et a., 2005; Thyregod et al., 2007). All these definitions, however, introduce purely arbitrary partitions of an entity that is a continuum, from prodromal to post herpetic pain. According to this more comprehensive view, in recent years PHN has been considered and valued differently. Some authors proposed to measure its total burden with a single comprehensive parameter. Coplan et al. used an area-under-the-curve (AUC) method to combine measures of HZ pain intensity and duration (Coplan et al., 2004). The AUC was calculated by multiplying the average of two consecutive worst pain scores by the number of days between the scores. AUC highly correlated with other pain, quality-of-life and activities-of-daily-living validated questionnaires, showing its efficacy to take into account the total burden of HZ pain. This approach was developed and validated to assess and quantify HZ burden of illness (HZBOI) in the Shingles Prevention Study (Oxman et al., 2005). The prospective Italian study already quoted had a very similar approach, using verbal rating pain scores instead of worst pain scores in the calculation of AUC (Parruti et al., 2010). A recent study (Drolet et al., 2010) used a slightly different measure (HZ severity of illness, HZSOI) in which scores below 3 on a 0-to-10 scale were considered as zero, as they have been demonstrated not to affect relevantly quality of life and activities of daily living (Thyregod et al., 2007). The predictive role of HZSOI for greater acute and post herpetic pain burden was assessed in 261 HZ patients enrolled within 14 days of rash onset, strictly followed with different pain questionnaires up to 6 months (Drolet et al., 2010). Greater acute burden was significantly associated with higher pain intensity at presentation, higher number of cutaneous lesions, lower income and conditions of immunodepression. Higher acute pain severity, lower income, being immunocompromised, older age and not receiving antivirals were also predictors of greater post herpetic burden. All these attempts introduced a potentially relevant tool to better estimate the impact of HZ and PHN in real life and to thoroughly assess the cost-efficacy of preventive extensive vaccination for HZ. In this approach to ZAP and PHN, structured tools for pain assessment have been valued. Verbal rating scales, asking to the patient to define his pain as no pain, mild, moderate, intense or very intense, are easy to handle in real clinical life, but don't allow to stratify and better characterize pain. Visual Analogue Scales (VAS) have been extensively investigated and used in various settings of pain clinical management (Hao et al., 1994; Thyregod et al., 2007), allowing a more precise identification of the single patient's pain level, and being easily understood by patients. Other structured tools have been defined in recent years: McGill Pain Questionnaire and its Short Form (Melzack 2005) are widely used for pain evaluation in a consistent part of more recent studies (Melzack & Togerson, 1971; Thyregod et al., 2007; Ursini et al., 2010) as they allow to evaluate different pain dimensions (sensory, affective and mixed features). Zoster Brief Pain Inventory (ZBPI) is the more specific tool designed on-purpose for HZ pain (Coplan et al., 2004): it includes discomfort other than pain, such as itch, occurring in the same area as HZ rash. It measures the severity of pain (current, least and worst) in the last 24 hours on an 0-to-10 scale, together with HZ pain interference with various activities of daily life. This tool

was shown to have a good validity in the context of ZAP and PHN (Coplan et al., 2004; Oxman et al., 2005). Both HZ and PHN have a considerable impact on patients' quality of life and daily life activities. A few studies investigated this impact, especially in recent years, in order to assess the total burden of these conditions and possibly to establish the cost-effectiveness of HZ vaccination. Poorer physical, role and social functioning and greater emotional distress was reported in a sample of 110 patients with intense acute pain in HZ (Katz et al., 2004), using a composite measure of overall pain burden in the first 30 days after rash onset. In this sample, patients experienced average pain of moderate intensity most of the time. In a multicenter prospective study enrolling 261 HZ patients followed up to 6 months, HZ had a major impact on the quality of life, especially on sleep (64%), enjoyment of life (58%) and general activities (53%). In the same study, PHN mostly affected enjoyment of life, mood and sleep (Drolet et al., 2010). An interesting study with a different methodology was conducted in Germany, enrolling patients by means of telephone interviews (Weinke et al., 2010). More than 11,000 subjects were contacted and 280 were enrolled, having experienced HZ in the previous 5 years. They were asked about ZAP and its characteristics and impact on quality of life. Both HZ and PHN had substantial impact on daily activities, mobility, work, sleep, social relationships and overall quality of life. Authors agreed that more attention should be paid to this aspect of HZ and PHN in designing research studies and health and prevention policies, as it is certainly the most important element from the patient's perspective.

The understanding of the pathophysiological mechanisms underlying the onset of chronic pain typical of PHN is still an open challenge. The initial viral replication causes direct damage by neuritic inflammation on the rear dorsal root, resulting in the involvement of the corresponding nerve and of spinal cord metamers. Necrosis of neural and scaffolding cells in the posterior root ganglia occurring during the acute phase of HZ is followed by fibrosis and destruction of nerve tissue at all levels of pain transmission, from peripheral afferent fibers to the spinal cord (Johnson, 2003; Bartley, 2009). Several studies have documented atrophy of the posterior horn in the spinal cord, fibrosis of the posterior root ganglia and loss of cutaneous innervation, with pathological degeneration of cell bodies and axons of primary afferent neurons (Dworkin et al., 2007). Therefore, patients with PHN often experience hypoesthesia (mainly as a result of peripheral denervation) and pallestesia (mainly for non-uniform loss of the various nerve fibers resulting in impaired sensory discrimination) in association with pain. Anyway, the precise mechanisms at the basis of typical pain in PHN remains still unclear and attempts to explain this by a single unifying theory elusive. The pathophysiology of PHN may involve both peripheral and central mechanisms. According to the gate control theory, a sensory input reduction from peripheral nerves starting from Aβ fibers causes an increase of Aδ and C fibers firing onto the posterior horn of the spinal cord: this last event, in turn, "opens the gate" to pain "from deafferentation". PHN, then, could be viewed as a chronic pain syndrome due to deafferentation (Oaklander et al., 2001). Other authors have tried to clarify the central mechanisms underlying the genesis and persistence of pain in PHN. Sensitized C fibers would not be responsible for hyperalgesia in PHN, but the mechanism involved would stand in the strengthening of existing synaptic connections between the central pain pathways and peripheral Aβ fibers (Baron & Saguez, 1993). The traditional theories of pain in PHN, as exposed above, have mainly focused on anatomical and functional changes of nerve cells and pain pathways. However, several studies revealed interesting aspects about CNS support cells and structures. It is known that glia (astrocytes and oligodendrocytes) and their receptors

produce factors influencing neuronal functioning. A study in 2001 showed that persistent inflammation in glial cells is involved in the induction and maintenance of various conditions characterized by chronic pain (Watkins et al., 2001). At the level of the peripheral nervous system, Schwann cells and satellite cells in dorsal root ganglia of the posterior roots constitute together the peripheral glia, with many similarities with oligodendrocytes and astrocytes (Sorkin et al ., 2007). Damage of myelinated fibers would activate Schwann cells and satellite cells, releasing in turn neuro-excitatory mediators such as TNF-α (Hanani et al., 2005). According to this hypothesis, these substances would act as the mediators of neuronal damage (Oaklander et al., 1998). Other support structures putatively involved in the pathogenesis of chronic pain are *vasa nervorum* and *nervi nervorum*, which are responsible for vascular and nervous support, respectively, of the nervous system itself. All the layers of a nerve are "innervated" and have a subtle but important complex of nociceptors: *nervi nervorum* are potentially able to induce a neurogenic inflammatory reaction (Sauer et al., 1999; Bove et al. 2008), through the release of substance P, calcitonin gene-related peptide and nitric oxide, increasing permeability of *vasa nervorum* of the neighboring blood vessels (Zochodne et al., 1997; Bove et al., 2008). The hypothesis that the activation of trophic (*vasa nervorum* and *nervi nervorum*) and support structures (Schwann and satellite cells) of the peripheral nerve would play an important pathogenic role in PHN may have important therapeutic implications (Bartley, 2009). In recent years, another interesting hypothesis has been worked out. In 2003, Gilden et al. reported the case of a patient with PHN followed for 11 year (Gilden et al., 2003). In the initial phase, the detection of VZV DNA in blood mononuclear cells in 2 consecutive occasions suggested the use of antivirals in an attempt to quenching pain. In random blood assays following treatment with famciclovir, VZV DNA was not detected. The patient, however, discontinued treatment for 5 five times: on all these occasions, the VZV genome was again detectable in blood mononuclear cells and pain resumed. Considering the recurrence of VZV DNA after discontinuation of treatment in parallel with the presence of segments of the VZV genome in blood mononuclear cells, the increase of cell-mediated response to VZV and the positive clinical response to the resumption of antiviral therapy induced the authors to speculate that PHN could be supported by chronic ganglionitis induced by VZV. Although this hypothesis was based on the persistence of VZV DNA in blood mononuclear cells, the mechanisms involved in the development of this syndrome are still unknown. To this end, several studies in recent years attempted to evaluate the role of the immune system in the pathogenesis of PHN. A Chinese work published in 2009 analyzed the relationship between the trigger pro-inflammatory cytokine produced by T lymphocytes in the acute phase of HZ and the development of PHN. The 74 subjects enrolled in the study were divided into 3 groups: a first group of patients who developed PHN, a second group with HZ in the acute phase and a control group. All subjects underwent clinical evaluation of pain (by VAS) and determination of serum levels of T-lymphocyte-derived cytokines. This study showed that patients with PHN had IL-6 serum levels higher than subjects with HZ. The levels of other cytokines (TNF-α, IL-1β, IL-8) were, however, similar between the two groups. These findings would indicate that these cytokines are implicated in the pathogenesis of HZ but not in that of PHN. However IL-6, a pro-inflammatory cytokine considered an early tissue damage marker, would play an important role in the pathophysiological mechanisms underlying the development of chronic pain in PHN, as demonstrated by the correlation between serum levels of this cytokine and the VAS scores obtained in patients with PHN (Zhu et al., 2009).

The different hypotheses so far postulated are not mutually exclusive, so that the factors involved in the pathophysiology of chronic pain in PHN may well be multifactorial. Therefore, further studies are needed to link all these findings together, to allow a more comprehensive view of this severe and disrupting condition and to develop targeted therapies for PHN.

Beyond PHN, other complications of HZ have been described, although much rarer that PHN (Dworkin et al., 2007, Gilden et al., 2000,; Nagel & Gilden, 2007). All of these are related to the endothelial and vascular involvement that relapsing bursts of VZV replication in HZ may cause, having been exploratory described both in vivo and in vitro (Gilden et al., 2009). They include stroke in its extreme manifestation, that is when endothelial damage lead to large vessel occlusion(s) (Kang et al., 2009). Other neurological syndromes with a vascular genesis have been related to VZV, including large vessel granulomatous arteritis, causing multifocal encephalitis in the immunocompetent host, and small-vessel encephalitis, relatively more frequent in the immunocompromised hosts (Gilden et al., 2000, Nagel & Gilden, 2007). Transverse myelitis is another fortunately rare but invalidating expression of small vessel involvement in the spinal cord (Gilden et al., 2000). Finally, retinal necrosis may occur in a small proportion of patients (Nagel & Gilden, 2007).

In summary, the updated epidemiology and clinical appraisal of HZ manifestations generate a renewed picture of a frequent disease that has per se a very relevant impact on the quality of life and social functioning of the affected patients. Adding to that the invalidating impact of PHN, still poorly treatable and ultimately incurable, as well as the major impact of the rarer but even more serious vascular and neurological complications of HZ, the questions as to whether HZ and its complications can be predicted and prevented become of the highest clinical interest.

5. Can ZAP and PHN be predicted?

Predictors of PHN in the acute phase of HZ have been extensively investigated in order to point out patients who are at higher risk of developing this painful syndrome and need to be monitored more carefully during follow-up. ZAP gained due attention only recently, even though pain at presentation was assessed in most of trials and cohorts on HZ and PHN (Dworkin et al., 1998; Chidiac et al., 2001; Dworkin et al., 2001). Acute pain at HZ presentation is rated as severe in a consistent proportion of patients (25%, 41%, 70%, …) and has been addressed for its impact on quality of life (Chidiac et al., 2001; Dworkin et al., 2001). Recently, an Italian study on 519 HZ patients showed that female patients who were older, present or past smokers, with a history of trauma or surgery at the site of HZ were more likely to have moderate-severe pain at HZ presentation (Parruti et al., 2010). In another Italian study on 533 HZ patients, the intensity of pain at presentation was associated with the extent of rash, presence of prodromal pain, dysesthesia, education level and depression, but not with gender, anxiety or quality of life (Volpi et al., 2007). In a Dutch study on 598 patients, female gender, younger age, severity of rash, shorter duration of rash prior to inclusion, longer duration of prodromal pain, and an anxious character were independently associated with higher intensity of acute zoster pain (Opstelten et al., 2007). Pain severity at presentation has not been investigated in other settings and more attention should be given to this element that dominates HZ clinics. More recently, acute HZ pain has been considered as a continuum and not only as a single point measure, and acute pain burden has been evaluated in a prospective study conducted across Canada (Drolet et al., 2010): greater acute

burden was associated with greater pain intensity at presentation, greater number of lesions, lower income and being immunocompromised. Further studies on acute pain in different settings could be similarly useful. PHN, on the other hand, has been extensively investigated in different settings and a great deal of information is now available. PHN has been repeatedly associated with **older age** (Dworkin & Portenoy, 1996; Choo et al., 1997,; Dworkin et al., 1998; Decroix et al., 2000; Opstelten et al., 2002; Kurokawa et al., 2002; Scott et al., 2003; Jung et al., 2004; Opstelten et al., 2007; Volpi et al., 2008; Parruti et al., 2010; Drolet et al., 2010). Some decades ago, Hope-Simpson already envisaged this association observing his own HZ outpatients (Hope-Simpson, 1975), and in the following years older age has been one of the factors more frequently associated in almost all studies where it was investigated. Indeed several cohort studies (Choo et al., 1997, Dworkin et al., 1998; Decroix et al., 2000; Opstelten et al., 2002; Kurokawa et al., 2002; Scott et al., 2003; Jung et al., 2004; Opstelten et al., 2007; Volpi et al., 2008; Parruti et al., 2010; Drolet et al., 2010) found significantly older age in patients developing PHN, in samples up to 1,900 patients. The SPS placebo arm, as well, provided evidence as to the predictive role of older age: enrolled subjects were stratified in two subgroups (60-69 years and ≥70 years), and PHN incidence in the 19,247 subjects was 0.74 cases/1,000 person-years in the first subgroup and 2.13 cases/1,000 person-years in the older (Oxman et al., 2005). Central and peripheral nervous systems in the elderly may probably tolerate less efficiently the damage associated to VZV reactivation and the consequent burst of immune response (Baron et al., 1997). **Pain at presentation**, together with older age, is the other best-established risk factor for PHN (*see Figure 2 and 3*): the more severe pain is at presentation, the more frequent PHN will be. It has to be considered that there are some difficulties in lumping up data from studies using different definitions and designs: trials have larger number of patients compared to cohort studies, but cohorts allow to search for a larger number of variables, even though not all planned at the beginning of the study. Some years ago, trials on antiviral therapy for HZ suggested the importance of pain intensity at presentation in predicting PHN (Dworkin et al., 1998; Whitley et al., 1999); several cohort studies confirmed these data in real life (Decroix et al., 2000; Scott et al., 2003; Jung et al., 2004; Katz et al., 2005; Opstelten et al., 2007; Volpi et al., 2008; Parruti et al., 2010) (*see Figure 2 and 3*). The pathogenesis of this correlation is still unclear: the intensity of acute pain may reflect central structural and functional processes, such as excitotoxic damage in the dorsal horn, and damage to primary afferent nociceptors (Bennett , 1994).

Other factors have been proposed as possible predictors of PHN. **Severity of rash**, assessed as the number of lesions appearing on the patients' skin at presentation, has been significantly associated with PHN in several studies (*see Figure 3*) (Dworkin et al., 1998; Whitley et al., 1999; Nagasako et al., 2002; Kurokawa et al., 2002; Jung et al., 2004; Opstelten et al., 2007; Volpi et al., 2008). HZ patients with greater rash severity at presentation have a greater risk of PHN, suggesting a relationship between the extent of neural damage and the development of PHN; this interesting and comprehensive hypothesis, however, has not been yet demonstrated (Nagasako et al., 2002). In a recent survey, rash severity was correlated with age and immunodepression but not with use of steroids and diabetes (Tontodonati, unpublished personal data). The presence of **prodromal symptoms** (pain, dysesthesia, allodynia, …) and their duration before the appearance of rash had a negative predictive value for PHN of 95% (Jung et al., 2004; Volpi et al., 2007; Decroix et al., 2000; Katz et al., 2005): this association may reflect a more intense involvement of nerve fibers by

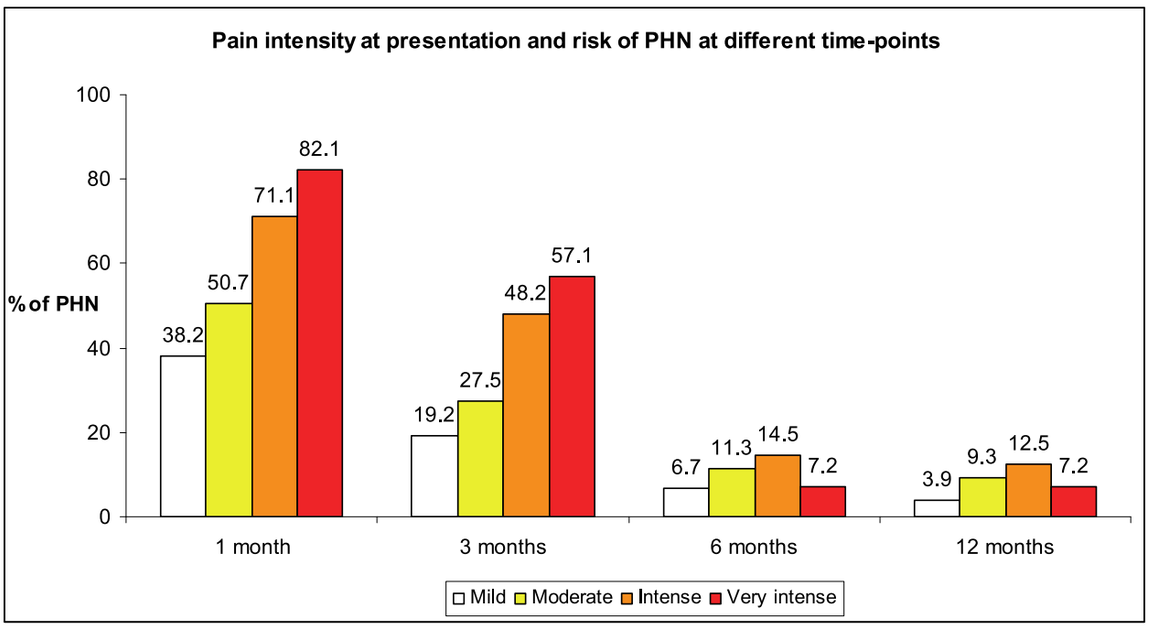
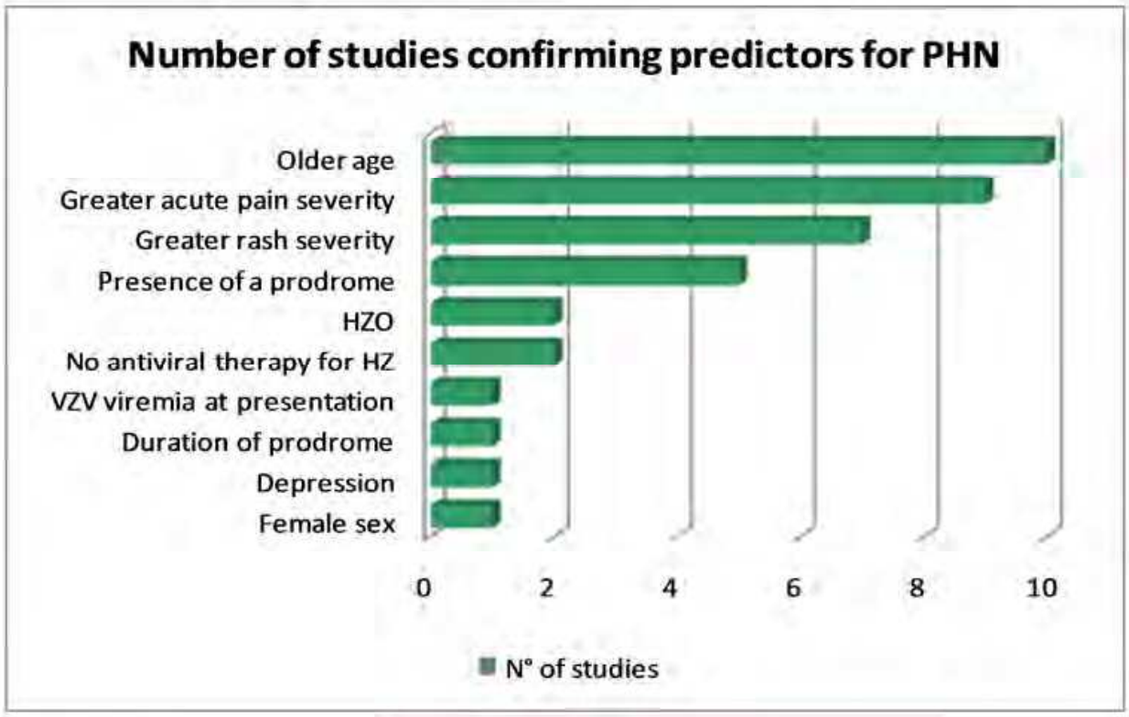


Fig. 2. Pain intensity at presentation and risk of PHN at different time-points. Pain at presentation predicts PHN: the higher pain at HZ presentation is, the higher risk of developing PHN will be (Parruti et al., 2010, with permission).



Authors	Patients	Design	PHN definition
Choo 1997	821 HZ – PHN n.d.	Retrospective	Pain persisting 1m and 2m after rash onset
Dworkin 1998	419 HZ – 129 (n.d.) PHN	Famciclovir trial	Pain following rash healing, 1 (and 3) m after HZ diagnosis
Whitley 1999	n.d.	Acyclovir and prednisone trial	Time to cessation of acute neuritis (Cox)
Decroix 2000	1897 HZ – PHN n.d	Open-label valacyclovir trial	Time to cessation of ZAP (Cox)
Opstelten 2002	837 HZ – 54 PHN	Retrospective	Pain 1m after HZ diagnosis
Nagasako 2002	1778 HZ – PHN n.d.	4 famciclovir trials	Pain present 3m after rash onset
Kurokawa 2002	263 HZ – PHN n.d	Prospective	Pain persisting >3m-6m after HZ diagnosis
Scott 2003	278 HZ – 42 (78) PHN	Prospective	Pain present at 6w (and 3m) after HZ diagnosis
Jung 2004	965 HZ – 114 PHN	2 famciclovir trials	Pain persisting 120d after rash onset
Katz 2005	129 HZ – 20 PHN	Prospective	Pain persisting 120d after rash onset
Opstelten 2007	598 HZ – 46 PHN	Prospective (in the PINE study)	Pain ≥30/100 VAS 3m after HZ diagnosis
Volpi 2008	219 HZ – 70 PHN	Prospective	Pain present 6m after HZ diagnosis
Parruti 2010	519 HZ – 226 (130) PHN	Prospective	Pain persisting / relapsing 1 (and 3) m after HZ diagnosis

Fig. 3. Evidence confirming predictors of PHN. Several studies with different size and designs have investigated predictors of PHN. Older age and greater pain at presentation are the best well-established risk factors, emerging in most studies with no regards to different designs.

Viral reactivation in the early phases of HZ, leading to extended damage and PHN (Watson et al., 1991). Uncertainties still remain about **antiviral therapy** for preventing the occurrence of PHN in ordinary clinical settings. Most data come from clinical trials where antivirals were administered ≤72 hours from the onset of rash: this could have been a bias as most patients in real practice seek for medical attention after 72 hours (Volpi et al., 2008), antivirals being anyhow prescribed usually in the first 7 days from rash onset. As a consequence, the preventive role of antiviral therapy has been questioned until recently: a recent meta-analysis including most of these trials concluded that the role of therapy in preventing PHN is still uncertain (Li et al., 2009). However, different data came from different study designs. Conflicting results emerged even in trials on antivirals (Gnann, 2007): in a famciclovir trial (Dworkin et al., 1998), treatment of acute HZ significantly reduced both the incidence and the duration of PHN, whatever defined. A recent cohort prospective study (Parruti et al., 2010) collected all the incident cases of HZ in a specifically created network of General Practitioners and Hospital Centers in a local health service in Central Italy, resuming data from 519 cases on an estimated reference population of nearly 35,000 persons. In multivariate analyses for both PHN and the total pain burden due to HZ and PHN, PHN appeared to be significantly more frequent in patients who did not receive antiviral therapy and total ZAP was much higher in this small proportion of patients. Indeed, antiviral therapy is now largely prescribed for its documented positive effect in reducing viral shedding, new vesicular eruptions and pain intensity in the acute phase of HZ; these results suggest that antiviral therapy may be useful even in reducing the incidence of PHN and total ZAP. Further studies are needed, however, as the best way to assess this point would be an on purpose designed RCT. **Localization of HZ** has been associated with PHN, being more frequent in ophthalmic and thoracic zoster (Volpi et al., 2008). Serological and laboratory findings have been investigated, in order to identify novel predictors among elements easily accessible in a blood sample, as specific antibodies or VZV viremia. A prospective observational cohort study collecting HZ cases occurring among a network of General Practitioners in East London (Scott et al., 2003) suggested that higher levels of VZV DNA at HZ presentation may be a strong independent predictor of pain persistence (*see Figure 3*). **Surgical interventions** and **mechanical trauma** have been suggested as predictors of VZV reactivation, but their possible role in predicting PHN has been poorly investigated. In a recent prospective survey on 519 HZ patients (Parruti et al., 2010), trauma and surgical interventions were associated with higher pain intensity at presentation, only trauma being associated with a higher risk of PHN. Furthermore **cigarette smoking** has been scantly evaluated as a possible risk factor for pain intensity at presentation or PHN. In the same survey (Parruti et al., 2010), it was associated with both higher pain at presentation and higher risk of PHN, probably due to the prospective and proactive nature of the investigation. Indeed, smoking has not been searched for PHN prediction in other studies, in spite of data suggesting a possible role in chronic pain syndromes (Weingarten et al., 2008), subclinical peripheral neuropathy (Agrawal et al., 2007) and smoke-induced impairment of cell-mediated immunity (Sopori & Zozak, 1998). Further studies are needed to confirm these interesting and novel predictors. **Psychosocial factors** have been proposed to be associated both with a higher ZAP burden and higher risk of PHN. Depression, together with the severity of HZ disease at presentation, was associated with higher pain intensity and ZAP burden (Volpi et al., 2007). In a small prospective study (Dworkin et al., 1992), greater anxiety, greater depression, lower life

satisfaction and greater disease conviction were predictors at baseline for chronic zoster pain. In a large prospective sample of HZ patients in the Netherlands (Opstelten et al., 2007), investigating different psychological predictors for PHN, only trust in healthcare was associated with PHN risk, that is patients who expect that others will find remedies to their own pain could have a higher incidence of chronic pain. Hence, psychological factors may be useful in evaluating patients with HZ, even though further studies are needed. Finally, **female sex** has been proposed as a predictor of PHN, not yet reaching, however, a convincing level of evidence so far (Jung et al., 2004; Volpi et al., 2008; Parruti et al., 2010).

6. What is the best therapy for acute HZ to control ZAP and PHN?

6.1 Antiviral therapy

HZ is a self limiting disease, as patient's immune response usually contains viral replication. Treatment of the acute phase with antiviral drugs is widely recommended at present to contain vesicular eruption and diffusion and to reduce acute pain and malaise in the affected patients. The FDA approved acyclovir, valacyclovir (prodrug of acyclovir), famcyclovir (prodrug of penciclovir) and brivudin for HZ therapy. All these molecules are nucleoside analogues needing phosphorylation from viral thymidin-kinase. Their triphosphate forms inhibit viral DNA synthesis by competing as a substrate for viral DNA polymerase (Gnann, 2007). There have been no serious adverse reactions to these drugs, nausea and headache being the most common side effects in 10-20% of patients (Gnann, 2007). Dosage reduction is required in patients with renal insufficiency according to creatinine serum levels because of their renal excretion. Clinical trials did not find any difference in their cutaneous and analgesic effect. In clinical practice, however, some factors should be considered in the choice of HZ antiviral therapy. Acyclovir is the cheapest antiviral, with 5 doses of 800 mg per day necessary to achieve adequate serum levels. Therapy with acyclovir should last for 7-10 days. Furthermore acyclovir is the only one available in parenteral formulation. Valacyclovir has a higher bio-availability, allowing 3 doses of 1,000 mg per day for 7 days. Famcyclovir recommended schedule for HZ is 500 mg 3 times daily for 7 days. Brivudin can be prescribed once daily, 125 mg for 7 days. Valacyclovir, famcyclovir and brivudin have been shown to achieve higher blood concentration, compared with acyclovir. This may be relevant, due to physiological barriers hampering antiviral penetration in VZV-infected tissues (nervous tissue, CNS) and to relatively poor sensitivity of VZV to these drugs. Pharmacokinetic differences among drugs may be relevant as to their impact on patient's compliance to therapy, always related to final efficacy. Oral antiviral therapy for HZ is widely recommended for all immunocompetent patients aged ≥50 years, with moderate to severe pain intensity at presentation, as they have been shown to have higher risk of complications. However, given the safety profile of antivirals, and the persistent risk of complications even in patients with no demonstrated risk factors, antiviral therapy is recommended at present for every patient with HZ onset to reduce the duration of viral shedding, promote resolution of skin lesions, and limit the duration of pain (Gnann, 2007). Most trials in the literature considered antivirals as worth prescribing only <72 hours from rash onset. This time-points, however, do not necessarily reflect the end of viral replication in the skin. In clinical practice nearly half of patients get to medical observation and start antiviral therapy within this time-point, the others starting in general within the first 7 days from rash onset (Volpi et al., 2007; Parruti et al., 2010). A recent trial on 156 HZ patients, investigating the effect of antiviral therapy started

before and after 72 hours from rash onset, showed no significant difference in pain reduction, healing of lesions and PHN incidence (Rasi et al., 2010), thus providing valuable evidence for prescription of antivirals even beyond the 72-hour threshold. In immunocompromised patients with a higher incidence of HZ per se, antiviral therapy reduces dissemination, severity of disease and mortality. Acyclovir is the first choice in its intravenous formulation, 10-15 mg/kg every 8 hours, to administer up to 7 days after the ending of new vesicular eruptions or until healing is complete (Gnann, 2007). Valacyclovir in immunocompromised patients has been valued in a small trial (Arora et al., 2008). Its use needs further evidence, acyclovir remaining the best recommended drug in such patients.
The end of viral replication is the main aim of antiviral therapy in acute HZ: this objective should be pursued in parallel with the attempt to reduce the pain perceived, which mainly influences patient's quality of life. The classes of drugs currently available for this purpose are the following: corticosteroids, tricyclic antidepressants, anticonvulsants, opioid analgesics.

6.2 Corticosteroids

Although corticosteroids have limited effectiveness in reducing chronic pain, they may have some beneficial effect on acute pain: a number of studies in the literature have shown their positive action in association with antiviral therapy. The addition of prednisolone to the treatment with acyclovir was effective in reducing pain, in accelerating the regression of skin lesions and facilitating the return of the patient to normal daily activities (Whitley et al., 1996). Dworkin et al. (Dworkin et al., 2007) have shown that the use of corticosteroids in combination with antiviral therapy reduced the time to return to a restful sleep and normal activities of daily life and the use of analgesics. The German Society of Dermatology recommended the use of corticosteroids in acute herpetic pain, based on the results of two large prospective studies that showed the efficacy of high-dose corticosteroids is association with antiviral therapy both in alleviating Zoster – related pain and in accelerating rash healing (Gross et al., 2003). No study has, however, showed a preventive role of corticosteroids for PHN.

6.3 Tricyclic antidepressants (TCAs)

Tricyclic antidepressants (amitriptyline, nortriptyline) have a documented effect in the treatment of neuropathic pain syndromes, but their use in the acute phase of HZ has not yet been adequately investigated. In fact, although TCAs reduce pain by inhibiting reuptake of serotonin and norepinephrine (Stankus et al., 2000), they require at least 3 months to exert positive effects. In a randomized trial of patients older than 60 years, it was observed that 25 mg amiptriptyline, administered within 48 hours of rash onset and continued for 90 days, yielded a 50% reduction in pain at 6 months compared to placebo (Bowsher, 1997). In this context, it is important to emphasize that such drugs should be used with extreme caution, taking into account the severe anticholinergic side effects associated with their use, as they may precipitate an acute confusional state and may cause cardiac arrhythmias up to sudden cardiac death, especially in elderly patients (Wareham & Breuer, 2007).

6.4 Opioids

Opioid analgesics, such as oxycodone, morphine and tramadol are widely used in acute herpetic pain, often in combination with acetaminophen (paracetamol) or other nonsteroidal anti-inflammatory drugs (NSAIDs). However, among these drugs, only oxycodone and

tramadol have been the subject of studies specifically designed for acute herpetic pain. Oxycodone reduces acute pain, but there is yet no evidence of a possible role of this drug in the prevention of PHN. A recent randomized placebo-controlled trial compared the effectiveness of oxycodone and gabapentin in reducing acute pain, showing that oxycodone provided a greater pain relief (Dworkin et al., 2009). Tramadol, however, is effective in the treatment of PHN, but its efficacy in the treatment of acute herpetic pain has not been evaluated (Boureau et al., 2003).

6.5 Antiepileptics

Among the antiepileptic drugs, pregabalin and gabapentin have a demonstrated effect on chronic neuropathic pain, documented in several clinical studies and lack of significant side effects or drug interactions. Based on these data and considering the effectiveness of these drugs in other conditions of acute pain, gabapentinoids are also used for acute herpetic pain. Berry et al. showed that gabapentin reduced acute HZ pain (Berry et al., 2005). Preliminary evidences suggest a similar efficiency of pregabalin, in conjunction with an even better tolerability profile (Jensen-Dahm et al., 2011). Further prospective and on purpose designed evaluations, however, appear opportune before their use for acute herpetic pain may be widely recommended.

6.6 Nerve blocks

Use of nerve block injections is another option in the conventional medical armamentary for acute herpetic pain. Local anaesthetics may be injected around the affected nerves, providing immediate pain relief, typically lasting 12-24 hours (Roxas, 2005). Location of the nerve block is dependent on the involved dermatome. If head, neck or arms are affected, a stellate ganglion block is performed, with injections placed at the base of the neck, just above the collarbone. Dermatomal patterns involving chest, trunk or lower extremities are addressed via epidural blocks. Long term relief can be accomplished by repeating the procedure 2-3 times within a two-week period, provided it is administered at an early stages of the disease (Roxas, 2005). Although epidural, intrathecal, and sympathetic nerve blocks have all been used in the treatment of pain caused by HZ and PHN, the effectiveness of nerve blocks in reducing or preventing PHN is still somewhat controversial (Johnson, 1997). However, there are a few controlled randomized trials of nerve blocks in the prevention of PHN. Yanagida et al. reported no prophylactic effect of early sympathetic blockade on PHN (Yanagida et al., 1987). Two randomized trials have been performed for the prevention of PHN by single or repetitive epidural injections of anesthetics and steroids in the acute HZ (van Wijck et al., 2006; Pasqualucci et al., 2000). Van Wijck et al. showed no significant effect of epidural injections in reducing the incidence of PHN; Pasqualucci et al. reported that repetitive epidural administration of bupivacaine and methylprednisolone was significantly more effective in preventing PHN at 12 months compared with acyclovir and prednisolone. More recently, Genlin and colleagues examined the effectiveness of repetitive paravertebral injections with local anaesthetics and steroids for the prevention of PHN in patients with acute HZ. The findings of this randomized study show that repetitive paravertebral injections with bupivacaine and methylprednisolone in acute herpetic phase within 7 days of rash onset reduce the incidence of PHN more effectively than standard treatments (oral administration of acyclovir and analgesics) (Genlin et al., 2009). This preliminary evidence, in conclusion, would suggest that the repetition of the blockade procedure may be crucial to the long-term efficacy of ZAP control. Further data, however, are auspicable.

6.7 Other treatment options

In addition to the use of the above mentioned medications, alternative medical practices have been recently investigated for controlling acute herpetic pain (Ursini et al, 2011; Fleckenstein et al., 2009). Acupuncture, an ancient form of medicine that originated in China several thousand years ago, has been used by Canadian physicians since the 1970s. Research on the neurophysiology of acupuncture analgesia supports the theory that it is primarily mediated via the selective release of neuropeptides in the central nervous system. Furthermore, evidence is rapidly accumulating on the immunomodulating actions of acupuncture, as well as on its effects on neuroendocrine regulation, muscle and cardiovascular tone and the psycho-emotional sphere (Rapson et al., 2008). Acupuncture has long been regarded as an effective therapy for pain management in different conditions. Although several reports documented its use in HZ and PHN (Coghlan, 1992; He et al., 2007), sizes in investigated samples were generally very small. A recent three-armed, partially blinded trial, known as ACUZoster, which is still ongoing and whose study protocol was recently published, represents the first randomized, controlled study attempting to directly compare acupuncture and standard analgesia (gabapentin) for acute herpetic pain (Fleckenstein et al., 2009). The first evidence of a potential role of acupuncture in the treatment of acute herpetic pain was provided by a randomized, controlled, open-label trial (Ursini et al., 2011). Patients with intense or very intense pain at presentation of HZ were randomized to receive acupuncture or standard pharmacological treatment. Despite the limited dimensions of the study populations (105 patients randomized, 66 patients treated), no significant differences in pain reduction after 4 weeks of treatment between the two study arms were evidenced Furthermore, under the assumption that acupuncture may have an immune-modulating activity (Quirico et al., 1996; Yan et al., 1991), evaluation of the incidence of PHN at 3, 6 and 12 months after rash onset, as well as of the total pain burden during follow-up, might have revealed an ability of this medical tool to influence the rate of pain persistence and relapses. However, the incidence of PHN at 3, 6 and 12 months, as well as the mean pain burden during follow-up, were overlapping in the 2 arms. Given that patients treated with acupuncture carry a lower risk of cumulative drug toxicity, should these findings be confirmed by the ensuing ACUZoster trial and/or by other investigations, acupuncture might be appropriately considered among the available therapeutic options for the control of severe acute HZ related pain.

6.8 Synthetic approach to acute herpetic pain

Under a practical point of view, the approach to the patient can be summarized as follows (Dworkin et al., 2007): in patients with mild to moderate pain, pain therapy may be based on the use of paracetamol or other NSAIDs, possibly associated with mild opioids as codeine; antiviral therapy should be added whatever the time interval between pain onset and patient's presentation (Dworkin et al., 2007; Parruti et al., 2010). In patients with moderate to severe pain, pain therapy should consider fist-line opioid analgesics (oxycodone), which can be administered in combination with gabapentin or pregabalin, nortriptyline or corticosteroids, associated in various possible combinations for those patients who do not respond promptly to single agent therapy. Only in severe pain, uncontrolled by antiviral and analgesic combinations, the use of nerve blocks may be taken into account, and better practised repeatedly (Dworkin et al., 2007). The acquisition of a growing body of evidence in favour of the effectiveness of acupuncture may make the management of acute herpetic

pain (and PHN, as described below) even more complex, allowing the patient suffering with VZV-related painful conditions to be eligible for acupuncture, in addition to conventional therapy *(see Figure 4)*.

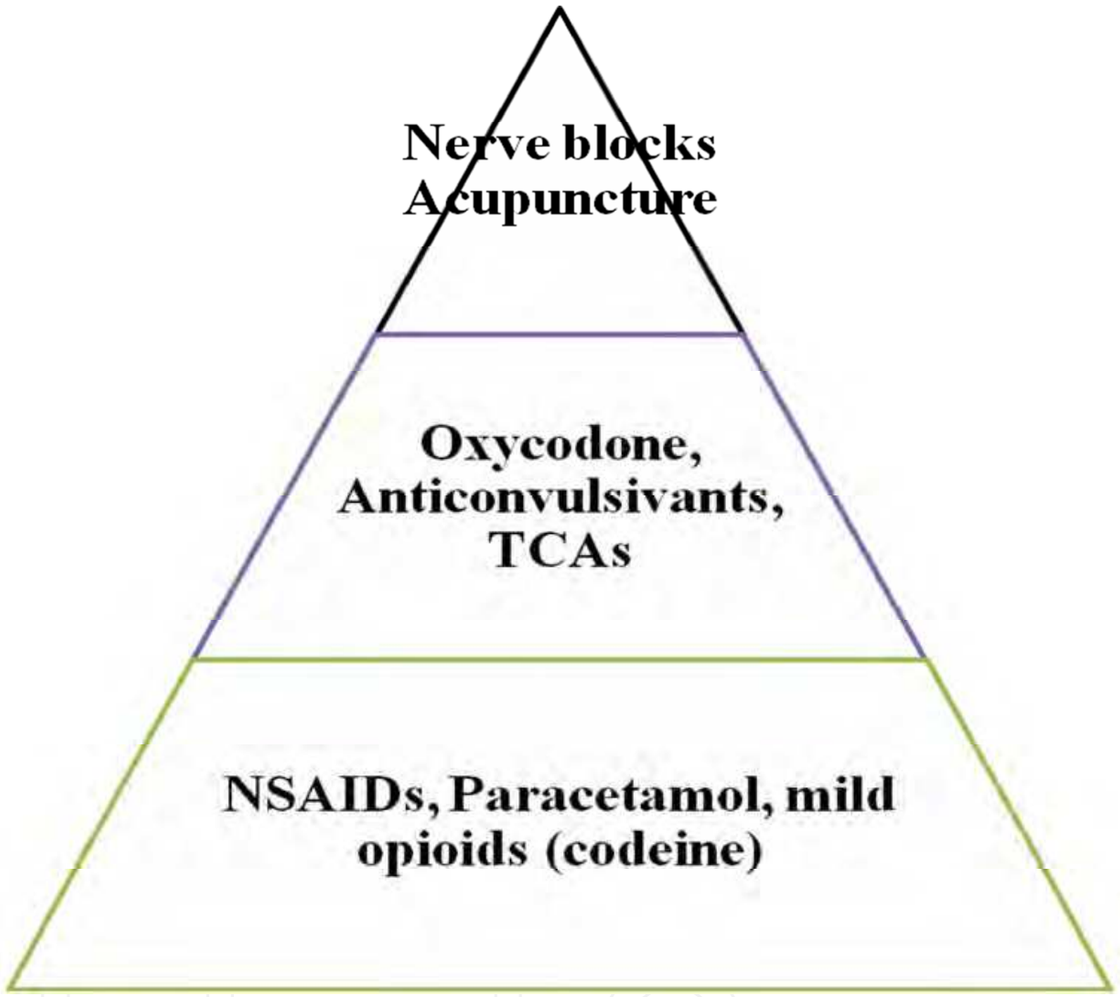


Fig. 4. Step-by-step strategy for management of acute herpetic pain.

Finally, it is important to underline that antiviral therapy can now be regarded as a cornerstone in the treatment of ZAP, according to recent acquired data on the genesis of pain and its persistence (Dworkin et al., 2007; Parruti et al., 2010).

7. What is the best therapy for PHN?

A large body of evidence indicates that some pharmacologic agents, including opioids, TCAs, antiepileptic drugs and lidocaine patches, may result in at least partial pain relief for a significant but limited proportion of patients with PHN, and that some of these patients may find the adverse effects of the above medications outweighing their benefits (Hempenstall et al., 2005; Wu & Raja, 2008). Therefore, the most formidable challenge in the framework of HZ is the treatment of PHN. The lack of fully effective treatments stands in

the nature of PHN, whose exact patho-physiological mechanisms are still elusive. Consequently, it is difficult to establish specifically targeted therapies, a task calling for further research efforts. Indeed, as this condition does not adequately respond in many cases to none of the conventional agents tested, many efforts are ongoing even in the field of alternative therapeutic options. The management of PHN, however, is and will be complex, requiring a multidisciplinary approach, including drug therapy and non-pharmacological adjunctive therapies.

7.1 Antidepressants

Several systematic reviews indicate that TCAs are effective in neuropathic pain and PHN (Attal et al., 2010; Hempenstall et al., 2005; Niv & Maltsman-Tseikhin, 2005), being superior to Selective Serotonin Reuptake Inhibitors (SSRI) (Attal et al., 2006; Saarto & Wiffen, 2010). No studies assessed the use of Serotonin-Noradrenalin Reuptake Inhibitors (SNRI) for this condition. It is believed that TCAs have an analgesic action by blocking the re-uptake of serotonin and norepinephrine, a blockade enhancing the inhibition of spinal cord neurons involved in pain perception (Basmaum & Fields, 1978). Among this class, the most commonly used compounds are amitriptyline, nortriptyline and desipramine. Amitriptyline led to a reduction in pain in 47-66% of patients, desipramine and nortriptyline in 55% to 63% (Schamder, 2001; Watson et al., 1998). Nortriptyline and desipramine are generally preferred to amitriptyline because of lower incidence of anticholinergic side effects such as sedation, orthostatic hypotension, cognitive decline, and constipation (Watson et al., 1998). Furthermore, despite amitriptyline is probably the most widely studied TCA for the treatment of PHN, nortriptyline and desipramine have recently been shown to be equally effective (Watson & Oaklander, 2002; Hempenstall et al., 2005; Rowbotham et al., 2005). A limiting factor in the clinical use of TCAs is represented by their side effects, including dry mouth, fatigue, dizziness, sedation, constipation, urinary retention, and palpitations. Other side effects include orthostatic hypotension, weight gain, blurred vision, and QT prolongation. Such side effects may be of particular concern in the elderly population and in patients with a history of cardiac arrhythmia or ischemic heart disease. Although there is no standard guidance for ECG screening prior to their administration, TCAs may cause ECG changes (prolonged QT) and it may be prudent to obtain a baseline ECG in patients with cardiac disease (Sansone et al., 2002; Vieweg et al., 2003; Dworkin & Schmader, 2003).

7.2 Antiepileptics

Among anticonvulsants, gabapentin and pregabalin have established efficacy in PHN, several trials showing the non inferiority of gabapentin versus nortriptyline (Gilron et al., 2009; Hempenstall et al., 2005). Although the precise mechanism of analgesia of gabapentin is uncertain, it is believed that gabapentin may act at the α2δ subunits of voltage-dependent channels to decrease calcium influx, which in turn inhibits the release of neurotransmitters (such as glutamate) from the central terminals of primary afferent fibers in the spinal cord (Fink et al., 2002). Several randomized controlled trials (RCTs) and a few meta-analyses have established the analgesic efficacy of gabapentin for the treatment of pain in PHN. RCTs have shown that a daily dose of 1800-3600 mg given for 1-2 weeks, is effective in reducing pain and improving sleep, mood and patients' quality of life (Rowbotham et al., 1998; Rice et al., 2001; Johnson, 2003). More recent studies have shown that a dose of 3600 mg daily can reduce pain by 43% (Niv & Maltsman-Tseikhin, 2005). The main reported side effects are

drowsiness, dizziness, ataxia, mild peripheral edema, and a worsening of cognitive impairment in elderly patients. To reduce adverse events and increase compliance, gabapentin should be initially used at lower doses (100-300 mg in a single dose at bedtime) and then continued at a dose of 100-300 mg three times a day (Mustafa et al., 2009), titring the analgesic effect and the occurrence of side effects (Dworkin & Schmader, 2003). Adjustment of its dose on the basis of renal function tests is also recommended, since the drug is excreted unchanged in urine (Johnson, 2003). Among gabapentinoids, both gabapentin and pregabalin are likely to provide analgesia by a similar mechanism of action. Although there are no meta-analyses examining the analgesic efficacy of pregabalin in PHN, there are a few RCTs in support. In 2004, the use of pregabalin for the treatment of diabetic neuropathy and PHN was approved in Europe and the United States. A randomized controlled trial in 2004 showed the effectiveness of this drug in the treatment of PHN: pregabalin was superior to placebo in reducing pain and improving mood, pain interference with sleep and patients' quality of life (Sabatowski et al., 2004). Pregabalin was well tolerated even by elderly patients. The commonly reported side effects were drowsiness, dizziness and mild peripheral edema. Studies conducted to date have shown an analgesic efficacy and good tolerability profile at doses of 150/600 mg, administered in 2 or 3 daily doses. The optimal dose to be administered, however, has not yet been thoroughly assessed. Other recently studied antiepileptic drugs are sodium divalproate and oxcarbazepine, which demonstrated a significant efficacy in reducing pain and improving patients' quality of life (Criscuolo et al., 2005; Kochar et al., 2005). Both of them have shown a good safety profile, with few side effects (dizziness and nausea, in particular). The use of other anticonvulsants such as phenytoin, carbamazepine, lamotrigine and sodium valproate for PHN is not adequately supported by the literature.

7.3 Opioids

Although opioid analgesics are accepted as a cornerstone for the treatment of nociceptive and cancer pain, their role in the management of chronic neuropathic pain such as that of PHN has been debated, as some clinicians consider neuropathic pain to be resistant to the analgesic effects of opioids. The controversy over their efficacy in relieving neuropathic pain reflects the use of multiple definitions and pain assessment methodologies for neuropathic pain in experimental trials and interindividual differences in opioid responsiveness (Wu & Raja, 2008). In addition, many other factors, such as opioid-related side effects, development of tolerance, exaggerated fear of addiction, and differences in governmental health policies contribute to such controversy (Wu & Raja, 2008). In spite of that, opioids may be considered as part of a comprehensive plan for the treatment of PHN (Cohen et al., 2006; Niv & Maltsman-Tseikhin, 2005; Johnson, 2003; Dworkin & Schmader, 2003), when pain is moderate to severe, with significant impact on quality of life after proven inefficacy of first-line agents. Among the investigated formulations, oxycodone, morphine, fentanyl, buprenorphine, methadone, and weaker opioids such as dihydrocodeine and tramadol were found to be effective. Treatment should be started with a short-acting opioid, replaced after 1-2 weeks with a long-acting formulation (controlled-release morphine, controlled-release oxycodone, methadone, transdermal fentanyl) when the first was not fully effective. Constipation, nausea, and sedation are common adverse effects associated with opioid use for chronic neuropathic pain. Tramadol has a unique pharmacological profile, which makes it one of

the most effective drug of its class in controlling neuropathic pain. It is a synthetic derivative of codeine with a dual mechanism of action: one of the opioid type (is a weak μ receptors agonist), and the other similar to that of TCAs (inhibition of norepinephrine and serotonin reuptake). An additional way of action of this compound consists in activating post-synaptic α2 adrenergic receptors. Such an activation results in a block of transmission of nociceptive stimuli to the central level. Several studies have shown the effectiveness of tramadol in reducing neuropathic pain, particularly PHN and diabetic neuropathy (Hempenstall et al., 2005; Boreau et al., 2003; Harati et al., 1998). As side effects, tramadol may causes nausea, vomiting, dizziness, constipation, drowsiness and headache; it also increases the risk of serotonin syndrome in patients using antidepressants such as SSRIs, TCAs or inhibitors of mono-amino oxidase in combination (Christo et al., 2007) *(see Table 1)*.

DRUG	INITIAL DOSAGE	TITRATION	ADVERSE EFFECTS
TCAs	10 mg every evening	Increase by 10 mg every 7 days to 50 mg, then to 100 mg and then to 150 mg nightly	Sedation, xerostomia, confusion, weight gain, dizziness
GABAPENTIN	100 mg three times daily	100-300 mg increases every 5 days to total dose of 1800-3600 mg/day	Somnolence, dizziness, ataxia, fatigue
PREGABALIN	75 mg twice daily	Increase to 150 mg twice daily within 1 week	Somnolence, dizziness
OXICODONE sustained-release	10 mg every 12 hours	As needed for pain while balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, hormonal changes
Transdermal FENTANYL	12 μg/hour, changed every 3 days	As needed for pain while balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, skin irritation, hormonal changes
Transdermal BUPRENORPHINE	35 μg/hour, changed every 3 days	As needed for pain while balancing analgesia and adverse effects	Nausea, constipation, sedation, cognitive dysfunction, skin irritation, hormonal changes
Immediate-release TRAMADOL	50 mg/day	Increase by 50 mg every 3-4 days to total dose between 100-400 mg/day divided dose	Nausea, emesis, dizziness, vertigo, somnolence, headache, constipation

Table 1. Summary of effective systemic drugs for PHN. Initial dosage, titration and adverse effects are reported.

7.4 Topical therapies

Local anesthetics may provide analgesia in neuropathic pain states, where an accumulation of neuronal-specific sodium channels may contribute to pain, including that of PHN (Mao & Chen, 2000). Topical treatments including lidocaine patches and capsaicin cream/patches have been studied for the treatment of PHN (Niv & Maltsman-Tseikhin, 2005). Topical adhesive patches containing 5% lidocaine (700 mg) have been used for the treatment of PHN with benefit (Comer & Lamb, 2000). Although there are few studies on their efficacy, the available clinical trials in patients with allodynia suggest that lidocaine is effective in providing pain relief with minimal systemic absorption and few side effects, the most frequent being mild skin irritation at the side of application (Khaliq et al., 2007; Binder et al., 2009; Hans et al., 2009). Furthermore, patients may respond well to topical lidocaine even if the skin is completely deprived of nociceptors (Wasner et al., 2005).

Capsaicin, the pungent ingredient in hot chili pepper, results in excitation of nociceptive afferents when applied topically. However, repeated application of capsaicin results in desensitization of unmyelinated epidermal nerve fibers and hypoalgesia (Nolano et al., 1999; Knotkova et al., 2008). Low-concentration (0.025% or 0.075) capsaicin creams have demonstrated efficacy in the topical treatment of PHN and neuropathic pain conditions (Knotkova et al., 2008). Recently, a high-concentration (8%) synthetic capsaicin dermal patch has been developed with the aim of providing more rapid and long-lasting pain relief after a single application. Banckonja et al. (Backonja et al., 2009) evidenced that a one–off application of high concentration (8%) of capsaicin patch for 60 minutes was more effective than a low concentration patch over 12 weeks. Adverse events reported were local reactions at the application site (pain, erythema). Therefore, as evidenced by a Cochrane review, capsaicin either as repeated application of a low dose (0.075%) cream, or even a single application of a high dose (8%) patch may provide a good degree of pain relief to some patients with painful neuropathic conditions (Derry et al., 2009). Capsaicin dermal patches have been approved in the EU for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other pain medications. Capsaicin dermal patches are also approved in the US only for management of neuropathic pain associated with PHN (McCormack, 2010).

7.5 Interventional management

A wide variety of interventional options, such as sympathetic and other nerve block, intrathecal injections and spinal cord stimulations have been analyzed as potential treatments for PHN. Interventional options are part of a comprehensive (invasive e non invasive) strategy for the treatment of PHN (*see Figure 5*). Selective sympathetic nerve blocks have been one of the more common interventional strategies used for pain relief for both acute HZ and PHN. Although the precise mechanisms by which the sympathetic nervous system contributes to neuropathic pain are unclear, experimental data indicate that abnormal activation of the α-adrenergic receptors in primary afferent neurons, direct interactions between primary afferent neurons and efferent sympathetic nerves resulting from neuronal regeneration and sprouting after nerve injury and tissue trauma may all contribute to sympathetically mediated pain (Janig et al., 1996; Wu et al., 2000). The incidence of severe complications from sympathetic nerve blocks is extremely low and, depending on the location of the nerve block, may consist of local anesthetic toxicity (such as seizures), pneumothorax, intraspinal/neuraxial injection, or neurologic injury (van Wijck et al., 2010; Wu & Raja, 2008). Some data suggest a link between

sympathetic activity and pain in PHN, as patients with PHN demonstrate increased levels of pain and worsening of their allodynia after local administration of adrenergic agonists (Choi et al., 1997). Thus, administration of sympathetic nerve blocks may theoretically interrupt the sympathetic-sensory interactions contributing to pain of HZ and PHN. Sympathetic nerve blocks for the treatment of PHN were evaluated mainly in retrospective studies. In a few of them, a reduction in pain was initially noted, but this effect was not maintained in the long run. Therefore, there is inadequate evidence for a long-term effect of sympathetic nerve blocks in PHN (van Wijck et al., 2010; Wu & Raja, 2008; Wu et al., 2000).

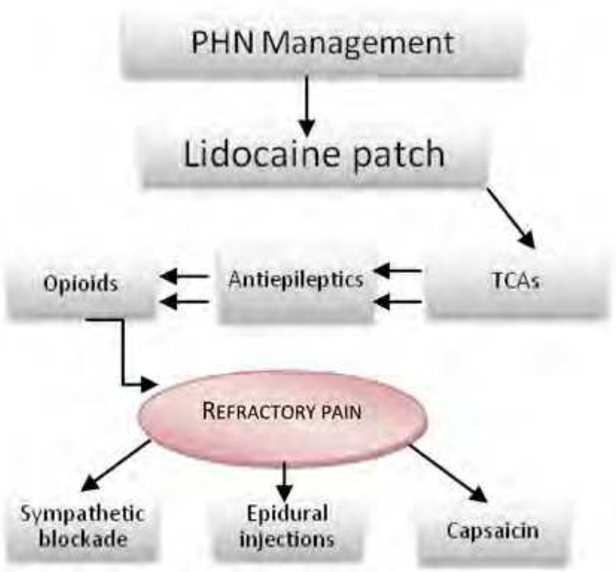


Fig. 5. Strategy for management of PHN.

Use of epidural blocks (through injections of corticosteroids with or without local anesthetics) has been reported for the treatment of acute HZ (Ahn et al., 2001) as an effective treatment shortening the total duration and reducing the severity of pain in combination with antiviral agent. A single epidural injection of steroids and local anesthetics in the acute phase of HZ may have a modest effect in reducing zoster-associated pain for 1 month after injection and is not effective for prevention of PHN. Furthermore, the value of epidural injections for the treatment of existing PHN has not been evaluated (van Wijck et al., 2010).

Continuous infusions of analgesic agents (typically an opioid or local anesthetic) via an externalized intrathecal catheter or internalized intrathecal pump may also be used for the treatment of PHN, although no controlled trials examining the analgesic efficacy of these modalities are available (Angel et al., 1998; Nitescu et al., 1998).

In extreme cases, refractory to all treatment options, other interventional strategies were described in the literature. Although there are limitations in the quality and quantity of available data, current evidence suggests that Spinal Cord Stimulation be effective in the management of severe neuropathic pain (Grabow et al., 2003).

The effect of subcutaneous injections, transcutaneous nerve stimulations, percutaneous nerve stimulations, and radiofrequency on HZ and PHN has not been established. There is minor anecdotal evidence for the efficacy of these techniques, and the risk for complications,

such as exacerbation of pain, is unknown. There are no controlled studies for any of these interventional procedures (van Wijck et al., 2010).
Reported surgical options for PHN include trigeminal or spinal peripheral neurectomy, deep brain stimulation, dorsal root entry zone lesions, cordotomy, and mesencephalotomy. Microsurgical DREZotomy or dorsal root entry zone lesions may interrupt small nociceptive fibers and neurons in the dorsal horn of the spinal cord. General indications for this procedure include well-localized pain, neuropathic pain including PHN, and excessive spasticity associated with severe pain The role of these invasive surgical treatments in the management of PHN is uncertain, as there are no controlled studies to date (Wu & Raja, 2008).

7.6 Other therapies

A number of other therapies have been explored, such as NMDA receptor antagonists, topical NSAIDs and TCAs, vincristine iontophoresis, botox, minocycline and cryoanalgesia. There is, however, little evidence that justifies evaluation of the efficacy of these therapeutic options. Acupuncture is another option to treat PHN. A clinical report (Lewith et al., 1983), the only one to date retrievable in English, on the possible role of acupuncture in PHN, lacks of sufficient methodological consistency to be quoted in terms of efficacy. A current Cochrane project, however, is due in the near future on this topic (Wang et al., 2009).

7.7 Psychological interventions

Neuropathic pain reduces quality of life, including mood, physical and social functioning. Depression and pain coping strategies, such as catastrophizing and social support, predict pain severity in chronic pain states. Therefore, the importance of psychosocial support and long-term follow- up for severe cases should, however, not be overlooked as sometimes it is the final tool to resort on for otherwise intractable cases (Wu & Raja, 2008).

7.8 Recommendations and combination therapies

Recent guidelines on evidence-based management of neuropathic pain and PHN provide distinct recommendations for first, second, and third line treatment, including possible drug combinations for each step. European Federation of Neurological Societies (EFNS) guidelines recommend TCA or gabapentin/pregabalin as first line treatment in PHN (level A). Topical lidocaine (level A, less consistent results), with its excellent tolerability, may be considered first line in the elderly, especially if there are concerns regarding the CNS side effects of oral medications. In such cases, a trial of 2–4 weeks is justified. Strong opioids (level A) and capsaicin creams are recommended as a second choice. Capsaicin patches are promising (level A), but the long-term effects of repeated applications are not clarified, particularly on sensation. (Attal et al., 2010) *(see Table 2).*
Although drugs and drug classes have been discussed individually for the purpose of this chapter, combination therapy associating more than 1 drug class may be useful in providing additive if not synergistic analgesia. The benefits of combination therapies are supported by a recent study, indicating that the combination of gabapentin and morphine achieved better analgesia at lower doses of each drug than either of the 2 drugs as a single agent in patients with PHN and diabetic neuropathy (Gilron et al.,2009).

Level A rating for efficacy	Level B rating for efficacy	Level A/B rating for inefficacy or discrepant results	Recommendations for first line	Recommendations for second line
Capsaicin 8% patch Gabapentin Lidocaine plasters Opioids Pregabalin TCA	Capsaicin cream Valproate	Benzydamide topical Dextromethorphan Memantine Lorazepam Mexiletine COX-2 inhibitor Tramadol	Gabapentin Pregabalin TCA Lidocaine plasters	Capsacin Opioids

Table 2. Classification of evidence for drug treatment in PHN and recommendations for use (adapted from EFNS guidelines, 2010).

8. Can PHN be prevented?

PHN is the most frequent complication of HZ, it hardly affects patients' life and it is often refractory to current combination treatments, pain persisting in spite of any therapy nearly in half of patients. Several approaches have been investigated for PHN prevention. Prevention clearly appears so far the most interesting path to face with this condition. Antivirals have been addressed for their potential role in prevention as the stop on viral replication in acute phase was hypothesized to reduce pathological damage to nerve fibers and the subsequent onset of PHN. As their role in accelerating rash healing and acute pain resolution is widely recognized, results on their role in PHN prevention are still controversial: a recent Cochrane review (Li et al., 2009) raises some doubts about their efficacy, concluding that there is insufficient evidence from RCTs to support their use with this peculiar aim. In spite of that, studies with different designs suggest some opposite results. Another review (Vander Straten et al., 2001) suggested that antivirals in the acute phase of HZ appear to be effective in reducing PHN severity and duration, but not its incidence. Dworkin et al. (Dworkin et al., 1998) found that patients receiving antiviral therapy (famciclovir *versus* placebo) had a significant lower prevalence of PHN in a cohort study of 419 HZ patients. Parruti et al. (Parruti et al., 2010) showed that HZ patients not prescribed antivirals in the acute phase have a significantly higher risk of developing PHN, in a prospective cohort of 519 HZ unselected patients addressing a real-life clinical setting. The role of antivirals in preventing PHN is still a matter of debate. Corticosteroids prescribed in the acute phase of HZ have been shown to be uneffective in preventing PHN onset in several trials and in a recent review (Chen et al., 2010), as well as antidepressants (Saarto & Wiffen, 2010). As greater acute pain severity predispose to higher risk of PHN onset, pain relief in acute HZ has been investigated as to its possible preventive role. Interventional techniques, such as topical local anesthetics, subcutaneous local anesthetics and corticosteroids, percutaneous electrical nerve stimulation, sympathetic and epidural blocks, have been proposed as prevention: they can produce an effective short-term pain relief in the acute phase, thus reducing the important burden of pain in this time frame, but their effect in reducing PHN incidence remains unclear (Opstelten et al., 2004).

In 1995, vaccination for varicella with a wild-type VZV Oka-strain was introduced under an FDA recommendation and at present a universal coverage vaccination program is ongoing in the USA and several other countries. Varicella vaccine at higher dosage (at least 14 times) than that used in Varicella vaccination was suggested to be protective for the development of HZ. The Shingles Prevention Study (Oxman et al. 2005) was a randomized double-blind placebo-controlled trial designed to demonstrate that vaccination against VZV can decrease the incidence and severity of HZ and PHN. 38,546 healthy subjects aged over than 60 years were recruited and randomly assigned to receive a mock vaccine or an investigational anti-VZV vaccine. They were trained to recognize early HZ sings and to refer quickly to study sites in the evenience of HZ. After vaccination, they were followed for 3.13 years on average. The incidence of HZ was significantly reduced, from 11.12 per 1,000 person-years in the placebo arm to 5.42 per 1,000 person-years in the vaccine arm (Oxman et al. 2005). The incidence of PHN, defined as pain ≥30/100 at 90 days from the onset of rash, was markedly reduced in the vaccine arm, from 1.38 to 0.46 per 1,000 person-years. Moreover, vaccinated subjects developing HZ and PHN had significantly less pain and discomfort, with the burden of illness due to HZ, calculated as described by Coplan et al. (Coplan et al., 2004), being reduced by 61.1%. Zoster vaccination reduced overall HZ and PHN incidence by 51.3% and 66.5%, respectively (*see Figure 6*) (Oxman et al., 2005), giving evidence for a major protective role. This cornerstone study, however, had some limitations, as it included only subjects aged >60 and excluded subjects with relevant and frequent comorbidities such as diabetes, chronic obstructive pulmonary diseases, cancer, HIV and other cases of immunodepression. For these reasons, it does not allow to draw conclusions as to safety and efficacy of HZ vaccine in these subsets of subjects that are relevant in real practice and that a priori would largely benefit from vaccine administration, having a higher risk to develop HZ and PHN and a heavier total burden of illness. Further studies are needed to better define these elements.

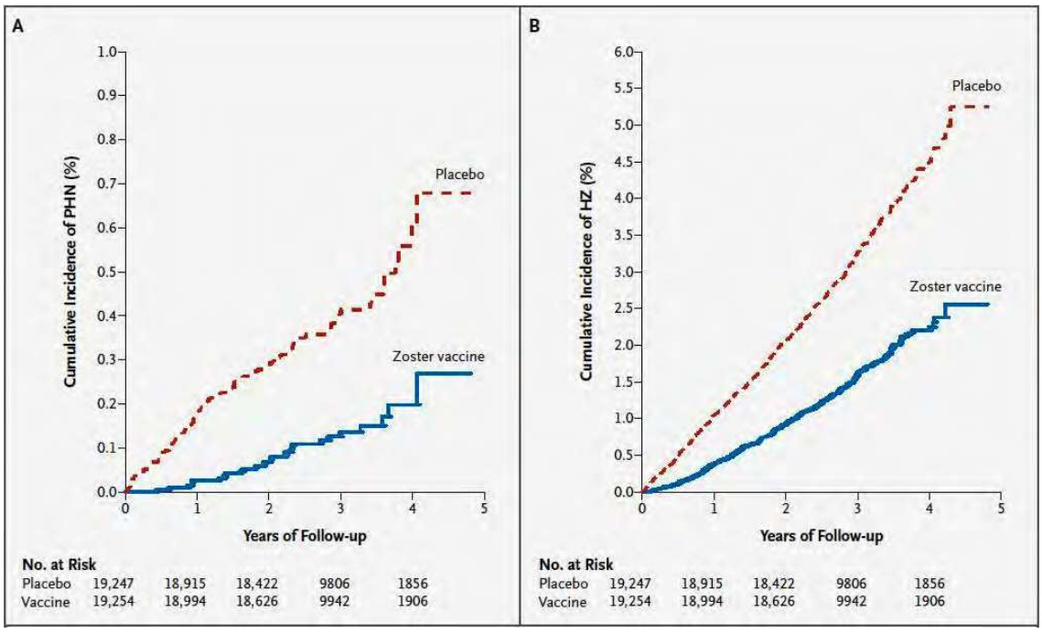


Fig. 6. Kaplan-Meier estimates of the effect of HZ vaccine on HZ (A) and PHN incidence (B). HZ and PHN incidence were significantly lower in the vaccine group compared to the placebo group (waiting for permission from Oxman et al., 2005).

Since 2006, when HZ vaccine was approved by FDA and recommended for adults aged >60 in the United States, the real cost-effectiveness of HZ vaccination for the general population has been widely investigated. Several studies assessed the economic burden of HZ and PHN, showing that they are frequent and costly conditions, also in terms of impact on quality of life, as discussed above (Scott et al., 2006; Stein et al.,2009; Gil et al., 2009; Gialloreti et al., 2010; Aunhachoke et al., 2011; Hornberger & Robertus, 2006). For instance, in Italy a recent study estimated that total annual costs for HZ and PHN were €41.2 Million, including both direct and indirect costs (Gialloreti et al., 2010). Vaccine cost-effectiveness was determined by decision models in multiple large countries (Canada, England and Wales, Italy), suggesting that immunization would increase quality-adjusted life-years (QALYs) (Najafzadeh et al., 2009; van Hoek et al., 2009; Gialloreti et al., 2011). In general, studies evaluating vaccine cost-effectiveness agree on its relevance in the elderly population (Hornberger & Robertus, 2006; Pellissier et al., 2007; Rothberg et al., 2007; van Hoek et al., 2011; Annemans et al., 2010; Gilden, 2011). Furthermore it has been supposed that vaccination could be equally cost-effective also in younger people, aged <50, as about 19% of HZ cases occur between 50 and 59 years of age. Further studies are once more needed to assess this point.

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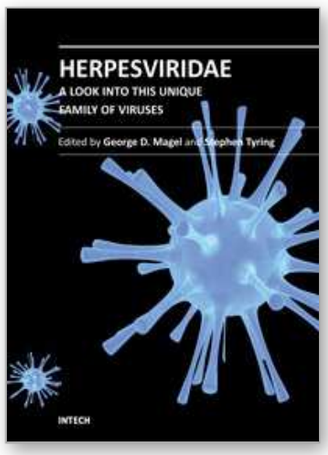

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In order to fully understand the nature of viruses, it is important to look at them from both, their basic science and clinical, standpoints. Our goal with this book was to dissect Herpesviridae into its biological properties and clinical significance in order to provide a logical, as well as practical, approach to understanding and treating the various conditions caused by this unique family of viruses. In addition to their up-to-date and extensive text, each chapter is laced with a variety of diagrams, tables, charts, and images, aimed at helping us achieve our goal. We hope that this book will serve as a reference tool for clinicians of various specialties worldwide.

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