REVIEW ARTICLE

Am J Clin Dermatol 2005; 6 (5): 317-325
1175-0561/05/0005-0317/$34.95/0

Current Management of Herpes Zoster

The European View

Antonio Volpi,[1] *Gerd Gross*,[2] *Jana Hercogova*[3] and *Robert W. Johnson*[4]

1 Department of Public Health, University of Rome, Rome, Italy
2 Department of Dermatology and Venereology, University of Rostock, Rostock, Germany
3 Department of Dermatology and Venereology, Charles University, Prague, Czech Republic
4 Pain Management Clinic, Bristol Royal Infirmary, University of Bristol, Bristol, UK

Contents

Abstract

The overall incidence of herpes zoster in Europe is approximately 3 per 1000 people per year and more than 10 per 1000 people per year in those aged >80 years. Post herpetic neuralgia (PHN) is a common debilitating complication of herpes zoster, particularly in patients aged >50 years, in persons with severe pain or rash at presentation, and in those with significant prodromal symptoms.

Antiviral drugs can effectively control acute symptoms and, if used early enough in the course of the illness, can help prevent the development of PHN and other complications. However, despite this, many patients do not receive such treatment. The economic impact of zoster and PHN is largely underestimated in Europe. Furthermore, there is considerable variation throughout Europe in the management of herpes zoster. Use of antiviral therapy including the newer potent antiviral agents such as brivudin, which requires less frequent administration than acyclovir, is improving patient outcomes in some European countries. However, in many countries, patient awareness of herpes zoster and, as a result, overall antiviral use is low.

Guidelines recommending the use of antiviral agents, particularly in patients at risk of developing PHN, are available but are not widely used. More needs to be done to educate the general public and increase awareness among primary healthcare providers of the benefits of timely and appropriate pharmacological therapy in patients with herpes zoster.

Herpes zoster (shingles) is the clinical manifestation of latent varicella zoster virus (VZV) reactivation, which can occur several decades after the primary varicella infection (chickenpox). Herpes zoster presents as a painful localized cutaneous rash. Triggers for reactivation include advancing age, co-morbidities (such as malignancies and HIV infection), and immunosuppressive treatments (such as chemotherapy and radiotherapy). Many patients develop persistent pain as a result of the herpes zoster infection, termed post herpetic neuralgia (PHN).

Public awareness of the potential severity of shingles and its complications is poor and management varies considerably among European countries. A panel of dermatology, venereology, and pain experts from several European countries was convened to identify unmet needs and critical issues in the management of herpes zoster and its complications. This review summarizes these discussions and suggests some ways in which management could be improved.

1. Epidemiological Patterns and Trends in Europe

The lifetime risk of herpes zoster is estimated at 10–20% and more than 50% in those aged >80 years.[1] Herpes zoster is more severe and more likely to result in hospitalizations and complications in older patients than in younger adults,[2] and is rare and generally benign in children.[3] In a US-based epidemiologic chart review of children and adolescents, the incidence rates were 0.2 per 1000 people per year in children <5 years of age and 0.6 per 1000 per year in those aged 15–19 years.[4]

It is known that reactivation of latent VZV is more likely in immunocompromised individuals and the elderly, but little is known about the risk factors in individuals with no underlying immunosuppression. This paucity of definitive clinical data regarding risk factors was highlighted in a recent review of population-based epidemiological studies;[5] most studies were carried out on a wide age range of adults and overall incidence rates were similar among European countries. In all studies, as expected, the incidence rates increased sharply with age. Annual incidence in Europe has been reported as 0.3–0.74 per 1000 people per year in children aged <10 years, 1.6 per 1000 in adults aged <40 years, 2.5 per 1000 in adults aged >20–50 years, 7.8 per 1000 in adults aged ≥60 years, and 10 per 1000 in elderly adults aged >80 years.[6,7]

Other risk factors for zoster are thought to be linked to loss of VZV immunity; a significant variation in incidence was seen among countries and races. Country and race are thought to be proxies for 'age of primary varicella infection' because certain geographical areas (namely, the Caribbean, Central America, India, Pakistan, Sri Lanka, Bangladesh, Singapore, and Malaysia) typically have late-onset varicella (primary varicella infection in adolescence or young adulthood). Significantly lower rates of zoster were seen in patients with childhood residence in countries with late-onset varicella. This was thought to be related to maintenance of VZV-specific immunity in older age due to the later acquisition of varicella.[5] The lack of significant variation among UK and mainland European countries is probably due to similarities in racial mix and varicella age of onset.

Individuals with increased contact with varicella (e.g. primary healthcare providers and parents) had a reduced risk of reactivation, demonstrating the protective effect of contact with varicella. Similarly, communities with higher incidences of varicella had lower rates of zoster in young adults (aged 15–44 years).[5]

Some epidemiological studies reported a higher incidence in women than men, but the evidence is not conclusive.[5] Socioeconomic status, seasonality, and urban/rural residence were not found to be risk factors for herpes zoster.[5]

Controversially, data from a US incidence study suggest that overall immunosuppressive conditions had little impact on the incidence of herpes zoster, but were associated with early recurrences.[8] More research is needed to determine risk factors conclusively.

1.1 Impact of Varicella Vaccination

Epidemiological trends may change as a result of varicella child vaccination programs; in the US, VZV appears to be in retreat following the introduction of mass vaccination with Oka vaccine in 1995, but the pool of latent wild-type virus in the adult population represents a continuing threat. The long-term effects of varicella vaccination in children on adult herpes zoster incidence are uncertain, although a recent study suggested that the vaccination-associated decrease in varicella disease was not associated with an increase in herpes zoster infection.[9]

Unlike the US, the UK and some other European countries have a targeted vaccination strategy, i.e. identification and vaccination of high-risk individuals only. The impact on herpes zoster may depend on which strategy (child or targeted) is used. Possible effects of child and targeted vaccination were shown in a mathematical modeling study.[10] Using this model and a child vaccination strategy, the incidence of herpes zoster would increase in the short-term as a result of the reduction in varicella infection, depriving adults with latent virus from intermittent boosts to their immunity (exogenous boosting) through contact with children with varicella. Eventually, after 20–40 years, the incidence of herpes zoster would probably begin to fall. The targeted strategy will prevent varicella in a group of high-risk individuals, but will have no effect on the incidence of varicella or zoster in the general population.

In the pre-vaccination era, hospitalization rates for zoster were 0.16 per 1000 people per year (four times higher than for primary varicella); 67% of patients were aged >64 years, no seasonality was seen, and the rates were higher in Hispanics and Blacks (4.1 and 2.6 times more likely, respectively).[11] A recent US study showed that the incidence and hospitalization rates of primary varicella and herpes zoster did not change significantly following introduction of widespread vaccination in children.[3]

Further surveillance studies are required to determine the ongoing effects of the various varicella-zoster vaccination strategies on the incidence and severity of herpes zoster. More research into the mechanisms of boosting immunity in adults with latent virus is also required to better understand the potential effect of vaccination.[12]

Developments in immunosuppressive therapies for cancer, organ transplantation, immunoreactive disorders, and allergy may also impact on the incidence of herpes zoster.

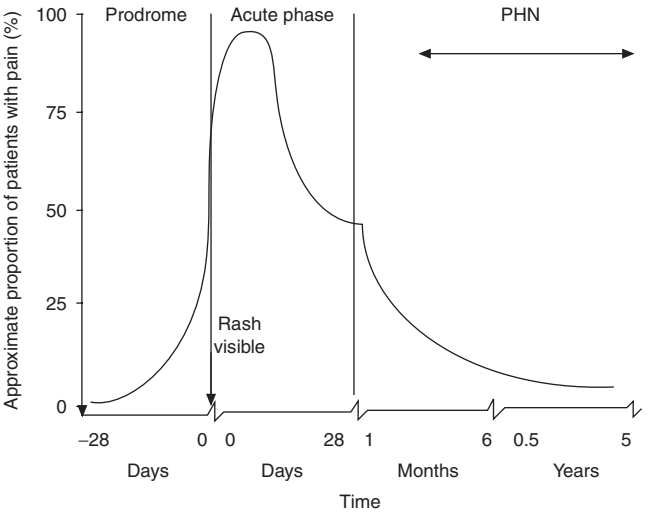

Fig. 1. Herpes zoster-associated pain (reproduced from Johnson,[15] with permission from Lippincott Williams & Wilkins). **PHN** = post herpetic neuralgia.

2. Nature of Disease and its Complications

2.1 Herpes Zoster

Herpes zoster progresses through several stages: prodromal (1–4 days before rash); acute (painful rash stage 7–10 days); and healing (2–4 weeks). Prodromal symptoms can include headache, photophobia, itching, and malaise, but rarely fever,[13] and may precede the appearance of the rash by 48–72 hours and possibly longer. The rash, a unilateral dermatomal erythematous maculopapular eruption, is often preceded by abnormal skin sensations (itching, tingling, and pain) lasting for up to 5 days. The characteristic clusters of vesicles form pustules, ulcerate, crust and heal, usually in a self-limiting fashion, resolving after 2–3 weeks. In rare cases, cutaneous dissemination can occur. In most patients, the rash is accompanied by pain for at least the first 2 weeks of the acute phase (figure 1). Pain is often under treated. Substantial alleviation of pain associated with acute herpes zoster is possible in most patients and should be the primary goal of treatment. In most patients, pain subsides gradually over the 6 months after the rash has disappeared, but a small percentage of patients develop persistent pain in the form of PHN. Other complications of herpes zoster can include ophthalmic involvement, Ramsay Hunt syndrome, or motor involvement. Life-threatening complications occur rarely in immunocompetent patients[14] and are not discussed here.

2.2 Post Herpetic Neuralgia (PHN)

PHN is defined as an intractable, chronic, neuropathic pain continuing for more than 3 months after resolution of rash (figure 1).[16,17] It is thought to be the result of virus- or immune response-induced damage to the affected sensory neurons and secondary changes in function at several levels of the nociceptive pathway.[6] Like zoster itself, the incidence and duration of PHN increases with age.[18] Overall, PHN occurs in 10–20% of all zoster patients, but it is rare in herpes zoster patients aged <40 years. In those aged >50 years the risk of PHN increases dramatically. More than 50% of herpes zoster patients >60 years[19] and over 70% of those >70 years[6] report pain 1 month after the onset of the disease. Unlike zoster, the risk of PHN is not increased in immunocompromised patients.[20] Variations in estimates from different sources are frequent and depend on the definition of PHN used.

Other risk factors for PHN include increased severity of pain and rash in the acute phase of zoster infection,[21] significant prodromal pain, extended rash duration, and cranial or sacral locations of zoster symptoms.[18] In a retrospective analysis of studies of the antiviral famcyclovir in 965 patients with herpes zoster receiving active treatment or placebo, older age, female sex, presence of prodromal pain, and increased acute rash and pain severity were identified as independent predictors of PHN.[22]

Psychological distress is also thought to be a risk factor for PHN.[21,23] In a case-control study, stressful events were found to be more common in zoster patients compared with controls. A hypothetical vulnerability-diathesis-stress model has been proposed in which higher levels of psychosocial stress predispose the herpes zoster patient to developing PHN.[24]

Viremia has also been associated with increased risk of PHN. In a study investigating the effect of viremia on zoster-associated pain in 119 patients, the prevalence and duration of pain was

greater in VZV DNA-positive patients ($p < 0.05$ vs VZV DNA-negative patients).[25]

3. Current Antiviral Therapy and Effect on PHN

3.1 Treatment of Acute Zoster

The objective of herpes zoster treatment is to control pain, hasten rash healing, and reduce the risk of PHN and other complications. An additional objective that is particularly important in immunosuppressed patients is to reduce the risk of dissemination of the VZV infection.[13]

Antivirals may be more effective if started earlier in the course of the disease.[26] A major limitation of current therapy is the delay between onset of symptoms and initiation of antiviral therapy. In many cases, viral activity and neural damage are ongoing for several days before the diagnosis is made and antivirals are prescribed. Early antiviral therapy has been shown to decrease the duration of rash and severity of pain in the elderly.[27]

The most important aim of therapy for herpes zoster is to control pain. Therefore, in addition to antiviral therapy, appropriately dosed analgesics in combination with a neuroactive agent (e.g. gabapentin, amitriptyline) are used to shorten the degree and duration of acute zoster pain.[28] Some indicative evidence of the effects of neuroactive agents has been established in mice, but an appropriate human study is awaited.[29] The German Dermatology Society also suggests that corticosteroids be considered in patients not responding properly to analgesics, based on the results of two large, prospective studies that showed high-dose corticosteroids in addition to antiviral therapy had some beneficial effect on acute pain and rash healing, although no significant impact on PHN was observed.[28]

3.1.1 Nucleoside Analogs

The oral nucleoside analogs acyclovir, famcyclovir, valacyclovir, and brivudin are used in the treatment of herpes zoster in adults aged >50 years. All slow the rate of new lesion development, leading to faster healing and resolution of pain. Antivirals have been shown to shorten the duration of viral replication; this may restrict further neuron damage and reduce the incidence, severity, and duration of PHN.[30]

Acyclovir, Famcyclovir and Valacyclovir

A meta-analysis of 691 patients with herpes zoster showed acyclovir (800mg five times daily for 7–10 days) to be more effective than placebo.[31] Benefits were particularly noticeable in patients aged >50 years and fewer acyclovir-treated patients had PHN at 3 and 6 months compared with placebo recipients. Overall, the duration of pain and its incidence at 3 and 6 months in the acyclovir group was approximately half that seen with placebo. Disadvantages of acyclovir include poor bioavailability for oral administration and the resulting need for five times daily administration.

Famcyclovir (the oral prodrug of penciclovir, which is poorly absorbed by oral administration) has similar efficacy to acyclovir in terms of loss of acute phase pain in immunocompromised[32] and immunocompetent patients.[33] Valacyclovir (the prodrug of acyclovir), which greatly increases the bioavailability of acyclovir, shows enhanced efficacy compared with oral acyclovir with respect to time to resolution of pain, although effects on acute pain and rash progression are similar.[34] Both prodrugs have the advantage of a reduced dose frequency compared with acyclovir. A study in immunocompetent patients aged >50 years showed that famcyclovir 500mg and valacyclovir were therapeutically equivalent in terms of both healing rate and pain resolution.[35]

Brivudin

Another antiviral agent used in herpes zoster is the synthetic pyrimidine analog brivudin. Brivudin, a virostatic agent activated by viral enzymes phosphorylation, has been launched in some European countries, and is indicated for the early treatment of acute herpes zoster in immunocompetent adults. Active brivudin triphosphate prevents viral replication by blocking the VZV DNA polymerase and is 200–1000 times more effective at inhibiting viral replication *in vitro* than acyclovir or penciclovir.[36] In uninfected cells, brivudin remains unchanged and diffuses from the cell in its inactive form. *In vitro* studies showed viral inhibition with brivudin to be considerably faster and more sustained than with acyclovir; its fast onset of activity is thought to be due to rapid accumulation inside virally infected cells.[37] Because of its greater potency and long plasma elimination half-life, brivudin is administered as a single 125mg tablet once daily. Other advantages of brivudin include the fact that it is eliminated via both the liver and kidney and, therefore, no dose modifications are required in patients with renal or hepatic impairment, and its lack of effect on cytochrome P450 enzymes. Drug interactions have been reported with 5-fluorouracil and other 5-fluoropyrimidines. The main metabolite of brivudin, bromovinyluracil, inhibits dihydropyrimidine dehydrogenase (DPD), which regulates the metabolism of pyrimidine derivatives, and causes accumulation and enhanced toxicity of these drugs. Consequently, 5-fluorouracil, capecitabine, floxuridine, flucitosine, or tegafur must not be administered before 4 weeks after the end of the treatment with brivudin. As a further precaution, DPD activity should be monitored before starting any treatment with 5-fluoropyrimidine drugs in patients who recently received brivudin.

Brivudin 125mg once daily was shown to be more effective than acyclovir in reducing the duration of rash and the severity of pain in 1227 immunocompetent patients with herpes zoster in a randomized, double-blind, multicenter study. The primary endpoint, time to last eruption, was significantly shorter (by 25%) with brivudin than with acyclovir, particularly in patients aged >50 years.[38] In a large randomized, double-blind, multicenter study in 2027 patients aged ≥50 years with acute herpes zoster, brivudin 125mg once daily had similar efficacy in reducing pain (i.e. prevalence of PHN at month 3, duration of PHN, and prevalence and duration of zoster-associated pain) and rash to famcyclovir 250mg three times daily.[39] Brivudin has a similar tolerability profile to acyclovir.[40,41] Brivudin and famcyclovir also have similar antiviral activity and a comparable tolerability profile.[39]

3.1.2 Analgesic Therapy

Analgesic therapy should be increased from acetaminophen (paracetamol) to acetaminophen plus codeine, and then to strong opioid analgesics, morphine or oxycodone, as required. The tricyclic antidepressants amitriptyline,[42,43] nortriptyline[42,43] or desipramine,[43] the antiepileptic α-2-δ ligands gabapentin[42] or pregabalin,[16,44] and strong opioids are used to treat significant persistent pain.[42,43] Topical lidocaine is also prescribed for persistent PHN.[42]

3.2 Prevention of PHN

Established PHN is difficult to manage and often refractory to treatment. Therefore, prevention is the best strategy, particularly in patients who have been identified as being at higher risk of PHN. Lowering viral activity in the acute phase reduces neural damage and this is thought to reduce the likelihood of PHN, as this condition results from virus- and immune response-induced neural damage and secondary changes within the nociceptive pathway. Early antiviral therapy (within 72 hours of rash onset) has been shown to reduce the risk and duration of PHN, especially in elderly[6,45] and immunocompromised[46] patients. However, in some studies, evidence supporting the use of antiviral agents is less striking.

Nucleoside analogs (acyclovir 800mg five times daily for 7 days; famcyclovir 250–500mg three times daily for 7 days; valacyclovir 1g three times daily for 7 days) have been shown to reduce the morbidity associated with PHN.[47]

In a large randomized, controlled trial of patients aged ≥50 years with acute herpes zoster, the prevalence of PHN among the 1712 per-protocol patients was similar with famcyclovir 250mg and brivudin treatment (9.6% and 11.3%, respectively).[39] In the 179 patients with PHN, the duration of PHN was similar with brivudin and famcyclovir, as was the case in a subset of patients aged ≥65 years. A retrospective analysis of zoster patients aged >50 years suggested that the relative risk of PHN and the incidence of chronic pain were significantly lower (by 25%) with brivudin than with acyclovir.[38]

Older studies, such as the report of Eaglstein et al.,[48] did not rule out the possibility that corticosteroids might reduce the incidence of PHN. Two large subsequent, well-designed studies suggested that corticosteroids offer some short-term benefits, although one study[47] showed an excess of corticosteroid-related adverse effects.[49,50] Neither study showed any significant protection against PHN.[49,50]

4. Economic Impact of Herpes Zoster and PHN

In addition to the clinical burden of disease on the patient, the overall economic burden of herpes zoster and PHN is considerable. Direct costs include primary care costs, particularly the cost of antiviral therapy and pain medication, and specialist and hospital costs. Indirect costs include the loss of ability to care for oneself, loss of productivity or ability to support oneself, and financial implications for family and caregivers.

Given the relatively high proportion of medication costs, drugs that engender a greater adherence to therapy can result in considerable cost savings. To estimate the impact of optimal management on the cost of the disease, the cost of prevention must be weighed against the relative risk of PHN without preventative therapy and the cost of care. The main cost of long-term PHN is the cost of pain relief. Clearly, more up-to-date and comparative pharmacoeconomic data are required to determine the relative risk of PHN with and without antiviral therapy, and the cost effectiveness of treatment of long-term PHN versus preventative therapy in all patients with herpes zoster and the various high-risk subgroups. These data also need to take into account the detrimental impact of pain on patients' quality of life.

The high costs of healthcare in elderly patients are a particular concern in many countries. A Spanish retrospective study of national surveillance system hospital data for patients hospitalized with herpes zoster showed that herpes zoster is more severe and more likely to result in hospitalizations in patients aged >50 years than in those aged ≤50 years.[51] Although hospitalization is a minor proportion of the total cost of care of this disease, the annual cost of hospitalization was estimated at €7 million (approximately $US10 million). Since herpes zoster and its complications are largely a disease of the elderly, the burden on healthcare resources will increase as the elderly population increases;[52] projected data from the 2001 UK census show a dramatic increase in the >65-year age group up to the year 2025.

A recently published study of a VZV (Oka strain) vaccine or placebo administered to patients aged ≥60 years showed a significant reduction in disease burden and incidence of herpes zoster and PHN in the vaccine group.[53] However, whether the vaccine provides cost-effective disease management in this or other patient groups remains to be determined.

5. Perceptions and Management Among European Countries

5.1 Treatment Guidelines

There are a number of local treatment guidelines for herpes zoster. The most well known are those provided by the International Herpes Management Forum (IHMF). The IHMF was established in 1993 to improve the awareness and understanding of herpes viruses among the general public and primary healthcare providers. IHMF guidelines and treatment algorithms[54,55] provide detailed recommendations for the management of acute herpes zoster. Other national guidelines include those from the German Dermatological Society,[28] the British Society for the Study of Infection (BSSI),[43] UK Department of Health,[56] the Italian Society of Dermatology, and the Italian Herpes Forum.[57,58] A number of other countries have local guidelines in development. There are no formal US guidelines produced by American societies, but a number of local guidelines are available. In general, guidelines recommend systemic antiviral therapy (acyclovir, famcyclovir, valacyclovir, or brivudin) to shorten the healing process of acute herpes zoster, to alleviate pain, and to alleviate or prevent acute and chronic complications. Antiviral agents are effective when given within 48–72 hours of rash onset and are strongly indicated in patients aged >50 years, patients with herpes zoster in the head or neck area (especially ophthalmic zoster), those with severe zoster on the trunk or extremities, immunosuppressed patients, and those with severe atopic dermatitis or eczema. Some guidelines suggest that antivirals should not be used if the rash has been present for more than 72 hours, although evidence of efficacy has not yet been established. If this is the case, the efficacy may be lower, but this should not preclude the use of antivirals, particularly in those at high risk of PHN and other complications. Some guidelines recommend the use of intravenous antivirals for treatment of ophthalmic zoster in immunosuppressed patients.[59] The IHMF guidelines clearly state that antiviral therapy should be given, even if the patient has had the rash for more than 72 hours, when there is ophthalmic or motor involvement.

5.2 Differences among European Countries

Discussions at the roundtable expert panel meeting arrived at the general view that there are substantial differences in the management of herpes zoster among European countries, and that treatment guidelines are used to varying degrees in the different countries. In Italy, the disease is well known but many patients seek medical advice at a late stage. Antivirals are prescribed, but not always according to local guidelines. In the UK, there is generally a moderate level of awareness among both the general public and primary care providers.[60] Guidelines published by the UK Department of Health and the BSSI[43,56,61] are widely available and are used, but drug costs may prevent optimal prescribing in many cases. In Spain, herpes zoster imposes a substantial burden on healthcare resources.[51] Considerable delays in treatment are seen in the public healthcare system, which treats approximately 50% of cases. In Germany, antiviral therapy is used for herpes zoster according to the German Dermatological Society guidelines.[28]

In Eastern European countries, such as the Czech Republic, primary-care providers were prohibited from prescribing systemic antiviral treatment for herpes zoster in immunocompetent patients. Since July 2005, acyclovir can be prescribed by both general practitioners and dermatologists without any limitation, while the other virostatics (valacyclovir, famcyclovir, and brivudin) can only be prescribed by dermatologists.

6. Suggested Revisions to Existing Treatment and Guidelines

Despite the availability of guidelines, in many cases antiviral initiation, dosage and course duration, and adjunctive pain management are inadequate. Some herpes simplex cases are wrongly identified as herpes zoster; correct diagnosis is essential for optimal treatment. As screening tests are expensive, most cases can be differentiated by the patient's age and clinical presentation; a younger individual presenting with recurrent painful rash in the cranial or sacral dermatomes is most likely to have herpes simplex, whereas herpes zoster is far more likely to present in older individuals. A lack of understanding of herpes zoster among patients may lead to under-treatment of this disease,[60] which exacerbates these limitations.

In view of these existing inadequacies, patients and primary healthcare providers would benefit from internationally accepted and widely circulated and publicized general guidelines. We propose that the IHMF and German Dermatology Society guidelines are used as a basis for the development of general guidelines that could be adapted for local use. Revision of the guidelines considers recommendations for antiviral treatment in immunocompetent

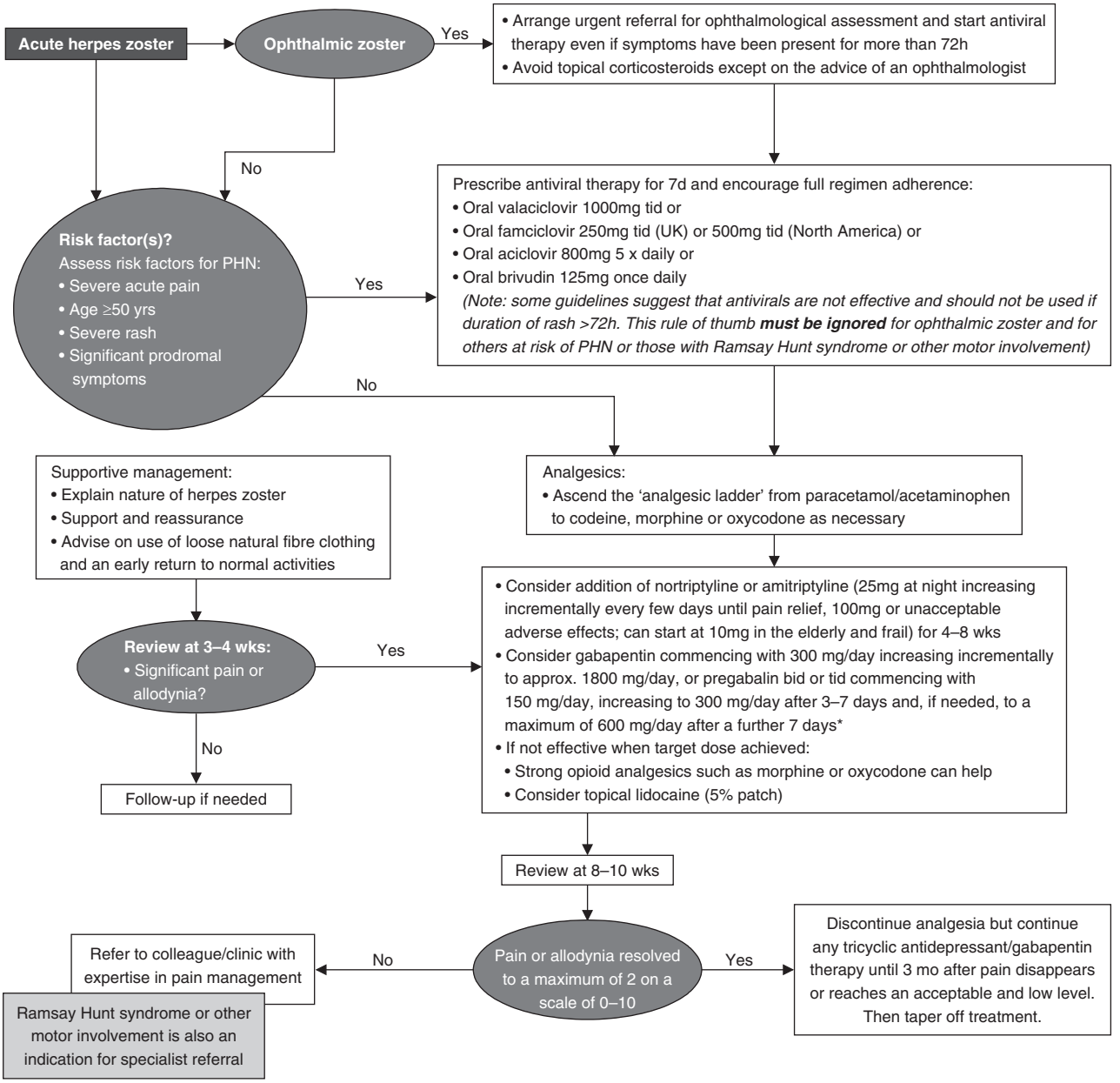

Fig. 2. Management algorithm for acute herpes zoster in immunocompetent patients based on the International Herpes Management Forum (IHMF)[54] and German Dermatological Society guidelines[28] (reproduced from IHMF Management Guidelines Series,[54] with permission of Cambridge Medical Publications, http://www.ihmf.org/Library/monograph/s_11.pdf). **bid** = twice daily; **PHN** = post herpetic neuralgia; **tid** = three times daily. * *Lyrica Summary of Product Characteristics*.[44]

patients and, although there is no evidence that antivirals affect the outcome of patients with Ramsay Hunt syndrome or other motor involvement, inclusion of these as indications for prompt antiviral therapy. Logic and clinical evidence suggest that if antiviral therapy is indicated, it should be given while there is an indication of ongoing viral activity, regardless of whether the rash has been present for more than 72 hours, to reduce the risk of PHN and other complications. A suggested treatment algorithm is shown in figure 2.

7. Conclusion

The burden of herpes zoster is underestimated, particularly in the very elderly. There is substantial variation in the management of herpes zoster and its complications among European countries.

More should be done to improve awareness of available management guidelines and algorithms and emphasize the cost-effectiveness of early antiviral therapy versus the long-term cost of treating the potential complications, particularly in high-risk patients. Published data show benefits in identifying patients at high risk of developing PHN and other complications and tailoring treatment accordingly.

The impact of herpes zoster-associated pain is also underestimated. A primary goal of treatment should be the acceptable alleviation of pain. This is possible in most patients and more can be done to improve outcomes in this area. The time to diagnosis and treatment is delayed in many cases, and more research is required to confirm the clinical and economic advantages of earlier antiviral therapy in the hope that this will accentuate the need for more timely intervention.

New potent highly bioavailable antiviral agents, such as once-daily brivudin, simplify the management of herpes zoster and should help to address current limitations in management and improve treatment compliance.

Acknowledgments

This manuscript was supported by an educational grant from Menarini, Italy and was prepared with editorial assistance by Mary Hines, Wolters Kluwer Health.

Antonio Volpi has undertaken educational or consultancy activities with Menarini, GlaxoSmithKline, Allen, Novartis, and Guidotti. Gerd Gross and Jana Hercogova have received assistance from and have undertaken educational or consultancy activities with Menarini. Robert W. Johnson has undertaken educational or consultancy activities with Menarini, Novartis, GlaxoSmithKline, Merck, Reliant and Yamanouchi.

References

1. Ragozzino MW, Melton LJ, Kurland LT, et al. Population-based study of herpes zoster and its sequelae. Medicine (Baltimore) 1982; 61 (5): 310-6
2. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine 2001; 19 (23-24): 3076-90
3. Coplan P, Black S, Rojas C, et al. Incidence and hospitalization rates of varicella and herpes zoster before varicella vaccine introduction: a baseline assessment of the shifting epidemiology of varicella disease. Pediatr Infect Dis J 2001; 20 (7): 641-5
4. Guess HA, Broughton DD, Melton LJ, et al. Epidemiology of herpes zoster in children and adolescents: a population-based study. Pediatrics 1985; 76 (4): 512-7
5. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis 2004; 4 (1): 26-33
6. Kost RG, Straus SE. Postherpetic neuralgia: pathogenesis, treatment, and prevention. N Engl J Med 1996; 335 (1): 32-42
7. Hope-Simpson RE. Postherpetic neuralgia. J R Coll Gen Pract 1975; 25 (157): 571-5
8. Donahue JG, Choo PW, Manson JE, et al. The incidence of herpes zoster. Arch Intern Med 1995; 155 (15): 1605-9
9. Jumaan AO, Yu O, Jackson LA, et al. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992-2002. J Infect Dis 2005; 191 (12): 2002-7
10. Edmunds WJ, Brisson M. The effect of vaccination on the epidemiology of varicella zoster virus. J Infect 2002; 44 (4): 211-9
11. Lin F, Hadler JL. Epidemiology of primary varicella and herpes zoster hospitalizations: the pre-varicella vaccine era. J Infect Dis 2000; 181 (6): 1897-905
12. Hambleton S, Gershon AA. Preventing varicella-zoster disease. Clin Microbiol Rev 2005; 18 (1): 70-80
13. Gnann JW, Whitley RJ. Clinical practice. Herpes zoster. N Engl J Med 2002; 347 (5): 340-6
14. Gnann JW. Varicella-zoster virus: atypical presentations and unusual complications. J Infect Dis 2002; 186 Suppl. 1: S91-8
15. Johnson RW. The future of predictors, prevention, and therapy in postherpetic neuralgia. Neurology 1995; 45 Suppl. 8: S70-S2
16. Dubinsky RM, Kabbani H, El-Chami Z, et al. Practice parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004; 63 (6): 959-65
17. Arani RB, Soong SJ, Weiss HL, et al. Phase specific analysis of herpes zoster associated pain data: a new statistical approach. Stat Med 2001; 20 (16): 2429-39
18. Meister W, Neiss A, Gross G, et al. A prognostic score for postherpetic neuralgia in ambulatory patients. Infection 1998; 26 (6): 359-63
19. Gershon AA. Epidemiology and management of postherpetic neuralgia. Semin Dermatol 1996; 15 (2 Suppl. 1): 8-13
20. Balfour HH. Varicella zoster virus infections in immunocompromised hosts: a review of the natural history and management. Am J Med 1988; 85 (2A): 68-73
21. Schmader KE. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain 2002; 18 (6): 350-4
22. Jung BF, Johnson RW, Griffin DR, et al. Risk factors for postherpetic neuralgia in patients with herpes zoster. Neurology 2004; 62 (9): 1545-51
23. Schmader K, Studenski S, MacMillan J, et al. Are stressful life events risk factors for herpes zoster? J Am Geriatr Soc 1990; 38 (11): 1188-94
24. Dworkin RH, Banks SM. A vulnerability-diathesis-stress model of chronic pain: herpes zoster and the development of postherpetic neuralgia. In: Gatchel RJ, Turk DC, editors. Psychosocial factors in pain: critical perspectives. New York: The Guilford Press, 1999: 247-69
25. Scott FT, Leedham-Green ME, Barrett-Muir WY, et al. A study of shingles and the development of postherpetic neuralgia in East London. J Med Virol 2003; 70 Suppl. 1: S24-30
26. Wood MJ, Shukla S, Fiddian AP, et al. Treatment of acute herpes zoster: effect of early (< 48 h) versus late (48-72 h) therapy with acyclovir and valaciclovir on prolonged pain. J Infect Dis 1998; 178 Suppl. 1: S81-4
27. Schmader K. Herpes zoster in older adults. Clin Infect Dis 2001; 32 (10): 1481-6
28. Gross G, Schofer H, Wassilew S, et al. Herpes zoster guideline of the German Dermatology Society (DDG). J Clin Virol 2003; 26 (3): 277-89
29. Kuraishi Y, Takasaki I, Nojima H, et al. Effects of the suppression of acute herpetic pain by gabapentin and amitriptyline on the incidence of delayed postherpetic pain in mice. Life Sci 2004; 74 (21): 2619-26
30. Davis LE, King MK. Shingles (herpes zoster) and post-herpetic neuralgia. Curr Treat Options Neurol 2001; 3 (5): 401-11
31. Wood MJ, Kay R, Dworkin RH, et al. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. Clin Infect Dis 1996; 22 (2): 341-7
32. Tyring S, Belanger R, Bezwoda W, et al. A randomized, double-blind trial of famciclovir versus acyclovir for the treatment of localized dermatomal herpes zoster in immunocompromised patients. Cancer Invest 2001; 19 (1): 13-22
33. Shen MC, Lin HH, Lee SS, et al. Double-blind, randomized, acyclovir-controlled, parallel-group trial comparing the safety and efficacy of famciclovir and acyclovir in patients with uncomplicated herpes zoster. J Microbiol Immunol Infect 2004; 37 (2): 75-81
34. Beutner KR, Friedman DJ, Forszpaniak C, et al. Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. Antimicrob Agents Chemother 1995; 39 (7): 1546-53
35. Tyring SK, Beutner KR, Tucker BA, et al. Antiviral therapy for herpes zoster: randomized, controlled clinical trial of valacyclovir and famciclovir therapy in immunocompetent patients 50 years and older. Arch Fam Med 2000; 9 (9): 863-9

36. Andrei G, Snoeck R, Reymen D, et al. Comparative activity of selected antiviral compounds against clinical isolates of varicella-zoster virus. Eur J Clin Microbiol Infect Dis 1995; 14 (4): 318-29

37. Crea AEG, Iafrate EM, Evangelista S, et al. Cellular and human pharmacokinetics of brivudin, a new antiherpetic drug. In: Recent research developments in drug metabolism & disposition. Trivandrum (India): Transworld Research Network, 2004: 27-37

38. Wassilew SW, Wutzler P. Oral brivudin in comparison with acyclovir for herpes zoster: a survey study on postherpetic neuralgia. Antiviral Res 2003; 59 (1): 57-60

39. Wassilew S. Brivudin compared with famciclovir in the treatment of herpes zoster: effects in acute disease and chronic pain in immunocompetent patients: a randomized, double-blind, multinational study. J Eur Acad Dermatol Venereol 2005; 19 (1): 47-55

40. Wassilew SW, Wutzler P. Oral brivudin in comparison with acyclovir for improved therapy of herpes zoster in immunocompetent patients: results of a randomized, double-blind, multicentered study. Antiviral Res 2003; 59 (1): 49-56

41. Keam SJ, Chapman TM, Figgitt DP. Brivudin (bromovinyl deoxyuridine). Drugs 2004; 64 (18): 2091-7

42. Johnson R, Patrick D, editors. In: Improving the management of varicella, herpes zoster and zoster-associated pain: recommendations from the IHMF Management Strategies Workshop [online]. Available from URL: http://www.ihmf.org/library/monograph/m_11.pdf [Accessed 2005 Sep 21]

43. Anonymous. Guidelines for the management of shingles. Report of a working group of the British Society for the Study of Infection (BSSI). J Infect 1995; 30 (3): 193-200

44. Lyrica summary of product characteristics [online]. Available from URL: http://www.emea.eu.int/humandocs/Humans/EPAR/lyrica/lyrica.htm [Accessed 2005 Sep 22]

45. Lilie HM, Wassilew S. The role of antivirals in the management of neuropathic pain in the older patient with herpes zoster. Drugs Aging 2003; 20 (8): 561-70

46. Jackson JL, Gibbons R, Meyer G, et al. The effect of treating herpes zoster with oral acyclovir in preventing postherpetic neuralgia: a meta-analysis. Arch Intern Med 1997; 157 (8): 909-12

47. Herne K, Cirelli R, Lee P, et al. Antiviral therapy of acute herpes zoster in older patients. Drugs Aging 1996; 8 (2): 97-112

48. Eaglstein WH, Katz R, Brown JA. The effects of early corticosteroid therapy on the skin eruption and pain of herpes zoster. JAMA 1970; 211 (10): 1681-3

49. Whitley RJ, Weiss H, Gnann JW, et al. Acyclovir with and without prednisone for the treatment of herpes zoster: a randomized, placebo-controlled trial. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Ann Intern Med 1996; 125 (5): 376-83

50. Wood MJ, Johnson RW, McKendrick MW, et al. A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. N Engl J Med 1994; 330 (13): 896-900

51. Gil A, San-Martin M, Carrasco P, et al. Epidemiology of severe varicella-zoster virus infection in Spain. Vaccine 2004; 22 (29-30): 3947-51

52. Johnson RW. Pain following herpes zoster: implications for management. Herpes 2004; 11 (3): 63-5

53. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005; 352 (22): 2271-84

54. Management of acute herpes zoster. In: Algorithms for managing varicella and herpes zoster (1 May 2002). IHMF Management Guideline Series [online]. Available from URL: http://www.ihmf.org/Library/monograph/s_11.pdf [Accessed 2005 Sep 20]

55. Algorithms for management of varicella and herpes zoster [online]. Available from URL: http://www.ihmf.org/guidelines/rcmmnd1.asp [Accessed 2005 Feb 15]

56. Immunisation against infectious disease 1996. 'The Green Book'. Chapter 34: Varicella (updated January 2004) [online]. Available from URL: http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?.CONTENT_ID=4097254&chk=isTfGX [Accessed 2005 Feb 16]

57. International Herpes Management Forum: Regional Management Forums [online]. Available from URL: http://www.ihmf.org/globallinks/wld_ita.asp [Accessed 2005 Jul 22]

58. Volpi A, Caputo R, Martino P, et al. Linee guida per la gestione del paziente con Herpes Zoster. G Ital Dermatol Venereol 1998; 133 (4): 308-11

59. Moorthy RS, Weinberg DV, Teich SA, et al. Management of varicella zoster virus retinitis in AIDS. Br J Ophthalmol 1997; 81 (3): 189-94

60. Johnson R, Levin M. Knowledge of shingles symptoms, risks, and treatments low among adults: widespread shingles education efforts may reduce long-term complications. In: Proceedings of the 11th International Association for the Study of Pain World Congress on Pain; 2005 Aug 21-26; Sydney

61. PRODIGY Guidance – shingles and postherpetic neuralgia [online]. Available from URL: http://www.prodigy.nhs.uk/guidance.asp?.gt=Shingles/postherpetic%20pain [Accessed 2005 Feb 16]

Correspondence and offprints: Prof. *Antonio Volpi*, Universita di Tor Vergata, Dipartimento di Sanita pubblica, Cattedra di malattie infettive, Via Montpellier 1, Roma, Italy.
E-mail: volpi@med.uniroma2.it