Treatment of herpes zoster in the immunocompetent host

Author: Mary A Albrecht, MD
Section Editor: Martin S Hirsch, MD
Deputy Editor: Jennifer Mitty, MD, MPH

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INTRODUCTION

Varicella-zoster virus (VZV) infection causes two clinically distinct forms of disease [1]. Primary infection with VZV results in varicella, also known as chickenpox, characterized by vesicular lesions in different stages of development on the face, trunk, and extremities. Herpes zoster, also known as shingles, results from reactivation of endogenous latent VZV infection within the sensory ganglia. This clinical form of the disease is characterized by a painful, unilateral vesicular eruption, which usually occurs in a restricted dermatomal distribution [2]. Although herpes zoster can occur at any age, it is mainly a disease of adults >60 years of age.

The treatment of herpes zoster will be reviewed here. The epidemiology, clinical manifestations, diagnosis, and prevention of herpes zoster are discussed elsewhere. (See "Epidemiology, clinical manifestations, and diagnosis of herpes zoster" and "Varicella-zoster virus infection in pregnancy" and "Vaccination for the prevention of shingles (herpes zoster)" and "Prevention and control of varicella-zoster virus in hospitals".)

UNCOMPLICATED HERPES ZOSTER

The clinical manifestations of uncomplicated herpes zoster typically include a dermatomal vesicular rash, and acute neuritis, which precedes or occurs simultaneously with the rash. The rash is generally limited to one dermatome, but can occasionally affect two or three neighboring dermatomes. Some patients can also have a few scattered vesicles located at some distance away from the involved dermatome. (See "Epidemiology, clinical manifestations, and diagnosis of herpes zoster".)

The management of herpes zoster includes:

- Antiviral therapy to hasten healing of cutaneous lesions and to decrease the duration and severity of acute neuritis. Whether antiviral therapy decreases the risk of post-herpetic neuralgia (PHN) is less clear. (See 'Antiviral therapy' below.)
- Analgesia for patients with moderate to severe acute neuritis. (See 'Analgesia for acute neuritis' below.)

The treatment of established PHN is discussed elsewhere. (See "Postherpetic neuralgia", section on 'Treatment'.)

Antiviral therapy — The goals of antiviral therapy are to [3,4]:

- Lessen the severity and duration of pain associated with acute neuritis
- Promote more rapid healing of skin lesions
- Prevent new lesion formation
- Decrease viral shedding to reduce the risk of transmission
- Prevent PHN

Several lines of evidence suggest that antiviral therapy hastens resolution of cutaneous lesions and the acute neuritis of herpes zoster [5-7]. However, it is unclear if antiviral therapy prevents PHN because of conflicting study results, which are due in part to different methodologies of pain assessment, definitions of PHN, and length of follow-up [5-8].

≤72 hours after onset — We recommend antiviral therapy for patients with uncomplicated herpes zoster who present within 72 hours of clinical symptoms. Antiviral therapy should be initiated within this time frame to maximize the potential benefits of treatment. (See 'Choice of agent' below.)

The benefit of antiviral therapy appears to be greatest in patients older than 50 years of age, in whom the pain of zoster generally persists longer [5,9]. Although the efficacy of antiviral therapy in patients less than 50 years of age has not been as well studied, the risk of adverse events secondary to antiviral therapy is very low.

>72 hours after onset — We administer antiviral therapy after 72 hours if new lesions are appearing at the time of presentation, as this indicates ongoing viral replication [10]. However, the clinical utility of initiating antiviral therapy more than 72 hours after the onset of lesions in immunocompetent persons is unknown. There is likely minimal benefit of antiviral therapy in the patient who has lesions that have encrusted.

Choice of agent — The nucleoside analogues acyclovir, valacyclovir, and famciclovir are the preferred antivirals for treatment of acute herpes zoster infection. Oral antiviral therapy is usually sufficient for the initial treatment of uncomplicated herpes zoster, unless the patient

has evidence of complicated disease (eg, acute retinal necrosis, encephalitis). (See 'Complicated zoster' below.)

We prefer valacyclovir or famciclovir compared with acyclovir given the need for less frequent dosing. Small comparative trials do not support the efficacy of one over the other [11-13].

The doses used to treat herpes zoster are as follows:

- Valacyclovir: 1000 mg three times daily for seven days
- Famciclovir: 500 mg three times daily for seven days
- Acyclovir: 800 mg five times daily for seven days

Acyclovir and its analogues are dependent upon renal function for clearance and dose adjustment is needed in moderate to severe renal insufficiency. Dosing information can be found in the Lexicomp drug information topics within UpToDate.

Although the doses used to treat herpes zoster infection are higher than those typically required for herpes simplex virus, these nucleoside analogs have well-established safety records at the currently recommended doses. Adverse events are uncommon, but can include nausea, diarrhea, or headache. More detailed information about the individual agents is found elsewhere. (See "Acyclovir: An overview" and "Valacyclovir: An overview" and "Famciclovir: An overview".)

Data supporting the efficacy of these agents for the treatment of herpes zoster include:

- **Oral** acyclovir — Oral acyclovir has been the mainstay of herpes zoster treatment. However, its poor bioavailability and need for frequent daily dosing (800 mg five times daily) prompted the development of later generation antiviral agents (valacyclovir and famciclovir) with improved pharmacokinetics and lower dosing frequency [5,6,14-16].

  In a meta-analysis of four placebo-controlled trials involving 691 patients (mean age 62 years), those who received acyclovir (800 mg five times daily) administered within 48 to 72 hours of the onset of rash were more likely to have resolution of moderate/severe acute neuritis (hazard ratio [HR] 1.46; 95% CI 1.1-1.93) and PHN, defined as the presence of pain at three and six months after resolution of the rash (HR 1.8; 95% CI 1.35-2.43) [5]. In a subsequent meta-analysis, which included one additional placebo-controlled trial, antiviral therapy decreased the risk of PHN (as defined by any pain at six months) by 46 percent [6].

- Famciclovir — Famciclovir, the prodrug of penciclovir, is well absorbed from the gastrointestinal tract. It is then rapidly converted in the intestinal wall and liver to the

active compound penciclovir, which has broad activity against varicella-zoster virus [9,16].

A placebo-controlled clinical trial was conducted in 419 immunocompetent adults (mean age 50 years) with uncomplicated zoster to evaluate the efficacy of standard-dose and high-dose famciclovir (500 or 750 mg three times daily) with placebo [9]. All patients initiated therapy within 72 hours of the rash and were treated for seven days. After five months of follow-up, famciclovir was associated with a modest improvement in lesion healing rates compared with placebo (median five to six versus seven days). While there was no difference in the incidence of PHN among the three treatment arms, the use of famciclovir therapy, regardless of dose, conferred a selective reduction in the median duration of PHN compared with placebo (62 and 55 days with low- and high-dose famciclovir, respectively versus 119 days).

- Valacyclovir — Valacyclovir is also well absorbed from the gastrointestinal tract. It is rapidly converted to acyclovir in vivo, thereby providing a three- to fivefold increase in acyclovir bioavailability [16,17].

  In a randomized, double-blind study of 1141 immunocompetent adults with herpes zoster (mean age 68 years), the efficacy and safety of valacyclovir (1000 mg orally three times daily for 7 or 14 days) was compared with acyclovir (800 mg orally five times daily for seven days) over six months of follow-up [17]. Cutaneous lesions resolved at similar rates in all treatment groups. However, valacyclovir for 7 or 14 days accelerated the resolution of acute neuritis compared with acyclovir (median duration of pain 38 and 44 days, respectively, for valacyclovir compared with 51 days for acyclovir). In addition, the proportion of patients with pain persisting for six months was modestly lower in the combined valacyclovir arms compared with the acyclovir arm (19 versus 26 percent). No additional benefit was observed with a longer duration of valacyclovir.

Special populations

Pregnant women — We treat pregnant women with early herpes zoster, regardless of the number of lesions, to hasten healing of cutaneous lesions and reduce the severity and duration of pain. However, there is no evidence to suggest that pregnant women are at increased risk for complicated disease, and some experts suggest treating only those with a severe zoster rash (eg, >50 lesions), and those with acute neuritis [4].

In general, we prefer oral acyclovir (800 mg five times daily) rather than other antiviral agents since there is the most experience with this medication in pregnancy. Although there are no clinical trials evaluating specific antiviral agents in pregnant women with herpes zoster infection, experience with acyclovir in both herpes simplex infection and varicella pneumonia suggests that this drug is safe in pregnancy. (See "Varicella-zoster virus infection

in pregnancy" and "Genital herpes simplex virus infection and pregnancy", section on 'Drug choice, dose, and safety'.)

Immunocompromised hosts — Antiviral therapy should be initiated in all immunocompromised patients with herpes zoster, even if they present after 72 hours. Rapid initiation of therapy is particularly critical in the severely immunocompromised patient, such as the organ transplant recipient [18]. Immunocompromised hosts with disseminated zoster should be hospitalized for intravenous acyclovir therapy.

Adjunctive therapies — For patients with uncomplicated zoster, there is **no** role for the routine use of agents, such as gabapentin, tricyclic antidepressants, or glucocorticoids, in the acute setting [19,20]. However, these agents may have a role in select patients with acute neuritis. (See 'Analgesia for acute neuritis' below.)

There are no definitive data to suggest that tricyclic antidepressants in patients with herpes zoster prevent PHN from developing, and the risk of adverse events with tricyclic antidepressants is increased in elderly patients. Although an early placebo-controlled trial of amitriptyline found that the risk of post-herpetic neuralgia was reduced by more than 50 percent among patients who received amitriptyline for 90 days, there were multiple limitations to this trial, and the additive benefit of tricyclics for pain reduction could not be adequately assessed [20].

With regards to glucocorticoids, early trials suggested a modest benefit of glucocorticoids on a limited number of clinical outcomes [15,21-24]. Thus, these agents were often used in combination with acyclovir for the treatment of uncomplicated acute herpes zoster in an attempt to improve quality of life and time to healing of lesions, and to reduce PHN. However, a subsequent meta-analysis of five placebo-controlled trials evaluating acyclovir alone compared with acyclovir plus glucocorticoids did not demonstrate any benefit of combination therapy on quality of life or the incidence of PHN [21]. Furthermore, corticosteroids could potentially increase the risk of secondary bacterial skin infection.

Analgesia for acute neuritis — Although antiviral therapy reduces pain associated with acute neuritis, pain syndromes associated with herpes zoster can still be severe. Management of acute neuritis must be individualized and requires the same principles as managing any pain: use of standardized pain measures, scheduled analgesia, and consistent and frequent monitoring to adjust dosing to the needs of the patient.

- For patients with mild pain, nonsteroidal anti-inflammatory drugs and acetaminophen can be useful agents to alleviate pain.
- For those with moderate to severe pain that disturbs sleep, management can be more difficult, and additional agents may be needed. The choice of treatment is based upon

the patient's comorbidities, concurrent medications, pain intensity, and preferences. Options include [25]:

- The use of agents such as short-acting narcotics (see "Prescription of opioids for acute pain in opioid naïve patients"), or a 10- to 14-day tapering course of oral prednisone (starting at 60 mg/day and administered in combination with antiviral therapy).
- If short-acting narcotics or prednisone are unsuccessful, treatments that are used for management of postherpetic neuralgia (eg, gabapentin or tricyclic antidepressants, anesthetic nerve blocks) may be reasonable. (See "Postherpetic neuralgia".)

Secondary bacterial infection — Although rare, secondary bacterial infections of the zoster rash can occur. Should a bacterial infection be suspected at the time of the initial evaluation, the patient should receive appropriate staphylococcal and streptococcal antibiotic coverage in addition to antiviral therapy. Patients should also be counseled to contact their clinician if they observe increased erythema, warmth, or purulence surrounding any lesions, which could suggest secondary bacterial skin infection.

Patient monitoring — After treatment for herpes zoster has been initiated, patients should be assessed for improvement in their clinical symptoms. Management of acute neuritis is also integral for patient management. Serial patient monitoring should include standardized pain measures and frequent follow-up to assess efficacy in relief of symptoms [4]. Approximately 10 to 15 percent of patients may develop PHN. The management of the pain associated with PHN is discussed elsewhere. (See "Postherpetic neuralgia".)

Recurrent zoster — Patients with recurrent zoster should be treated with antiviral therapy using similar a dose and duration as treatment of their initial episode. (See 'Antiviral therapy' above.)

However, episodes of recurrent zoster are uncommon [26]. Thus, viral cultures or other detection assays (eg, antigen or DNA detection) should be performed since some patients (eg, those who present with recurrent herpes simplex outside of the mouth or genital area) may be misdiagnosed as having recurrent zoster. (See "Diagnosis of varicella-zoster virus infection" and "Epidemiology, clinical manifestations, and diagnosis of herpes zoster", section on 'Recurrent herpes zoster'.)

There are no data regarding the potential benefit of zoster vaccine in this scenario. (See "Vaccination for the prevention of shingles (herpes zoster)".)

COMPLICATED ZOSTER

Certain immunocompetent patients with herpes zoster will present with ocular, otic, or neurologic manifestations. Such patients may require intravenous and/or prolonged therapy. In addition, there may be a role for adjunctive glucocorticoids in certain conditions.

Herpes zoster ophthalmicus — Herpes zoster ophthalmicus, a serious sight-threatening condition, has been linked to varicella zoster virus (VZV) reactivation within the trigeminal ganglion [27,28]. Patients can develop conjunctivitis, episcleritis, keratitis, and/or iritis. (See "Epidemiology, clinical manifestations, and diagnosis of herpes zoster", section on 'Herpes zoster ophthalmicus'.)

Early diagnosis and treatment is critical to prevent progressive corneal involvement and potential loss of vision [29].

- The standard approach to herpes zoster ophthalmicus includes oral antiviral therapy (acyclovir, valacyclovir, or famciclovir) to limit VZV replication, and the use adjunctive topical steroid drops to reduce the inflammatory response and control immune-associated keratitis and iritis [27-30].

- Intravenous acyclovir (10 mg/kg three times daily for seven days) should be administered if the patient is immunocompromised or requires hospitalization for sight-threatening disease.

Acute retinal necrosis — For immunocompetent patients with acute retinal necrosis (ARN), we administer intravenous acyclovir (10 mg/kg every 8 hours for 10 to 14 days) followed by oral valacyclovir 1 g three times daily (or equivalent) for approximately six weeks. This approach is based upon expert opinion since there are no clinical trial data to guide treatment decisions [4,31]. Such patients should be managed in conjunction with an ophthalmologist to evaluate the need for intraocular therapy and/or vitrectomy.

In addition, we typically administer empiric systemic glucocorticoids, especially if there is decreased visual acuity secondary to inflammation or optic nerve involvement. However, there are no definitive data to guide which patients are most likely to benefit from adjunctive glucocorticoids or which regimens should be used. In one study, oral prednisolone was administered at 1 mg/kg/day and was tapered by 10 mg every five days [32].

Intravenous acyclovir therapy usually affords clinical improvement in 48 to 72 hours [33]. In one report of patients presenting with ARN, the use of acyclovir when administered for up to three months was associated with a decreased risk of contralateral eye involvement over a median follow-up period of 12 months [34]. A pharmacokinetic study that evaluated intravitreal drug concentrations in 10 patients with ARN found substantial penetration after 24 hours of oral valacyclovir, even in the uninflamed eye [35]. However, there are few data on the use of oral agents for the initial treatment of infection [36].

Ramsay Hunt syndrome — The major otologic complication of VZV reactivation is the Ramsay Hunt syndrome, which typically includes the triad of ipsilateral facial paralysis, ear pain, and vesicles in the auditory canal and auricle. (See "Epidemiology, clinical manifestations, and diagnosis of herpes zoster", section on 'Ramsay Hunt syndrome (herpes zoster oticus)'.)

For most patients, we administer valacyclovir (1 g three times per day for 7 to 10 days) and prednisone (1 mg/kg for five days, without a taper). In severe cases (eg, vertigo, tinnitus, or hearing loss), IV therapy can be initiated, and the patient can then be transitioned to an oral antiviral agent when the lesions begin to crust.

However, there are few data to guide treatment decisions about management of this complication. Although a systematic review found no evidence that antiviral agents have a beneficial effect on outcomes in Ramsay Hunt syndrome [37], a subsequent retrospective review of 101 patients found that patients who received acyclovir and glucocorticoids recovered significantly more than those who had only one or no pharmacologic treatment [38].

Neurologic complications — Intravenous acyclovir should be administered to patients with neurologic complications where viral replication likely plays an important role (eg, symptomatic meningitis, encephalitis, and myelitis) [4]. Treatment is generally administered for 10 to 14 days. This approach is supported by expert opinion. An additional discussion on the treatment of neurologic manifestations of VZV is found elsewhere. (See "Varicella zoster virus vasculopathy".)

POSTHERPETIC NEURALGIA

The diagnosis of postherpetic neuralgia (PHN) is typically made when pain persists beyond four months in the same distribution as a preceding documented episode of acute herpes zoster. A detailed discussion of the management of patients with PHN is found elsewhere. (See "Postherpetic neuralgia".)

PREVENTING TRANSMISSION TO OTHERS

Patients with herpes zoster can transmit varicella zoster virus (VZV) to individuals who have not had varicella and have not received the varicella vaccine. VZV is transmitted from person to person by direct contact or by aerosolization of virus from skin lesions. In general, VZV is much less transmissible from a person presenting with herpes zoster than from a person presenting with varicella. (See "Epidemiology, clinical manifestations, and diagnosis of herpes zoster", section on 'Transmission'.)

Patients with localized zoster are not infectious before vesicles appear and are no longer infectious when the lesions have re-epithelized. For those with active lesions, there are no specific precautions within the community setting. However, patients should be counseled about the risk of viral transmission to others [4]. In addition, until the rash has crusted, patients should be advised to:

- Keep the rash covered, if feasible, and to wash their hands often to prevent the spread of virus to others.
- Avoid contact with pregnant women who have never had chickenpox or the varicella vaccine, premature or low birth weight infants, and immunocompromised individuals [39].

A discussion of how to prevent transmission of VZV in the hospital setting is found elsewhere. (See "Prevention and control of varicella-zoster virus in hospitals".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Varicella-zoster virus".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Shingles (The Basics)")
- Beyond the Basics topic (see "Patient education: Shingles (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Uncomplicated herpes zoster** – Reactivation of latent varicella-zoster virus (VZV) infection within the sensory ganglia results in herpes zoster, or "shingles." The clinical manifestations of uncomplicated herpes zoster typically include a dermatomal vesicular rash, and acute neuritis, which precedes or occurs simultaneously with the rash. (See 'Uncomplicated herpes zoster' above.)

  - **Antiviral therapy** – The goals of antiviral therapy are to promote more rapid healing of skin lesions, lessen the severity and duration of pain associated with acute neuritis, and potentially reduce the incidence or severity of chronic pain, referred to as postherpetic neuralgia. (See 'Antiviral therapy' above.)

    - We recommend antiviral therapy for patients with uncomplicated herpes zoster who present within 72 hours of clinical symptoms (**Grade 1B**). The benefit of antiviral therapy appears to be greatest in patients older than 50 years of age, in whom the pain of zoster generally persists longer. (See '≤72 hours after onset' above.)

    - For patients who present after 72 hours, we administer antiviral therapy if new lesions are appearing at the time of presentation. There is likely minimal benefit of antiviral therapy in the patient who has lesions that have encrusted. (See '>72 hours after onset' above.)

    - The nucleoside analogues acyclovir, valacyclovir, or famciclovir can be used for treatment of acute herpes zoster infection. We prefer valacyclovir (1000 mg three times daily) or famciclovir (500 mg three times daily) because of their lower dosing frequency compared with acyclovir (800 mg five times daily). All regimens should be given for seven days. (See 'Choice of agent' above.)

  - **Analgesia for acute neuritis** – Analgesic drugs are often needed to control mild to severe pain associated with acute neuritis. There is no clear role for the use of glucocorticoids or tricyclic antidepressants in patients with uncomplicated herpes zoster since clinical benefit has not been demonstrated and there are significant risks associated with these medications. (See 'Analgesia for acute neuritis' above and 'Adjunctive therapies' above.)

- **Considerations during pregnancy** – We treat pregnant women with early herpes zoster to hasten healing of cutaneous lesions and reduce the severity and duration of pain. Although there are no clinical trials examining the role of antiviral therapy in pregnant woman with herpes zoster infection, experience with acyclovir therapy in

both herpes simplex infection and varicella pneumonia suggests that this drug is safe in pregnancy. (See 'Pregnant women' above.)

- **Secondary bacterial infection** – Should secondary bacterial infection be suspected at the time of the initial evaluation, or at any time during the course of treatment, the patient should receive appropriate staphylococcal and streptococcal antibiotic coverage in addition to antiviral therapy. (See 'Secondary bacterial infection' above.)

- **Complicated infection** – On occasion, immunocompetent patients with herpes zoster can present with ocular, otic, or neurologic manifestations. Such patients may require intravenous and/or prolonged antiviral therapy. In addition, there may be a role for adjunctive glucocorticoids in certain conditions. (See 'Complicated zoster' above.)

- **Preventing transmission to others** – Patients with herpes zoster can transmit VZV to individuals who have not had varicella and have not received the varicella vaccine. Until the rash has crusted, patients should be advised to keep the rash covered, if feasible, and to wash their hands often to prevent the spread of virus to others. They should also avoid contact with pregnant women who have never had chickenpox or the varicella vaccine, premature or low birth weight infants, and immunocompromised individuals. (See 'Preventing transmission to others' above.)

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