



Complete Summary

GUIDELINE TITLE

Recommendations for the management of herpes zoster.

BIBLIOGRAPHIC SOURCE(S)

Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, Betts RF, Gershon AA, Haanpaa ML, McKendrick MW, Nurmikko TJ, Oaklander AL, Oxman MN, Pavan-Langston D, Petersen KL, Rowbotham MC, Schmader KE, Stacey BR, Tyring SK, van Wijck AJ, Wallace MS, Wassilew SW, Whitley RJ. Recommendations for the management of herpes zoster. Clin Infect Dis 2007 Jan 1;44 Suppl 1:S1-26. [243 references] [PubMed](#)

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- [June 15, 2005, COX-2 Selective \(includes Bextra, Celebrex, and Vioxx\) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs \(NSAIDs\)](#): Labeling revised to include a boxed warning and a Medication Guide, highlighting the potential for increased risk of cardiovascular (CV) events and life-threatening gastrointestinal (GI) bleeding.
- [April 7, 2005, Bextra \(valdecoxib\), Cox-2 inhibitors, Celebrex \(celecoxib\), Non-steroidal anti-inflammatory drugs \(NSAIDs\) \(prescription and OTC, including ibuprofen and naproxen\)](#): Bextra (valdecoxib) withdrawn from the market and labels for other Cox-2 inhibitors and NSAIDs revised to include a boxed warning and a Medication Guide, highlighting the potential for increased risk of cardiovascular (CV) events and life-threatening gastrointestinal (GI) bleeding.

Additional Notice

- [May 2, 2007, Antidepressant drugs](#): Update to the existing black box warning on the prescribing information on all antidepressant medications to include warnings about the increased risks of suicidal thinking and behavior in young adults ages 18 to 24 years old during the first one to two months of treatment.

COMPLETE SUMMARY CONTENT

** REGULATORY ALERT **

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

CATEGORIES

IDENTIFYING INFORMATION AND AVAILABILITY

DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Herpes zoster (HZ)

GUIDELINE CATEGORY

Management

Treatment

CLINICAL SPECIALTY

Anesthesiology

Dermatology

Emergency Medicine

Family Practice

Geriatrics

Infectious Diseases

Internal Medicine

Neurology

Nursing

Obstetrics and Gynecology

Oncology

Ophthalmology

Otolaryngology

Pediatrics

INTENDED USERS

Advanced Practice Nurses

Clinical Laboratory Personnel

Nurses

Pharmacists

Physician Assistants

Physicians

GUIDELINE OBJECTIVE(S)

To improve the care of patients with herpes zoster (HZ) by providing practical, evidence-based recommendations that take into account clinical efficacy, adverse effects, impact on quality of life, and costs of treatment

TARGET POPULATION

Patients with herpes zoster (HZ) including:

- Immunocompetent patients
- Immunocompromised patients (patients with lymphoproliferative malignancies, organ transplant recipients, patients receiving systemic corticosteroids, and patients sero-positive for human immunodeficiency virus [HIV])
- Patients with complicated presentations of HZ (HZ ophthalmicus and varicella-zoster virus [VZV] retinitis; vulnerable and frail elderly patients; pregnant and nursing patients; neurologic complications of HZ; renal failure)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Treatment of immunocompetent patients
 - Systemic antiviral therapy such as acyclovir, famciclovir, valacyclovir, and brivudin (brivudin is not approved in the United States)
 - Supplementation to antiviral therapy such as acetaminophen, nonsteroidal antiinflammatory drugs [NSAIDs], opioids, tricyclic antidepressants, gabapentin or pregabalin, corticosteroids
 - Patient education
 - Referral to pain specialist if necessary
 - Referral to an ophthalmologist if ophthalmic zoster
 - Management of acute pain
2. Treatment of immunocompromised patients
 - Intravenous acyclovir; oral acyclovir, famciclovir, or valacyclovir
 - Referral to an ophthalmologist if ophthalmic zoster
 - Alternative antivirals (e.g., intravenous foscarnet or cidofovir) for acyclovir-resistant patients
 - Management of acute pain
3. Treatment of complicated presentations of HZ
 - *HZ ophthalmicus and VZV retinitis*: antivirals, referral to an ophthalmologist, pain medication, wet compresses, antibiotic ophthalmic ointment, topical steroids, mydriatic agents, ocular pressure-lowering drugs, therapy for chronic problems
 - *Vulnerable and frail elderly patients*: pharmacotherapy with lower dosages; nonpharmacologic approach including maintaining physical activity, enhancing nutrition, assisting in daily living; close monitoring with particular attention to patients with dementia
 - *Pregnant and nursing patients*: consideration of benefits versus risks of treatment, acyclovir or valacyclovir, preferably during the late stages of pregnancy for patients with severe rash, severe acute pain, or HZ ophthalmicus; opioid analgesics
 - *Neurologic complications of HZ*: intravenous acyclovir as indicated

- *Renal failure*: Reduced dosages of antivirals, gabapentin, and pregabalin

MAJOR OUTCOMES CONSIDERED

- Treatment effects on viral clearance, acute pain, postherpetic neuralgia (PHN), and other complications of herpes zoster (HZ)
- Safety, tolerability, and adverse effects associated with drugs used for treatment
- Quality of life

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Relevant publications were identified by Medline searches, examination of reference lists of published articles and book chapters, and the personal knowledge of the authors.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review
Review of Published Meta-Analyses

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Participants of the consensus meeting on which the treatment recommendations were based were selected on the basis of research and clinical expertise relevant to herpes zoster (HZ) and its management and represent the fields of anesthesiology, geriatrics, infectious diseases, internal medicine, neurology, ophthalmology, outcomes research, pain management, and virology. Before the meeting, all participants were provided copies of systematic literature reviews and meta-analyses, existing guidelines relevant to the management of HZ, and published randomized clinical trials. This literature and the authors' clinical and research experience were reviewed during the consensus meeting. Information on additional randomized trials that were not identified before the meeting was provided on request after the meeting. Recommendations for practice guidelines, best-evidence synthesis, and narrative systematic reviews were followed in developing recommendations for the management of HZ and summarizing the literature on which they are based.

Recommendations for first-line pharmacologic treatments are based on positive results from multiple randomized clinical trials. The methods and results of these trials, in combination with the clinical experience of the authors, provide the basis for specific recommendations regarding these treatments. Because recommendations for first-line treatments are consistent with the results of multiple trials and the clinical experience of the authors, they are made with a high degree of confidence.

Recommendations for additional treatments that should be considered in combination with first-line treatment are based on the results of single clinical trials, inconsistent results of multiple trials, or uncontrolled trials, considered together with the clinical experience of the authors. These recommendations are made with moderate confidence that these treatments should be considered because they may provide additional benefits when used in combination with first-line treatment.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The initial version of the present article was prepared by the first 5 authors, revised by the other authors, and recirculated until all authors agreed with the text.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Treatment of Immunocompetent Patients

The principal goals of the treatment of herpes zoster (HZ) are reduction of pain in immunocompetent patients and cessation of viral replication in immunocompromised patients and those with ophthalmic HZ. All patients should have a medical and psychosocial history evaluation and targeted physical examination performed to confirm the diagnosis, document comorbid illnesses, and provide a basis for treatment. Prompt referral to an ophthalmologist is required for all patients with ocular involvement, whether immunocompetent or immunocompromised. Elderly patients may be socially isolated, have cognitive impairment or depression, or have had recent adverse major life events (e.g., bereavement), all of which may impact treatment compliance and response to treatment. Anxiety or depression may also develop secondary to severe HZ, which may further complicate treatment and disease resolution.

Patient Education

The treatment of HZ should occur in conjunction with appropriate education and support from the health care provider. Careful explanation of the disease, including the risk of viral transmission to individuals who have not had chickenpox, and of the proposed treatment plan is essential for adherence to therapy and is beneficial to patient well-being; for example, providing reassurance and education can dispel myths and fears about HZ and its implications for the patient's health. Encouragement, reassurance, and advice on quality of life are also important and include supporting adequate nutrition and optimal levels of mental, physical, and social activity. Patients should be told to keep the rash clean and dry to reduce the risk of bacterial superinfection, to avoid use of topical antibiotics and of dressings with adhesive that can cause irritation and delay rash healing, and to inform their physician if a secondary increase in temperature develops, which is often an indication of bacterial infection. For some patients, discomfort may be reduced by sterile wet dressings.

Recommendations for Antiviral Therapy

Topical antiviral therapy lacks efficacy in patients with HZ and is not recommended. Systemic antiviral therapy is strongly recommended as first-line treatment for all immunocompetent patients with HZ who fulfill any of the following criteria (see table 1 below): (1) ≥ 50 years of age; (2) have moderate or severe pain; (3) have moderate or severe rash; or (4) have nontruncal involvement. In patients who have a low risk for complications of HZ—for example, those who are younger with mild acute pain and rash and truncal involvement—the potential benefits of treatment are unknown but may be meaningful because such patients can still develop postherpetic neuralgia (PHN).

Acyclovir, famciclovir, and valacyclovir are all exceptionally safe, which contributes to a favorable balance of potential benefit versus risk. It is, therefore, recommended that antiviral therapy be considered even for patients whose risk of developing PHN and other complications of HZ is likely to be low.

There are no systematic data addressing the effectiveness of antiviral therapy administered outside of the clinical trial setting. Nevertheless, in clinical practice, brivudin, famciclovir, and valacyclovir can be expected to have greater overall effectiveness than acyclovir, on the basis of their potentially superior efficacy, the greater patient compliance associated with their more convenient dosing, and their higher and more reliable levels of antiviral activity in blood, which is important because of the existence of barriers to the entry of antiviral agents from the bloodstream into tissues that are sites of HZ complications.

In patients presenting >72 h after rash onset, the potential benefits of initiating antiviral therapy are unknown but might be meaningful, given the minimal risks of treatment with acyclovir, famciclovir, and valacyclovir. The presence of new vesicles or complications of HZ may identify patients with continuing viral replication who could benefit from treatment. It is, therefore, recommended that the initiation of antiviral therapy be considered for patients presenting >72 h after rash onset with continued new vesicle formation or when there are cutaneous, motor, neurologic, or ocular complications. Advanced age and severe pain (which are potent risk factors for PHN) are additional factors that can prompt consideration of initiating antiviral therapy >72 h after rash onset.

In patients who still have new vesicles forming or who have cutaneous, motor, neurologic, or ocular complications after 7 days of antiviral therapy, close monitoring is recommended to assess the need for further evaluation. Because the potential benefits are unknown but may be meaningful, and given the minimal risks of treatment, it is also recommended that consideration be given to extending the duration of antiviral therapy for >7 days for these patients. In patients who have been given an incorrect diagnosis or who develop toxicity, antiviral therapy should be discontinued immediately.

When rash healing has not occurred in a normal fashion in an immunocompetent patient with HZ, further evaluation by an infectious diseases specialist is recommended. Infection with varicella zoster virus (VZV) resistant to acyclovir (mediated by absent or altered expression of thymidine kinase) has been reported in immunocompromised but not in immunocompetent patients.

Table 1. Oral Antiviral Medications for Herpes Zoster

Medication	Dosage	Duration of Treatment	Most Common Adverse Effects	Precautions and contraindications
Acyclovir	800 mg 5 times daily (every 4–5 h)	7–10	Nausea, headache	Dosage adjustment required for patients with renal insufficiency
Brivudin ¹	125 mg once daily	7	Nausea, headache	Contraindicated for patients treated with 5-fluorouracil or

Medication	Dosage	Duration of Treatment	Most Common Adverse Effects	Precautions and contraindications
				other 5-fluoropyrimidines, because of drug interaction associated with severe and potentially fatal bone marrow suppression
Famciclovir	500 mg 3 times daily (approved dosage in United States; in some other countries, 250 mg 3 times daily is approved)	7	Nausea, headache	Dosage adjustment required for patients with renal insufficiency
Valacyclovir	1000 mg 3 times daily	7	Nausea, headache	Dosage adjustment required for patients with renal insufficiency; thrombotic thrombocytopenic purpura/hemolytic uremic syndrome reported at dosages of 8000 mg daily in immunocompromised patients

¹Not available in the United States.

Recommendations for Supplementing Antiviral Therapy

Even if the risk of developing PHN is not reduced by combining antiviral therapy with analgesic or corticosteroid treatment in patients with HZ, effective relief of acute pain is a very desirable treatment goal. Pain should be assessed and treated promptly, and the choice of treatment approaches depends on the patient's pain severity and underlying conditions and on any prior response to specific medications. The principles of state-of-the-art pain management, such as the use of standardized pain measures, scheduled analgesia, and consistent and frequent follow-up to adjust dosing to the needs of the patient, should be applied to the management of pain in patients with HZ. It is important to recognize that HZ pain changes over time and can become more severe as the acute infection progresses.

Patients with mild to moderate pain may be managed with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), alone or in combination with a weak opioid analgesic (e.g., codeine) or tramadol. It is important to prescribe these medications to achieve a constant level of analgesia (e.g., every 6 hours) rather than to use as-needed dosing for increased levels of pain. These commonly used medications, however, have not been studied for the treatment of HZ. For pain that is moderate to severe in intensity, which is often accompanied by disturbed sleep, treatment with a strong opioid analgesic (e.g., oxycodone or morphine) is recommended on the basis of the consistent efficacy of this class of

medications in patients with inflammatory and neuropathic pain (see table 2 below). Various approaches may be used to treat HZ-associated pain with the numerous short- and long-acting opioid analgesics that are available. One approach is to begin treatment with a short-acting medication at an oxycodone equianalgesic dosage of 5 mg given 4 times daily as needed. Commonly used short-acting opioid analgesics include oxycodone alone or in combination with acetaminophen or aspirin. Once an effective dosage is determined, treatment can be switched from a short-acting to a long-acting medication, which is more convenient for patients and may also provide a more consistent level of pain relief; for exacerbations of pain, treatment with a short-acting opioid can be continued on an as-needed basis, in combination with the long-acting opioid. One of the most common adverse effects of opioid analgesics is constipation, which can be managed with preemptive laxative and stool-softener therapy. The risk that substance abuse will develop in patients who do not have a history of substance abuse is unknown, but is thought to be low in older individuals with HZ.

If moderate to severe pain in patients with HZ has not responded rapidly to treatment with an opioid analgesic, the prompt addition of one of the following 3 classes of oral medications in combination with the opioid analgesic should be considered, even though few studies have examined whether the risk of PHN is reduced by such treatment: (1) gabapentin or pregabalin; (2) tricyclic antidepressants (TCAs), especially nortriptyline; or (3) corticosteroids (e.g., prednisone), if there are no contraindications (see table 2 below). For those patients with moderate or severe pain who are unable to tolerate an opioid analgesic, treatment with these 3 classes of medications, alone and in combination, can be considered.

Gabapentin and pregabalin can both cause sedation, and tolerability may be improved with initial doses given only at bedtime and subsequent dosage increases administered 3 times daily for gabapentin and twice daily for pregabalin. The first 2 weeks after rash onset can be expected to be associated with the greatest benefit of treatment. Aggressive titration to rapidly reach the maximum dosages of 3600 mg of gabapentin daily and 600 mg of pregabalin daily must be balanced against the risk of greater adverse effects. Final dosages of gabapentin and pregabalin should be determined by relief of pain or the development of unacceptable adverse effects that do not resolve within 1 or 2 days.

Although most clinical trials of TCAs for the treatment of neuropathic pain have examined amitriptyline, it is not recommended for elderly patients, because of the risk of significant adverse events. In a randomized double-blind trial, nortriptyline was found to provide equivalent analgesic benefits for patients with PHN, when directly compared with amitriptyline, but was better tolerated. Nortriptyline is, therefore, preferable, although desipramine can be considered for patients with excessive sedation from nortriptyline. Nortriptyline treatment can be initiated at a dosage of 25 mg (or less for frail or elderly patients) at bedtime and then titrated by 25 mg daily every 2 to 3 days as tolerated, until relief of pain or a maximum dosage of 150 mg daily is reached. Patients must understand that TCAs have an analgesic effect that is independent of their antidepressant effect.

Corticosteroids can be considered as soon as possible after diagnosis for patients with at least moderately severe pain and no contraindications. In addition, corticosteroids should be considered for patients with VZV-induced facial paralysis

and cranial polyneuritis to improve motor outcomes, peripheral nerve damage from foraminal compression, or evidence of central nervous system (CNS) involvement, although the benefit of such treatment has not been systematically studied. Contraindications (e.g., hypertension, diabetes, gastritis, osteoporosis, and psychosis) and risks associated with the use of corticosteroids must be carefully evaluated. Treatment with corticosteroids should be initiated only in combination with antiviral therapy. There is no evidence base for the use of topical corticosteroids for treatment of patients with HZ, and such treatment is not recommended.

For patients with pain that is inadequately controlled by antiviral agents in combination with oral analgesic medications and/or corticosteroids, referral to a pain specialist or pain center is recommended to evaluate eligibility for neural blockade. Although long-term benefits of neural blockade in HZ have not been established, these procedures can reduce severe acute pain, and their risk-benefit ratio is therefore likely to be favorable. Patients with the most severe lesions and pain may benefit from hospitalization and administration of epidural analgesics.

Table 2. Corticosteroid and Analgesic Medications That Can Be Considered for Treatment of Patients with Herpes Zoster

Medication	Beginning Dosage	Titration	Maximum Dosage	Most Common Adverse Effects
Opioid analgesics (dosages given are for oxycodone) ¹ <i>or</i>	5 mg every 4 h as needed; dosage can be converted to long-acting opioid analgesic combined with short-acting medication continued as needed	Increase by 5 mg 4 times daily every 2 days as tolerated	No maximum dosage with careful titration; consider evaluation by a pain specialist at dosages >120 mg daily	Nausea/vomiting, constipation, sedation, dizziness
Tramadol ¹	50 mg once or twice daily	Increase by 50 to 100 mg daily in divided doses every 2 days as tolerated	400 mg daily (100 mg 4 times daily); for patients >75 years of age, 300 mg daily in divided doses	Nausea/vomiting, constipation, sedation, dizziness, seizures, postural hypotension
Gabapentin ² <i>or</i>	300 mg at bedtime or 100 to 300 mg 3 times daily	Increase by 100 to 300 mg 3 times daily every 2 days as tolerated	3600 mg daily (1200 mg 3 times daily); reduce if renal function is impaired	Sedation, dizziness, peripheral edema
Pregabalin ²	75 mg at bedtime or 75 mg twice daily	Increase by 75 mg twice daily every 3 days as tolerated	600 mg daily (300 mg twice daily); reduce if renal	Sedation, dizziness, peripheral edema

Medication	Beginning Dosage	Titration	Maximum Dosage	Most Common Adverse Effects
			function is impaired	
Tricyclic antidepressants, especially nortriptyline ²	25 mg at bedtime	Increase by 25 mg daily every 2 to 3 days as tolerated	150 mg daily	Sedation, dry mouth, blurred vision, weight gain, urinary retention ³
Oral corticosteroid (dosages given for prednisone) ⁴	60 mg daily for 7 days	After 60 mg daily for 7 days, decrease to 30 mg daily for 7 days, then decrease to 15 mg daily for 7 days, and then discontinue	60 mg daily	Gastrointestinal distress, nausea, changes in mood, edema

¹ Consider lower starting dosages and slower titration for frail and elderly patients (e.g., 5 mg twice daily for oxycodone); dosages given are for short-acting formulations.

² Consider lower starting dosages and slower titration for frail and elderly patients (e.g., 10 mg at bedtime for tricyclic antidepressants).

³ Consider a screening electrocardiogram for patients ≥ 40 years of age.

⁴ Should be initiated only in combination with antiviral therapy.

Treatment of Immunocompromised Patients

Patients with disorders of cell-mediated immunity (due to disease or medical interventions) are at increased risk for development of HZ. Those patients with the greatest degree of immunosuppression are at highest risk for VZV dissemination and visceral organ involvement. Populations at special risk include patients with lymphoproliferative malignancies, organ transplant recipients, patients receiving systemic corticosteroids, and patients with acquired immunodeficiency syndrome (AIDS).

HZ in the Setting of Malignancy or Organ Transplantation

Initial clinical trials with intravenous acyclovir for localized or disseminated HZ in immunocompromised patients demonstrated that treatment halts disease progression and reduces the duration of viral replication. Subsequent studies of bone marrow transplant recipients proved that acyclovir, in addition to promoting faster disease resolution, is highly effective at preventing VZV dissemination. Because most VZV-related fatalities result from disseminated infection, the ability to prevent dissemination has markedly reduced the rate of death due to HZ in transplant recipients.

Intravenous acyclovir remains the therapy of choice for VZV disease in severely immunocompromised patients, including (1) allogeneic hematopoietic stem cell transplant recipients within 4 months of transplantation, (2) hematopoietic stem cell transplant recipients with moderate to severe acute or chronic graft-versus-host disease, or (3) any transplant recipient receiving aggressive antirejection therapy. In addition, any transplant recipient with suspected visceral dissemination (e.g., encephalitis or pneumonitis) should receive intravenous acyclovir. The recommended dose is 10 mg/kg (or 500 mg/m²) every 8 h. When the infection is controlled, intravenous administration can be stopped, and oral antiviral medication can be initiated for the remainder of the course of therapy.

For immunocompromised patients, treating HZ with oral antiviral agents on an outpatient basis is an attractive approach, although data are limited. One small study randomized 27 allogeneic hematopoietic stem cell transplant recipients with HZ to receive either oral or intravenous acyclovir. No VZV dissemination occurred in either group, and no differences in healing or clinical outcome were apparent. Published data from clinical trials of famciclovir and valacyclovir for the treatment of HZ in immunocompromised patients remain limited, but a growing body of clinical experience suggests that these medications are safe and effective in this setting. For less severely immunosuppressed patients, oral therapy with acyclovir (800 mg 5 times daily), valacyclovir (1000 mg 3 times daily), or famciclovir (500 mg 3 times daily), coupled with close clinical observation, is a reasonable option. The higher plasma drug concentrations achievable with famciclovir and valacyclovir, along with their simplified dosing schedule, favor the use of these medications rather than oral acyclovir. Brivudin is not recommended for immunocompromised patients, even though it is effective, because of its potentially fatal interaction with 5-fluorouracil and other 5-fluoropyrimidines used in cancer chemotherapy. Because of the risk of ocular involvement, intravenous acyclovir and evaluation by an ophthalmologist is recommended for highly immunocompromised patients who present with HZ ophthalmicus.

HZ in Human Immunodeficiency Virus (HIV)-Seropositive Patients

Prospectively acquired data to guide clinicians when selecting antiviral therapy for HZ in HIV-seropositive patients are currently limited. Nearly 300 HIV-infected patients with HZ were enrolled in controlled studies comparing orally administered acyclovir (800 mg 5 times daily) with sorivudine (40 mg once daily). Times to cessation of new vesicle formation, total crusting, and resolution of HZ-associated pain were 3 to 4 days, 7 to 8 days, and ~60 days, respectively. Although sorivudine was never marketed, these studies clearly confirmed the efficacy and safety of oral antiviral therapy for HZ in patients with HIV infection. Famciclovir was judged to be effective and safe for treatment of HZ in patients with AIDS when evaluated in a small, open-label clinical trial. Valacyclovir has not been systematically evaluated as a treatment for HZ in HIV-infected patients, although preliminary data and anecdotal clinical experience suggest therapeutic benefit. Patients who have HZ ophthalmicus should always be treated to reduce the risk of serious ocular complications, even when presenting >72 h after rash onset. Because of the documented risk of relapsing infection, VZV disease in HIV-seropositive patients should be treated until all lesions have healed, which is often longer than the standard 7- to 10-day course. What impact VZV therapy may have on the risk of subsequent complications, such as CNS infection or retinitis, is unknown. Adjunctive therapy for HZ with corticosteroids has not been evaluated

in HIV-infected patients and is not currently recommended. Long-term administration of anti-VZV medications to prevent recurrences of HZ is not routinely recommended for HIV-infected patients.

Although rare, acyclovir-resistant VZV has been reported in immunocompromised patients, especially those with HIV infection, and results from mutations in the thymidine kinase gene. The presence of atypical lesions or a failed clinical response should prompt evaluation for drug susceptibility to determine whether resistance has developed. When acyclovir resistance occurs, treatment with alternative medications (e.g., intravenous foscarnet or cidofovir) is required.

Management of acute pain in HZ and PHN is similar in immunocompromised and immunocompetent patients, although NSAIDs that are not cyclooxygenase II-specific inhibitors are contraindicated in thrombocytopenic patients.

Treatment of Complicated Presentations of HZ

HZ Ophthalmicus and VZV Retinitis

HZ ophthalmicus is second only to thoracic HZ in frequency. Without antiviral therapy, 50% to 72% of patients with periocular HZ will have involvement of the ocular structures and develop chronic disease; in one recent study, 20% of patients with HZ uveitis were found to be legally blind in the involved eye.

The list of complications is protean: scarred lid malfunction or loss; paralytic ptosis; conjunctivitis; episcleritis; scleritis; infectious or neurotrophic keratitis; iridocyclitis; hemorrhagic retinitis; acute retinal necrosis; choroiditis; papillitis; retrobulbar neuritis; optic atrophy; Argyll Robertson pupil; partial or complete third, fourth, or sixth nerve palsy (always self-resolving); isolated pupillary paralysis; internuclear ophthalmoplegia; acute and chronic glaucoma; orbital apex syndrome; PHN; and sympathetic ophthalmia.

Therapy for HZ ophthalmicus is similar to that for HZ elsewhere in the body but should include the care of an ophthalmologist familiar with the disease. Treatment includes the following: (1) approved dosages of famciclovir or valacyclovir for 7 to 10 days, preferably started within 72 h of rash onset (with intravenous acyclovir given as needed for retinitis), to resolve acute disease and inhibit late inflammatory recurrences; (2) pain medications, as discussed above; (3) cool to tepid wet compresses (if tolerated); (4) antibiotic ophthalmic ointment administered twice daily (e.g., bacitracin-polymyxin), to protect the ocular surface; (5) topical steroids (e.g., 0.125%–1% prednisolone 2 to 6 times daily) prescribed and managed only by an ophthalmologist for corneal immune disease, episcleritis, scleritis, or iritis; (6) no topical antivirals, because they are ineffective; (7) mydriatic/cycloplegia as needed for iritis (e.g., 5% homatropine twice daily); and (8) ocular pressure-lowering drugs given as needed for glaucoma (e.g., latanoprost once daily and/or timolol maleate ophthalmic gel forming solution every morning). Systemic steroids are indicated in the presence of moderate to severe pain or rash, particularly if there is significant edema, which may cause orbital syndrome through pressure on the nerves entering the orbit. The dosage is commonly 20 mg of prednisone administered (together with an oral antiviral agent) orally 3 times daily for 4 days, twice daily for 6 days, and then once daily every morning for 4 days.

Therapy for chronic problems includes the following: (1) lubricating, preservative-free artificial tear gels or tears administered 4 times daily, antibiotic ointment administered once daily, and, possibly, lateral tarsorrhaphy to protect the corneas (which are often hypesthetic/anesthetic as a result of neuronal damage) from breakdown; (2) continuous-wear, therapeutic soft contact lenses and antibiotic drops (e.g., polymyxin-trimethoprim given 4 times daily as needed for corneal ulceration); (3) topical steroids and antibiotics for inflammatory disease (iritis, episcleritis, scleritis, and immune keratitis); (4) dilation for iritis; (5) glaucoma therapy as needed; and (6) surgical management as needed—for example, for amniotic membrane transplantation, tissue-adhesive seal ulcers, keratoprosthesis, and glaucoma trabeculectomy. Chronic pain management is generally similar to that for PHN in other dermatomes and includes gabapentin or pregabalin, TCAs, opioid analgesics, and lidocaine gel (which is preferable to the lidocaine patch for periophthalmic use). Local nerve blocks or sympathetic blocks can be used for pain that is refractory to first-line therapy, although there are no controlled studies of these treatments.

The optimal antiviral therapy for VZV-induced, rapidly progressive herpetic retinal necrosis in immunocompromised patients remains undefined. Responses to intravenous acyclovir or ganciclovir have been inconsistent and disappointing, with 49% to 67% of involved eyes progressing to no light perception. Several case reports have reported improved preservation of vision in patients treated with a combination of intravenous ganciclovir plus foscarnet, with or without intravitreal antivirals. Cidofovir has also been used successfully in a small number of patients. The optimal duration of induction therapy and options for long-term maintenance therapy have not been established.

Acute retinal necrosis in immunocompetent patients is a less virulent disease and responds better to antiviral therapy. For such patients, acyclovir is clearly beneficial for preserving useful vision. A suggested antiviral regimen for acute retinal necrosis in the otherwise healthy host is intravenous acyclovir (10 to 15 mg/kg every 8 h for 10 to 14 days) followed by oral valacyclovir (1 g 3 times daily for 4 to 6 weeks), although this treatment approach has not been studied in a controlled fashion.

Vulnerable and Frail Elderly Patients

The health status of older adults varies widely, from well elderly individuals who have no diseases or functional problems to chronically ill elderly individuals who have multiple comorbidities and disabilities. Vulnerable elderly individuals are people ≥ 65 years of age who are at increased risk for death or functional decline in a 2-year period, as defined by older age, poor self-rated health, and decreased functional status. Frail elderly individuals, a subset of vulnerable elderly individuals, are at the highest risk for death and functional decline and are characterized clinically by weakness, easy exhaustion, low levels of physical activity, slow walking speed, undernutrition/weight loss, and functional decline. Importantly, functional status is a more important predictor of death and functional decline than are specific clinical conditions. These individuals have markedly diminished physiologic reserves for responding to stressors, including such acute illnesses as HZ.

When HZ occurs in this population, it is important to modify pharmacotherapeutic approaches and augment non-pharmacotherapeutic approaches to management. Starting dosages of medications should be lower than those recommended for younger individuals, and the dosage should be titrated more slowly, particularly for opioid analgesics, gabapentin, pregabalin, TCAs, and NSAIDs. These individuals experience significant age- and disease-related declines in glomerular filtration rate, so the dosages of renally excreted medications (e.g., antiviral agents, gabapentin, and pregabalin) must be adjusted. Furthermore, these individuals are at high risk for adverse drug effects because of multiple comorbidities, age-related changes in pharmacokinetics and dynamics, use of multiple medications, and frequent inappropriate prescribing. The choice of medications should take into account the patient's diseases, medication regimen, and adverse event experiences. For example, NSAIDs should be avoided in elderly individuals with congestive heart failure and chronic kidney disease. For non-pharmacotherapeutic approaches, it is critically important for the practitioner to recognize that these treatments are just as important as the use of medications. Nonpharmacologic approaches include maintaining physical activity, enhancing nutrition, maintaining or increasing social contact, and providing assistance for problems with basic and instrumental activities of daily living during the acute episode. These interventions usually require a multidisciplinary approach that involves nursing, social work, physical therapy, occupational therapy, and the family.

The clinical course of vulnerable and frail elderly individuals needs to be monitored more closely than does that of well elderly individuals, to detect inadequate responses to therapy and early functional decline and to step up interventions, if needed. Pharmacotherapeutic and nonpharmacologic approaches require particular attention in individuals with dementia. HZ pain and acute inflammation may worsen cognition in these individuals with dementia, who then may require additional assistance in obtaining proper treatment and performing activities of daily living. The management of HZ pain is more complicated in patients with dementia, because of the risk for adverse cognitive effects of opioid analgesics, gabapentin, pregabalin, and TCAs.

In addition, traditional pain measures (e.g., the 0 to 10 numerical rating scale) used to track response to analgesics are not useful in assessing patients with advanced dementia. Finally, when frail elderly individuals are residents of nursing homes, prompt recognition and initiation of antiviral treatment of HZ can prevent the spread of VZV to susceptible individuals, such as younger nurses and aides in the facility.

Pregnant and Nursing Patients

Maternal varicella can be transmitted to the fetus and cause significant morbidity, but congenital varicella has never been documented in association with maternal HZ. There are no adequate studies of the effects that antiviral therapy during pregnancy has on the developing child, although rates of birth defects reported in registry data for acyclovir and valacyclovir are reassuring (similar data are not available for famciclovir and brivudin). Because the safety of antiviral therapy during pregnancy has not been firmly established, pregnant women with HZ should be treated only in cases in which the potential benefits of antiviral therapy to the mother outweigh the potential risks to the fetus. The majority of pregnant

women with HZ are expected to have a relatively low risk of developing PHN, because of their age. However, patients with severe rash, severe acute pain, or HZ ophthalmicus can be treated with acyclovir and valacyclovir, especially during the late stages of pregnancy, when any potential risks to the fetus should be lower. However, during the early stages of pregnancy, the potential benefit of antiviral therapy to the mother must be great enough to outweigh the unknown but potentially greater risk to the fetus. Antiviral therapy is not routinely recommended for eclamptic, preeclamptic, or diabetic pregnant women.

Because acyclovir is excreted in breast milk, antiviral therapy should be administered to nursing mothers with caution and only in circumstances in which the benefits are well established (e.g., within 72 h of rash onset). Severe acute pain in pregnant patients with HZ can be safely treated with opioid analgesics, but this must then be considered in the management of the neonate.

Neurologic Complications of HZ

The role of antiviral agents in the management of neurologic complications of HZ has not been evaluated in a controlled fashion. For those diseases in which viral replication likely plays an important role in pathogenesis (e.g., meningitis, encephalitis, and myelitis), therapy with intravenous acyclovir is recommended; this approach is supported by benefits noted in anecdotal experience. For such conditions as delayed contralateral hemiparesis, in which the role of active viral replication is less clear, the value of antiviral therapy is uncertain, but the potential benefits of antiviral therapy outweigh any potential risks.

Renal Failure

Dosages should be adjusted if renal insufficiency is present when acyclovir (creatinine clearance, <25 mL/min), famciclovir (creatinine clearance, <60 mL/min), or valacyclovir (creatinine clearance, <50 mL/min) is used. Because brivudin undergoes hepatic as well as renal excretion, dosage reduction for renal insufficiency is less critical, but hepatic function must be considered when this antiviral agent is used. Dosages of gabapentin and pregabalin should be reduced when renal function is impaired.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Recommendations for first-line pharmacologic treatments are based on positive results from multiple randomized clinical trials. The methods and results of these trials, in combination with the clinical experience of the authors, provide the basis for specific recommendations regarding these treatments.

Recommendations for additional treatments that should be considered in combination with first-line treatment are based on the results of single clinical

trials, inconsistent results of multiple trials, or uncontrolled trials, considered together with the clinical experience of the authors.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of herpes zoster (HZ)

POTENTIAL HARMS

Adverse Effects of Medications

- *Antiviral drugs* are associated with nausea and headache. Dosage adjustment is required in patients with renal insufficiency. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome was reported at dosages of 8000 mg daily of *valacyclovir* in immunocompromised patients. Antiviral therapy should be administered to nursing mothers with caution and only in circumstances in which the benefits are well established (e.g., within 72 h of rash onset).
- Common side effects of *opioid analgesics* including *oxycodone* and *tramadol* are nausea/vomiting, constipation, sedation, dizziness, seizures (*tramadol*), and postural hypotension (*tramadol*).
- *Gabapentin* and *pregabalin* are associated with sedation, dizziness and peripheral edema. Dosage reduction is required if renal function is impaired.
- *Tricyclic antidepressants (nortriptyline)* are associated with sedation, dry mouth, blurred vision, weight gain, urinary retention.
- Side effects of *oral corticosteroids* are gastrointestinal distress, nausea, change in mood, edema, and granulocytosis.

CONTRAINDICATIONS

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- *Brivudin* is contraindicated in patients treated with 5-fluorouracil or other 5-fluoropyrimidines because of drug interaction associated with severe and potentially fatal bone marrow suppression.
- *Corticosteroids* are contraindicated in patients with hypertension, diabetes, gastritis, osteoporosis, and psychosis.
- *Nonsteroidal antiinflammatory drugs (NSAIDs)* that are not cyclooxygenase II-specific inhibitors are contraindicated in thrombocytopenic patients. NSAIDs should also be avoided in elderly patients with congestive heart failure and chronic kidney disease.

QUALIFYING STATEMENTS

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It was not possible to formally consider the cost-effectiveness of treatment, because of limited data and differences related to geographic region and third-party coverage. Clinicians should familiarize themselves with medication

acquisition costs and the reimbursements provided by their patients' insurance plans, to protect their patients' finances and encourage treatment compliance.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, Betts RF, Gershon AA, Haanpaa ML, McKendrick MW, Nurmikko TJ, Oaklander AL, Oxman MN, Pavan-Langston D, Petersen KL, Rowbotham MC, Schmader KE, Stacey BR, Tying SK, van Wijck AJ, Wallace MS, Wassilew SW, Whitley RJ. Recommendations for the management of herpes zoster. Clin Infect Dis 2007 Jan 1;44 Suppl 1:S1-26. [243 references] [PubMed](#)

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

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Neuropathic Pain Institute - Medical Specialty Society
VZV Research Foundation - Professional Association

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GUIDELINE COMMITTEE

Neuropathic Pain Special Interest Group

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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J.B. has served on advisory boards for GlaxoSmithKline, Merck, and Sanofi Pasteur

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R.J.W. is on the Scientific Advisory Board for Gilead and the speakers bureaus for GlaxoSmithKline and Novartis

All other authors: no conflicts.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) to subscribers of the [Clinical Infectious Diseases Journal](#).

Also available to subscribers of the Clinical Infectious Diseases Journal as a [PostScript file](#).

Print copies: Available from Dr. Robert H. Dworkin, Dept. of Anesthesiology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Ave., Box 604, Rochester, NY 14642; Email: robert_dworkin@urmc.rochester.edu.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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