Varicella zoster virus

Recent advances in management

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ABSTRACT

OBJECTIVE To provide an update on strategies for managing varicella zoster virus (VZV) and for preventing and treating established postherpetic neuralgia (PHN).

QUALITY OF EVIDENCE Treatment guidelines are based on randomized clinical trials. Recommendations concerning other aspects of VZV management (eg, vaccination) are based mainly on expert opinion.

MAIN MESSAGE Varicella and herpes zoster caused by VZV can give rise to serious morbidity and mortality and should be treated. For preventing chickenpox, safe and effective immunization is widely recommended. Treating varicella-exposed seronegative pregnant women requires special attention because the virus can harm expectant mothers, fetuses, and newborns. The antiviral drugs, acyclovir, valacyclovir, and famciclovir, have been approved for treating herpes zoster and have a role in reducing the duration of PHN. Established PHN can be managed with analgesics, tricyclic antidepressants, and other agents.

CONCLUSION Vaccination and antiviral and other systemic agents can substantially reduce the morbidity associated with VZV infection.

RÉSUMÉ

OBJECTIF Présenter une mise à jour sur les stratégies de prise en charge du virus varicelle-zona (VZV) ainsi que de prévention et de traitement de l'algie post-zona (APZ).

QUALITÉ DES DONNÉES Les directives sur le traitement se fondent sur des essais cliniques aléatoires. Les recommandations concernant d'autres éléments de la prise en charge du VZV (la vaccination, par exemple) s'appuient surtout sur l'opinion d'experts.

PRINCIPAL MESSAGE La varicelle et le zona causés par le VZV peuvent se traduire par une morbidité et une mortalité graves, et un traitement s'impose. Pour prévenir la varicelle, on recommande largement une vaccination sûre et efficace. Le traitement des femmes enceintes séronégatives exposées à la varicelle exige une attention particulière, parce que le virus peut être nuisible à la mère, au fœtus et au nouveau-né. Les médicaments antiviraux comme l'acyclovir, le valacyclovir et le famciclovir ont été approuvés pour le traitement du zona et contribuent à réduire la durée de l'APZ. Une APZ établie peut être prise en charge avec des analgésiques, des antidépresseurs tricycliques et d'autres agents.

CONCLUSION La vaccination ainsi que les agents antiviraux et autres médicaments systémiques peuvent réduire considérablement la morbidité associée à une infection au VZV.

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Varicella zoster virus (VZV), which belongs to the subfamily Alphaherpesvirinae[1] (along with herpes simplex virus types 1 and 2) and is a double-stranded DNA virus (**Table 1**), causes chickenpox in childhood and lies latent in dorsal root ganglia after the primary infection. Chickenpox, commonly a mild and self-limited illness, can progress to bacterial superinfection,[2] central nervous system involvement,[2] varicella pneumonia,[3] and death, especially in immunocompromised patients.[4]

Varicella is a potentially serious pathogen for pregnant women, fetuses, and newborns. After a primary infection, it sometimes re-emerges later in life as herpes zoster (shingles), taking advantage of the decline in immune function that occurs with age. Herpes zoster can lead to chronic postherpetic neuralgia (PHN)[5] and ocular[6] and central nervous system[2] complications. Its associated morbidity and mortality justify therapeutic intervention.

Three antiviral agents, acyclovir, famciclovir (FCV), and valacyclovir (VACV), are used to treat VZV-related infections and their long-term sequelae. All three drugs are nucleoside analogs that are incorporated into and terminate viral DNA synthesis following phosphorylation by virus-produced thymidine kinase. The two prodrugs, FCV and VACV, have been shown to have substantially greater bioavailability than acyclovir.[7-9] They are effective in accelerating healing of the herpes zoster rash and in reducing patients' period of infectivity. They also lessen the chronic pain associated with herpes zoster, but appear to differ in their efficacy.

Quality of evidence

A large body of literature describes management of varicella infection, zoster, and PHN. MEDLINE was searched using the terms varicella, zoster, varicella zoster, varicella vaccine, Oka, acyclovir, famciclovir, valacyclovir, and postherpetic neuralgia. Evidence supporting treatment options is based mostly on randomized placebo-controlled studies.

Treatment of acute varicella

Although oral acyclovir administered to immunocompetent children with VZV infection reduces the number of cutaneous lesions and accelerates resolution of lesions and fever,[10] there is no evidence that the drug decreases the incidence of serious complications. Using acyclovir for normal children has not received widespread acceptance due to the high cost of treatment, difficulty in starting therapy rapidly enough (needs to be given within 24 hours of appearance of rash), and concern over development of acyclovir-resistant strains of VZV. Dosage for oral acyclovir is 20 mg/kg every 6 hours for 5 days (to a maximum of 800 mg/d) for those between 3 months and 12 years and 800 mg/dose five times daily for 7 to 10 days for older people. Intravenous acyclovir decreases incidence of the visceral dissemination seen in 30% of immunocompromised patients.[11,12] The recommended intravenous dosage is 10 mg/kg every 8 hours for 5 to 10 days; duration depends on clinical progress.[13]

In December 1998, a live attenuated Oka strain varicella vaccine (Varivax®, Merck Frosst Canada Inc) was licensed for use in Canada. The National Advisory Committee on Immunization (NACI) recommended the vaccine for primary immunization of healthy, susceptible people 1 year and older.[14] This was endorsed by a National Varicella Consensus Conference with the proviso that 90% immunization of the general population could be ensured.[15] So far, only Prince Edward Island has started universal vaccination.[16]

The American Academy of Pediatrics recommends initial varicella immunization at 12 to 18 months old and that all susceptible children receive the vaccine before their 13th birthday. Immunization is also approved for susceptible adolescents and adults. Children 12 to 15 months old have seroconversion rates of up to 98% after a single dose. Those 13 years old and older require two doses a minimum of 4 to 8 weeks apart. The vaccine has been shown to prevent disease in 81% of exposed children in household settings.[17]

Recently, a randomized, double-blind controlled trial demonstrated that live attenuated VZV vaccine could significantly increase VZV cell-mediated immunity in healthy elderly people.[18] Results of this trial might indicate whether actively immunizing older people can prevent herpes zoster.[19]

Published data consistently show the varicella vaccine to have an excellent safety profile[20] and few side effects (rash, fever, painful reactions at the injection site).[21,22] Oka strain herpes zoster can develop in immunocompetent vaccine recipients, and rare cases of secondary transmission of vaccine virus have been reported.[23] Although some more serious side effects have been reported, they have not been conclusively linked to the vaccine itself. Monitoring is ongoing.[23]

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Table 1. Human herpesvirus family

ABBREVIATION	VIRUS NAME	DISEASE
HSV 1	Herpes simplex virus type 1	Herpes labialis
HSV 2	Herpes simplex virus type 2	Herpes genitalis
VZV	Varicella-zoster virus	Varicella/zoster
EBV	Epstein-Barr virus	Mononucleosis
CMV	Human cytomegalovirus	CMV retinitis
HHV6	Human herpesvirus 6	Erythema subitum
HHV7	Human herpesvirus 7	Erythema subitum
HHV8	Human herpesvirus 8	Kaposi sarcoma

Varicella during pregnancy

Seronegative women who have been exposed for more than 1 hour to varicella virus should be given prophylactic varicella zoster immune globulin (VZIG) within 96 hours of exposure to prevent maternal varicella, which is associated with high risk of varicella pneumonia.[24] Pregnant women with varicella should be monitored closely for 24 to 48 hours after onset of rash to assess whether infection is progressing. A decision to treat with antiviral therapy should be made within 72 to 96 hours. Untreated, the mortality rate for varicella pneumonia could be higher than 40%. Thus, varicella pneumonia in pregnant women is an indication for hospitalization, immediate initiation of intravenous acyclovir (10 to 15 mg/kg every 8 hours for 7 days), and supportive care.[25]

Infection of a fetus after maternal varicella in the first or early second trimester of pregnancy occasionally results in varicella embryopathy, such as limb atrophy, scarring of the skin, and central nervous system and eye manifestations. We do not know whether a fetus is protected by administration of VZIG or acyclovir to its mother.[26]

Neonates born to mothers who develop varicella between 5 days before and 2 days after delivery have high rates of morbidity and mortality. Although transplacental viral transmission is the usual route of infection, contact with maternal lesions during or after delivery could also lead to neonatal infection. Infants born within the risk period should receive VZIG prophylaxis at delivery or at onset of maternal infection if it occurs within 2 days of delivery. Some experts suggest treating infants who develop varicella with acyclovir.[25]

Treatment of herpes zoster

Treatment of herpes zoster has three main objectives: treatment of the acute viral infection, treatment of the acute pain associated with herpes zoster, and prevention of PHN. Antiviral agents and oral corticosteroids are the mainstay of therapy, along with other individualized pain-management modalities as needed.

Studies have shown that acyclovir,[27] FCV,[28,29] and VACV[30] can effectively treat zoster rash. At 800 mg five times daily for 7 days, acyclovir accelerates healing and reduces associated pain.[31-36] Several studies have shown, however, that acyclovir does not help reduce PHN.[37-39] Adverse effects seen with acyclovir include headache, nausea, diarrhea, and renal toxicity. On rare occasions, central nervous system toxicity occurs with symptoms of disorientation, delirium, seizures, tremor, or slurred speech.[40]

Valacyclovir, the prodrug of acyclovir, has increased oral bioavailability (65%).[41,42] One randomized controlled trial showed it to be as effective as acyclovir in decreasing the appearance of new lesions and the time to crusting and 50% healing of zoster.[30] In addition, VACV was found to be more effective than acyclovir in resolving PHN,[43] although the statistical analyses in that study have been questioned.[44] Valacyclovir has a similar safety profile to acyclovir, with some reports of nausea, vomiting, diarrhea, abdominal pain, and headache.[45] No nephropathy or neurotoxicity has been seen.[45] Dosage must be modified when patients have renal insufficiency (**Table 2**).

The active metabolite of FCV is penciclovir, another guanosine analogue. It has more bioavailability than acyclovir (77%).[46] A randomized study comparing FCV with acyclovir found them similarly effective for cutaneous healing (when treatment was initiated within 72 hours of onset of zoster rash) as demonstrated by time to full crusting, cessation of new lesion formation, loss of vesicles, and loss of crusts. In addition, FCV was found to decrease duration of PHN among

Table 2. **Dose adjustments for renal-impaired patients with herpes zoster:** *Dose modification is suggested for patients with creatinine clearance < 50 mL/min and required for those with creatinine clearance < 30 mL/min.*

DRUG	CREATININE CLEARANCE >60 ML/MIN	CREATININE CLEARANCE 20-59 ML/MIN	CREATININE CLEARANCE <20 ML/MIN
Acyclovir	None	800 mg every 8 h	800 mg every 12 h
Valacyclovir	None	1 g every 12 h	1 g every 24 h
Famciclovir	None	500 mg every 12-48 h	250 mg every 48 h

Table 3. **Regimens commonly prescribed for herpes zoster patients**

DRUG	DOSE	AVERAGE COST OF 7-DAY TREATMENT*
Acyclovir	800 mg five times a day for 7 days	$80-$100
	10 mg/kg IV every 8 h for 7-10 days†	$294‡
Valacyclovir	1000 mg three times a day for 7 days	$133
Famciclovir	500 mg three times a day for 7 days	$135

**Based on community pharmacy prices (not including dispensing fee).*

†Acyclovir can be administered intravenously to severely immunocompromised patients or patients unable to take medications orally.

‡Cost is based on a 70-kg man.

elderly patients when compared with placebo.[29] Like VACV, it offers the more convenient dosing of three times daily. Studies comparing FCV with VACV for treatment of herpes zoster are in progress.[47]

Choosing which antiviral to use is a case-specific decision based on dosing and cost. Recommended doses for acyclovir, FVC, and VACV are shown in **Table 3**. Acyclovir and VACV should be instituted within 72 hours, and FCV within 48 hours, of rash onset.

Because patients frequently present more than 72 hours after rash onset, physicians are often uncertain whether to initiate therapy after this time. The answer is unclear, but it seems reasonable to institute therapy after 72 hours if new vesicles are forming; if vesicles are not completely crusted; or if patients are older than 50 years and have severe pain, compromised immunity, or trigeminal zoster.[47]

Orally administered corticosteroids, either alone or in combination with antiviral agents, are frequently used to treat herpes zoster in an attempt to decrease neural inflammation. Although results of some studies have shown reductions in persistent pain[48] or accelerated healing[49] in patients treated with oral corticosteroids, a recent randomized study has demonstrated no long-term benefit and no effect on PHN[50] when corticosteroids were added to acyclovir.[51] Another large placebo-controlled study found no difference in pain at 6 months when acyclovir combined with prednisone was used compared with acyclovir alone, prednisone alone, or double placebo.[52] Given the theoretical risk of immunosuppression with corticosteroids, some investigators believe that they should be used only for patients older than 50 because these people are at greatest risk of developing PHN.[52]

When herpes zoster affects the eyes, it should be treated just as it is treated in other anatomic regions. Complications, including loss of vision, can occur, and ophthalmologic consultation is always advised.

Treatment of established PHN

Despite optimal therapy during the acute phase of herpes zoster, some patients still go on to develop PHN. A range of therapies including topical, systemic, and nonpharmacologic modalities have been used in an attempt to reduce this chronic pain.

Topical capsaicin in high concentrations (Zostrix) depletes substance P, a principal neurotransmitter peptide, causing a burning sensation and then anesthesia. One third of patients find the burning intolerable.[5] Topical lidocaine and prilocaine cream provides temporary anesthesia. Acetylsalicylic acid and other mild analgesic drugs are commonly used by patients with PHN, but they have little effect. Neuropathic pain is generally less responsive to narcotic drugs than nonneuropathic pain is.

Tricyclic antidepressant drugs (TCAs) are important components of PHN therapy. By blocking reuptake of norepinephrine and serotonin, TCAs relieve pain by increasing inhibition of the spinal neurons involved in pain perception. In five clinical trials, four of which evaluated amitriptyline, 47% to 67% of patients reported moderate-to-excellent pain relief.[5] Amitriptyline should be started at a low dose (12.5 to 25 mg) at bedtime and can be increased weekly until pain subsides or side effects become unacceptable (confusion, urinary retention, postural hypotension, and arrhythmias).

Anticonvulsant drugs can reduce the lancinating component of neuropathic pain. Gabapentin has also been used for treatment of PHN. Anesthetic drugs, such as lidocaine, procaine, and mepivacaine, are often injected locally and offer a transient benefit.[52] Transcutaneous electrical nerve stimulation can offer some relief of PHN in recalcitrant cases.[5] Neurosurgical procedures, such as sympathetic blockade, should be reserved as treatments of last resort for intractable pain.

Conclusion

For primary prevention in healthy and susceptible people, safe and effective immunization awaits universal implementation. Exposure of seronegative pregnant women and newborns to varicella requires immediate intervention with VZIG upon exposure and then acyclovir. Management of herpes zoster and PHN includes early institution of antiviral and pain medications to reduce duration of pain and associated morbidity.

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Editor's key points

- Varicella zoster virus causes so much morbidity and mortality in chickenpox and shingles that prevention and treatment are warranted.
- Chickenpox can be prevented by safe and effective immunization. Immunocompromised patients should be treated with acyclovir.
- Seronegative pregnant women and newborns exposed to VZV should be treated immediately with varicella immune globulin and acyclovir.
- Herpes zoster responds to early administration of antivirals. Duration of postherpetic neuralgia can be reduced by administering valacyclovir or famciclovir within 72 hours of onset.

Points de repère du rédacteur

- Le virus varicelle-zona est à l'origine d'une morbidité et d'une mortalité si considérables dans la varicelle et le zona que la prévention et le traitement s'imposent.
- On peut prévenir la varicelle par une immunisation sûre et efficace. Les patients immunodéprimés devraient être traités avec de l'acyclovir.
- Les femmes enceintes séronégatives et les nouveau-nés exposés au VZV devraient être traités immédiatement avec de la gammaglobuline avec anticorps contre la varicelle et de l'acyclovir.
- Le zona réagit à une administration sans délai d'agents antiviraux. La durée de l'algie post-zona peut être réduite grâce à l'administration de valacyclovir ou de famciclovir dans les 72 heures suivant l'apparition.

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