Herpes simplex virus (HSV) and varicella-zoster virus (VZV) are related viruses that both cause blistering rashes and are characterised by the ability to establish latent infection. Primary infections typically involve the skin or mucous membranes, causing a characteristic vesicular rash. Following the resolution of active virus infection the virus establishes a clinically silent infection primarily in neurones within the trigeminal and dorsal root ganglia.

This latent infection is life-long and may subsequently give rise to reactivated infection in which new infectious virus is produced in the ganglion and travels via the axon to the original site of infection or another site within the same dermatome. This in turn may give rise to a lesion, although asymptomatic shedding of reactivated HSV, particularly at mucosal sites, is common. Reactivation of viral replication may be triggered by physical or psychological stress events such as sunlight, illness or anxiety.

The immune system controls and eliminates viral replication in both primary and reactivated infections, and those with poor immune function are susceptible to more extensive viral replication, more frequent reactivations and more severe accompanying symptoms.

This article reviews the clinical features of HSV and VZV infection that are likely to be encountered in primary care, excluding genital herpes. Presenting features and complications are discussed, along with recommendations on when to use diagnostic tests, when to treat and when to refer for hospital assessment or specialist services. Advice on managing contacts is also given where appropriate.

**Herpes simplex virus infection**

Primary HSV infection is acquired by contact with infectious secretions, and lesions occur at the site of initial infection after an incubation period of 2–12 days. In the UK HSV type 1 more commonly infects the oral mucosa, while HSV type 2
is more likely to be the cause of genital infection, although exceptions to this anatomical distinction are increasingly observed.

Rarer manifestations at other sites include meningitis, encephalitis, Bell’s palsy, hepatitis and, in the immunocompromised, pneumonitis and oesophagitis.

**Gingivostomatitis**

Primary HSV infection in children usually involves the oral mucosa, with painful vesicles and ulcers present on the gums, lips, tongue, buccal mucosa and soft and hard palates. Fever and lymphadenopathy may also be present.

The differential diagnosis includes herpangina, aphthous ulcers, erythema multiforme major and Stevens-Johnson syndrome.

**Pharyngitis**

In older individuals primary HSV infection more commonly presents with upper respiratory symptoms. On examination pharyngeal erythema or exudate is often present.

Pharyngitis due to HSV infection is difficult to differentiate from that due to other infections, including infectious mononucleosis, group A streptococcal infection, *Mycoplasma pneumoniae* or influenza and other respiratory viruses.

**Herpes labialis**

Recurrent HSV infection most commonly presents as cold sores (see Figure 1). A prodromal phase characterised by a tingling sensation precedes the appearance of vesicles by several hours up to a few days.

Vesicles occur on the lip, the margin of the lip or sometimes on other areas of the skin. They are itchy and painful, and after a day or so coalesce to form a weeping ulcer, which then crusts and heals.

Recurrences may occur sporadically, or at regular intervals, typically two to three times a year, although a few patients suffer recurrence at a higher frequency.

**Ocular HSV infection**

HSV is one of many infectious causes of keratitis. Ocular infection may occur in primary HSV infection, probably due to autoinoculation, and typically involves the eyelid and conjunctiva (blepharoconjunctivitis). Recurrent infection may present as a superficial dendritic ulcer (epithelial conjunctivitis). Symptoms include foreign body sensation, photophobia, blurred vision and a red eye.

Stromal keratitis involves deeper layers of the cornea and may lead to scarring of the cornea that results in visual impairment. Acute retinal necrosis may occur in the elderly or immunocompromised patient.

**Herpetic whitlow**

HSV infection of the finger (see Figure 2) may result from autoinoculation, for example thumb sucking in children, although dentists and other healthcare workers may acquire this infection from direct contact with infected patients. The infected finger appears swollen, red and tender, with small vesicles during the early stage.

**Eczema herpeticum**

In individuals with atopic eczema HSV infection may spread over large areas of skin, particularly on the face and neck. Fever and lymphadenopathy may be present. Affected areas of skin are painful and contain fluid-filled blisters that break down and then crust over.

A similar condition may be seen more rarely in eczema patients with other vesicular rashes, including varicella, zoster or enterovirus infections. The rash may also be confused with impetigo.

**Neonatal HSV infection**

Babies born to women who have active HSV infection at the time of delivery may become infected and this may be

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**Figure 1.** Topical antiviral treatment may be adequate for mild HSV infections such as cold sores

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**Figure 2.** HSV infection of the finger, or whitlow, is often seen in healthcare workers who come into contact with infected patients; the lesions usually heal in two to three weeks.
The breakdown in the integrity of the skin may allow skin flora such as *Staphylococcus aureus* to enter the bloodstream, resulting in secondary bacterial infection. Other complications include varicella pneumonia, particularly in smokers, pregnant women and immunocompromised patients, and meningitis or rarely encephalitis. Ataxia may occur as a postinfectious complication 7–10 days after chickenpox onset.

Chickenpox during the first trimester of pregnancy carries a small risk of congenital varicella syndrome, resulting from congenital infection and subsequent *in-utero* reactivation of the virus infection. At birth the infected infant may present with microcephaly and brain damage, chorioretinitis, limb hypoplasia and skin lesions. Mortality is high.

When maternal chickenpox occurs during the last few weeks of pregnancy or the week after delivery, neonatal varicella may be present at birth or may develop in the first two weeks of life. Neonatal varicella carries a risk of pneumonia and other complications and is life-threatening, particularly when maternal varicella occurs during the week before or the week after delivery, due to the lack of transplacentally acquired maternal antibody.

**Zoster**

Following chickenpox, viral reactivation leads to zoster, which may occur at any age but is more common with increasing age due to the decline of cellular immune functions that serve to contain virus replication and prevent dissemination.

**Varicella-zoster virus infection**

VZV causes two major diseases: varicella (chickenpox) is associated with primary infection, whereas zoster (shingles) is the clinical manifestation of reactivated VZV infection.

**Varicella**

Varicella is an itchy rash that frequently covers the entire body (see Figure 3). The incubation period is 10–21 days, and the rash is often preceded by fever and nonspecific influenza-like symptoms. The spots are initially red, usually begin on the face and scalp and continue to appear in waves, spreading over the trunk and limbs. The spots become fluid-filled vesicles, then pustules, and finally crust over and heal. The illness is more severe in adolescents and adults than in children.

**Figure 3.** In chickenpox oral aciclovir should be started within 24 hours of the rash appearing.

**Figure 4.** Oral aciclovir started within 72 hours of the rash appearing in shingles reduces the risk of postherpetic neuralgia.
to eliminate viral reactivation before it becomes clinically apparent.

The zoster rash is vesicular and is usually limited to the dermatome served by the spinal nerve in which the virus has reactivated (see Figure 4), although lesions may cross the dermatome border and satellite lesions may appear in other dermatomes. Multidematomal or disseminated (varicelliform) zoster suggests underlying immunodeficiency, as does recurrent zoster, which unlike recurrent HSV infection is rare.

The rash is often itchy or painful; indeed, pain and tingling may precede the rash and persist after its resolution. Pain without a vesicular rash is also described (zoster sine herpete).

Zoster involving the ophthalmic division of the trigeminal nerve gives rise to ophthalmic zoster. Symptoms include periorbital lesions, blepharitis, conjunctivitis and keratitis. The latter occurs in about two-thirds of cases and may lead to significant loss of vision.

Postherpetic neuralgia Persistence of zoster-associated pain for more than 30 days after resolution of zoster rash is classified as postherpetic neuralgia. The pain is localised to the region of the original lesion, may be burning or stabbing, and can be debilitating.

Diagnosis

The clinical presentations of HSV, varicella and zoster are often highly characteristic and laboratory confirmation is not required. However, laboratory testing is useful where there may be diagnostic uncertainty in early stages of the rash, in atypical rashes, rashes in unusual anatomic sites and in suspected recurrent zoster.

Serological testing is used primarily to determine the immune status of an individual who may require prophylaxis; it is not usually helpful for acute-phase diagnosis because symptoms occur prior to the development of detectable antibody.

HSV and VZV infection is more readily diagnosed by polymerase chain reaction (PCR), which can detect viral DNA in a vesicle fluid sample (collected on a dry viral swab), a lesion swab or eye swab placed in viral transport medium, or (in the case of VZV infections) a blood sample.

Check with local pathology providers for the availability of this service and the preferred sample types.

Treatment and prophylaxis

Both HSV and VZV are susceptible to aciclovir, ganciclovir (Virgan) and penciclovir (Vectavir). Aciclovir is available as a topical cream or eye ointment for HSV infections, tablets or suspension for oral therapy, and an intravenous infusion for severe infections or infections in immunocompromised patients.

A penciclovir cream is available for nonmucosal lesions and a ganciclovir ophthalmic gel for HSV keratitis.

Inosine pranobex has also been used for mucocutaneous HSV infection, but studies indicate that aciclovir is superior.

Topical therapy may be adequate in mild HSV infections, although oral or combined topical/oral therapy may be preferable.
Aciclovir prophylaxis may be considered in patients with frequent HSV recurrence and patients reporting VZV exposure who are not eligible for immunoglobulin prophylaxis (see below). Analgesia and emollients are useful for relieving the pain and itch of the rash.

Valaciclovir and famciclovir are oral prodrugs of aciclovir and penciclovir respectively that have improved bioavailability. Often used in immunocompromised patients, they may also be beneficial in patients with recurrent HSV infection that is poorly controlled by oral aciclovir.

In chickenpox oral aciclovir started within 24 hours of rash onset may reduce the duration and severity of symptoms. Oral aciclovir therapy for shingles reduces the risk of subsequent postherpetic neuralgia if started with 72 hours of rash onset.

Figure 5. Decision pathway for use of varicella zoster immune globulin; *neonates are at risk if the mother is nonimmune or the infant is premature or low birth weight. It is usually preferable to test a maternal blood sample. If the mother has varicella the infant should receive VZIG without delay; serological testing is not required.
### Table 1. Patients with HSV or VZV infection requiring referral

<table>
<thead>
<tr>
<th>HSV</th>
<th>Varicella</th>
<th>Zoster</th>
</tr>
</thead>
<tbody>
<tr>
<td>neonate (&lt;1 month) immunocompromised ophthalmic zoster</td>
<td>neonate (&lt;1 month) pregnant immunocompromised complications (eg symptoms of chest infection, menigitis, encephalitis, hepatitis)</td>
<td>ophthalmic zoster multidermatomal zoster or varicelliform rash complications (eg symptoms of chest infection, menigitis, encephalitis)</td>
</tr>
<tr>
<td>immunocompromised eczema herpeticum HSV keratitis frequent HSV</td>
<td>dense or haemorrhagic rash</td>
<td>immunocompromised postherpetic neuralgia</td>
</tr>
<tr>
<td>recurrence complications (eg symptoms of chest infection, menigitis, encephalitis, hepatitis)</td>
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</tr>
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</table>

and should be given to patients with zoster who are over 50 years of age or immunocompromised, or have ophthalmic zoster, moderate to severe pain or moderate to severe rash. Once postherpetic neuralgia is established antiviral therapy is not useful.

Pregnant women, immunocompromised patients and neonates who become exposed to patients with varicella or zoster are eligible for prophylaxis with varicella-zoster immune globulin if they have not previously had varicella and if immunoglobulin can be administered within 10 days of exposure.

Those without a history of varicella should be tested for serological evidence of immunity if time permits, since 80 per cent of adults with no history are in fact immune. Immunocompromised patients should be tested irrespective of history.

In the case of neonates the mother should be tested for immunity, unless the mother is the index case. (Maternal zoster is not a risk for severe neonatal infection.) However, infants born prematurely or with low birth weight may not have maternal antibody.

Immunoglobulin prophylaxis may prevent infection or result in attenuated or asymptomatic infection.

The procedure for managing contacts is summarised in Figure 5.

### When to refer

Patients with suspected severe or life-threatening HSV or VZV infection should be referred urgently for hospital assessment for possible intravenous therapy. Hospital assessment should also be considered in those who are at risk of complications, such as women in the second half of pregnancy and immunocompromised patients.

Specialist referral or advice is appropriate for patients with keratitis, first-episode HSV conjunctivitis, ophthalmic zoster, postherpetic neuralgia, eczema herpeticum or frequent HSV recurrence that is poorly controlled with oral aciclovir (see Table 1).

### Conclusion

HSV and VZV infections are common and are occasionally associated with significant morbidity and even mortality. Prophylactic and therapeutic options have reduced the frequency of severe infections, but this is dependent on timely recognition of early symptoms and identification of high-risk patients.

The importance of clinical vigilance and the contribution of primary care physicians in this area should not be underestimated.

### Further reading


### Declaration of interests

None to declare.

Dr Muir is consultant clinical scientist, Public Health England, Public Health Laboratory Bristol

### Resources

**Prescriber articles**

- Recommended management of common STIs in general practice. *Prescriber* 19 September 2011;22(18):35–44.

**Guidelines**

Prescription review

In 2012/13, GPs in England wrote 737,000 prescriptions for oral antivirals to treat herpes simplex and varicella-zoster infection at a total cost of almost £10 million. This continues the increase in volume (up 35 per cent) but decreasing cost (down 23 per cent) evident since 2008. There were also about 300,000 prescriptions for antiviral preparations for the eye and skin at a cost of £1.2 million.

Aciclovir, the least expensive oral agent, accounts for 95 per cent of prescribing but only 57 per cent of spending, with relatively low volumes of famciclovir (<2 per cent) and valaciclovir (<3 per cent) taking a disproportionate share of the cost (28 and 15 per cent respectively).

Over the past five years, prescribing of famciclovir has declined and use of aciclovir has increased, with little change in valaciclovir. Prescribing of inosine pranobex, designated as less suitable for prescribing by the BNF, has also changed little over this period.

<table>
<thead>
<tr>
<th></th>
<th>No. scrips (000s)</th>
<th>NIC (£000s)</th>
<th>NIC per scrip (£)</th>
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<td><strong>Oral</strong></td>
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Table 2. Number and cost of prescriptions for antiviral agents for herpes simplex and varicella-zoster, England, 2013

CPD: Viral skin infections

Answer these questions online at Prescriber.co.uk and receive a certificate of completion for your CPD portfolio. Utilise the Learning into Practice form to record how your learning has contributed to your professional development.

For each section, one of the statements is false – which is it?

1. Herpes simplex virus (HSV) infection:
   a. causes lesions at the site of initial infection after an incubation period of 2–12 days
   b. is always due to HSV type 2 in genital infections
   c. may cause acute retinal necrosis in elderly patients
   d. may be life-threatening to neonates born to mothers with active infection at the time of delivery

c. frequent HSV recurrence that is poorly controlled with oral aciclovir is an indication for specialist referral or advice
   d. referral should be considered for patients at risk of complications

4. In the treatment of HSV and VZV infections:
   a. VZV is not susceptible to aciclovir
   b. famciclovir is a prodrug of penciclovir
   c. inosine pranobex is inferior to aciclovir for HSV infection of the skin
   d. valaciclovir may be useful in patients with recurrent HSV infection poorly controlled by oral aciclovir

5. When considering drug treatment for HSV and VZV infections:
   a. oral aciclovir started within 24 hours of rash onset of chickenpox may reduce the duration and severity of symptoms
   b. patients with zoster who are over 50 years old should receive oral aciclovir
   c. antiviral therapy is not useful once postherpetic neuralgia is established
   d. topical therapy is always the treatment of choice for mild HSV infection

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