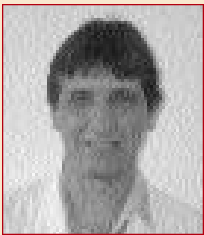


Antiviral therapy in herpesvirus infections

Herpesviruses are commonly seen in clinical practice. This article discusses their management in some detail.



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Herpesviruses are large, enveloped DNA viruses. There are currently 8 known human herpesviruses and 1 primate species that is a rare human pathogen. Most people have been infected with several human herpesviruses. In immunocompetent individuals primary infections with herpesviruses are generally mild, self-limiting infections. After primary infection, herpesviruses remain latent in either sensory nerve ganglia or immune cells. Latency may persist indefinitely unless immune suppression develops, in which case recurrent disease can become life-threatening. In the immunocompetent patient, clinical recurrences that are milder than the primary infection are the hallmark of herpesvirus infections.

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This article focuses on the role of antiviral therapy of common, treatable human herpesviruses — herpes simplex virus (HSV), varicella zoster virus (VZV) and cytomegalovirus (CMV). It is important to recognise that currently available antiviral therapy is unable to cure infection (latency persists after therapy) and has relatively modest clinical benefit.

ANTIVIRAL DRUGS

Aciclovir is a nucleoside analogue of guanosine. In infected cells it is activated

to the active phosphorylated form by the viral thymidine kinase enzyme. Aciclovir has activity against HSV and VZV. Higher doses of aciclovir are required to treat VZV, as it is less sensitive. Aciclovir is well tolerated, although renal dysfunction may occur with high intravenous doses. It is available in parenteral, topical and oral formulations, but is poorly absorbed orally. Valaciclovir (a pro-drug of aciclovir) and famciclovir (also a nucleoside analogue of guanosine) have better absorption, allowing less frequent dosing intervals.

Ganciclovir, another guanosine analogue, is used to treat serious CMV infection almost exclusively in immunocompromised patients. It causes significant bone marrow suppression. Foscarnet and cidofovir (not registered in South Africa) are alternatives to ganciclovir for CMV infection and are useful for aciclovir-resistant HSV infections. Ganciclovir, foscarnet and cidofovir should be used only by specialists in infectious diseases or transplantation.

HERPES SIMPLEX INFECTIONS

There are two HSVs — types 1 and 2. Type 1 typically produces disease of the mouth or lips, whereas type 2 produces genital lesions. However, genital infection with type 1 is becoming more common because of the widespread practice of oral sex. Similarly, oral infection caused by type 2 also occurs. When type 1 infections affect the genitals the disease is milder and recurrences less frequent. The commonest indication for antiviral therapy in adults is genital herpes, whereas in children it is herpes stomatitis. Recommen-

Table I. Recommendations for treating HSV infections (adult doses)

Clinical syndrome	Antiviral dose and administration	Duration	Notes
Primary HSV	Aciclovir 400 mg 8 hourly Valaciclovir 500 mg 12 hourly Famciclovir 250 mg 8 hourly	10 days	May need initial parenteral therapy
Recurrent HSV	Aciclovir 400 mg 8 hourly Valaciclovir 500 mg 12 hourly Famciclovir 125 mg 12 hourly	5 days	Commence within 24 hours. Minimal clinical benefit
Mucocutaneous HSV – immunocompromised	Aciclovir 400 mg 8 hourly Valaciclovir 500 mg 12 hourly Famciclovir 125 mg 12 hourly	10 days	Higher doses may be necessary
Frequent recurrences of genital HSV	Aciclovir 400 mg 12 hourly Valaciclovir 250 mg 12 hourly Famciclovir 250 mg 12 hourly	6 months	May need repeated courses
Ocular HSV	Aciclovir ointment 5 times daily	5 - 10 days	Ophthalmologist referral essential
Life-threatening HSV	Aciclovir 5 - 10 mg/kg 8 hourly IV	14 days	Use higher dose for encephalitis

Note that antiviral therapy is of minimal clinical benefit in some circumstances (e.g. recurrent HSV in immunocompetent individuals).
IV = intravenously.

ded doses, administration and duration of therapy for HSV infections are given in Table I.

Primary HSV infection

Primary infection with either HSV type 1 or 2 (Fig. 1) affects a fairly extensive mucocutaneous area and is often accompanied by considerable discomfort, fever and tender enlargement of the draining lymph nodes. A typical primary attack lasts about 10 - 14 days. Although primary infections are self-limiting and complications uncommon, the morbidity is significant. Antiviral therapy is effective for primary infection, but it has no effect whatsoever on the subsequent rate of recurrences.



Fig. 1. Primary genital herpes is often extensive. Antiviral therapy will shorten the course of the illness, but has no effect on subsequent recurrences.

Recurrent HSV

After a primary infection, clinically apparent recurrent attacks occur in most cases. Recurrences are derived from a latent reservoir inside nerve tissue of the patient and not from external re-infection. Clinical recurrences are much milder infections affecting a small area and lasting a few days (the typical ‘cold sore’). The frequency of recurrences is highly variable, with about one-third of patients experiencing frequent attacks. Over years the frequency of recurrences decreases. Antiviral therapy is of minimal clinical benefit in recurrent disease. Oral therapy must be commenced within 24 hours of onset of the recurrence to have an effect. Even then, the duration of clinical disease is reduced by only 1 day. Topical therapy has been shown to have no clinical benefit in recurrent disease. Antiviral therapy is seldom indicated for recurrent herpes labialis. Avoiding exposure to ultraviolet light substantially reduces the incidence of this condition.

Patients who suffer frequent recurrences of genital herpes (6 a year) should be considered for prophylactic antiviral therapy, which

should be given for 6 months and possibly longer (Table I). In immunocompetent subjects the development of resistance to aciclovir is very rare. A further benefit of prophylaxis is the reduction in viral shedding, including shedding in the absence of lesions or symptoms, which is more pervasive than shedding associated with visible lesions. It is estimated that most cases of initial infection are acquired from people who do not have overt herpes lesions. Promoting condom use is the most cost-effective strategy to prevent HSV transmission.

Women with recurrent or primary genital HSV at the time of delivery can transmit HSV to the neonate, which can cause severe disease. Caesarean section before membrane rupture is recommended to prevent neonatal HSV where the mother has acquired HSV infection in the third trimester of pregnancy, but the management of women with recurrent HSV in late pregnancy is controversial, since the risk for the baby is much lower. Aciclovir appears to be safe in pregnancy. Trials of prophylactic aciclovir have shown a reduction in recurrence and viral shedding in

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pregnant women. There is contradictory evidence from clinical trials regarding the effect of prophylactic aciclovir on caesarean section rates.

HSV ocular infection

HSV can cause primary infection involving the eye, with follicular conjunctivitis, vesicles on the eyelids and regional adenopathy. Corneal ulceration is common. Herpes simplex keratitis caused by recurrent HSV is more common. It typically results in a dendritic corneal ulcer. Topical aciclovir is effective for superficial ocular HSV infections. All cases should be followed up by an ophthalmologist.

Mucocutaneous HSV in immunocompromised patients

Patients with eczema can develop extensive, cutaneous HSV, i.e. eczema herpeticum (Fig. 2). The commonest mucocutaneous manifestation of HSV in patients with impaired cellular immunity is chronic ulceration, typically in the anogenital area (Fig. 3). When these ulcers persist for 4 weeks or more in HIV-infected individuals the disease is considered AIDS-defining. Chronic HSV ulceration is one of the more common AIDS-defining illnesses in southern Africa and is frequently misdiagnosed. Less commonly, HSV can cause oesophagitis or tracheobronchitis in immunocompromised patients.

Life-threatening HSV infection

The two commonest life-threatening HSV infections are encephalitis and disseminated neonatal disease. Disseminated disease can occur in immunocompromised patients, and also rarely in pregnant women and immunocompetent persons, in whom the diagnosis is often missed. Intravenous aciclovir is mandatory for all life-threatening HSV infections.



Fig. 2. Extensive, cutaneous HSV infection can occur in patients with eczema. Antiviral therapy is necessary.



Fig. 3. Chronic mucocutaneous HSV ulceration is a common manifestation of advanced HIV disease.

Aciclovir-resistant HSV infections

Aciclovir resistance is rare. It generally occurs in immunocompromised patients given prolonged or repeated courses of the drug. It is caused mainly by thymidine kinase-deficient virus mutants that are less fit than the 'wild type' HSV (therefore resistance can be reversed if therapy is stopped). Aciclovir-resistant mutants are also resistant to valaciclovir and famciclovir.

Foscarnet or cidofovir are effective if there is aciclovir resistance, but both have significant side-effects and should be used only under the direction of an infectious disease specialist.

VARICELLA ZOSTER VIRUS INFECTIONS

Primary infection with VZV results in chickenpox. Latent infection in nerve ganglia follows chickenpox, and disease may recur decades later in the form of a painful vesicular eruption in a dermatomal distribution known as shingles. A variety of neurological syndromes due to VZV have been described in immunocompromised patients, and less often in immunocompetent patients. Recommended doses, administration and duration of therapy for VZV infections are given in Table II.

Chickenpox (varicella)

Antiviral therapy is of very limited benefit in otherwise healthy patients with chickenpox. Therapy should be started within 24 hours of onset, which shortens the duration of the illness by only 1 - 2 days. The complication rate and mortality of chickenpox is generally low, but is highest in adults. Therefore it may be reasonable to offer antiviral therapy in adults.

Chickenpox in immunocompromised patients, especially those with leukaemia, is severe and may be life-threatening. The commonest life-threatening complication of chickenpox in immunocompetent patients is pneumonia (Fig. 4), which occurs in 1 - 2% of adults with chickenpox. Smoking and pregnancy are risk factors for the development of chickenpox pneumonia. In life-threatening chickenpox antiviral therapy is mandatory

Table II. Recommendations for treating VZV infections (adult doses)

Clinical syndrome	Antiviral dose and administration	Duration	Notes
Chickenpox	Aciclovir 800 mg 5 times/day Valaciclovir 1 g 8 hourly Famciclovir 250 mg 8 hourly	7 days	Commence therapy within 24 hours of onset – illness shortened 1 - 2 days
Shingles	Aciclovir 800 mg 5 times/day Valaciclovir 1 g 8 hourly Famciclovir 250 mg 8 hourly	7 days	Commence within 72 hours (except in immunosuppressed patients). Consider parenteral aciclovir if sight is threatened
Life-threatening VZV (e.g. disseminated shingles, chickenpox pneumonia, neurological disease)	Aciclovir 10 mg/kg 8 hourly IV	7 - 14 days	

IV = intravenously.

and should be given intravenously. There is no good evidence to support the co-administration of corticosteroids in chickenpox pneumonia.



Fig. 4. Chickenpox pneumonia is a life-threatening complication – intravenous aciclovir is mandatory.

Shingles (zoster)

The course of shingles in immunocompetent patients (Fig. 5) is shortened by about 2 days if antiviral therapy is commenced within 72 hours of onset. Acute pain is dramatically shortened, but it is unclear if the subsequent development of postherpetic neuralgia is modified by antiviral therapy.

In immunocompromised patients shingles is more prolonged and may be multidermatomal. Antiviral therapy should be strongly considered in immunocompromised patients even if they present more than 72 hours after onset. Shingles with dissemination (Fig. 6) may also occur in immunocompromised patients, in which cases intravenous aciclovir is mandatory.



Fig. 5. Shingles involving the ophthalmic branch of the left trigeminal nerve. This patient presented 5 days after onset, too late to benefit from antiviral therapy.

Neurological VZV complications in immunocompromised patients

VZV can cause a myelopathy or a small vessel encephalitis in immunocompromised patients. Both can present without a rash

and diagnosis is made by a nucleic acid amplification test (usually the polymerase chain reaction) on cerebrospinal fluid. Intravenous aciclovir is indicated.



Fig. 6. Multidermatomal shingles with dissemination in a patient with lymphoma. Intravenous aciclovir was administered and she made an uneventful recovery.

CYTOMEGALOVIRUS INFECTIONS

In immunocompetent individuals primary CMV is subclinical or causes a mild glandular fever-type illness. Serious complications are rare. Antiviral therapy for CMV has serious side-effects, consequently there is virtually never a

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role for antiviral therapy in this setting.

In contrast, patients with impaired cellular immunity (e.g. AIDS, immunosuppressant drugs) experience life-threatening disease involving tissues outside the reticulo-endothelial system, or develop sight-threatening CMV retinitis. Most disease is caused by reactivation of latent CMV infection. Intravenous ganciclovir is the drug of choice for initial therapy of CMV disease in immunocompromised patients. Unless immunity can be improved (e.g. reducing dose of immunosuppressants in transplant recipients or using highly active antiretroviral therapy in AIDS patients), maintenance therapy with lower dose intravenous ganciclovir or oral ganciclovir (or its pro-drug valganciclovir) is required to prevent recurrent CMV disease.

Prevention of CMV disease can be achieved in transplant recipients by either pre-emptive therapy of sub-clinical reactivation (diagnosed by increasing levels of antigenaemia or rising CMV viral load) or prophylaxis (especially with a seronegative recipient and seropositive donor). Ganciclovir is generally used for prophylaxis.

Treatment and prophylaxis of CMV disease in immunocompromised patients are highly specialised and should be undertaken only by infectious disease or transplant specialists.

FURTHER READING

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SINGLE SUTURE

Whole grain cereals and health

Yet more evidence linking whole grain cereals to a longer, healthier life appeared in the *American Journal of Clinical Nutrition* in March this year (2003; **77**: 594-599). The data show that male doctors who eat whole grain cereals for breakfast are less likely to die from cardiovascular disease — in fact less likely to die from anything — than colleagues who eat refined cereals instead. The effect is moderate, but probably real. The researchers accounted for all the usual confounders.

IN A NUTSHELL

Antiviral therapy for primary HSV infection has no effect on the subsequent rate of recurrences.

Antiviral therapy is of minimal clinical benefit for recurrent HSV infection in immunocompetent persons.

Patients who suffer frequent recurrences of genital herpes ((6 a year) should be considered for prophylactic antiviral therapy for 6 months.

Avoiding exposure to ultraviolet light substantially reduces the incidence of recurrent herpes labialis.

Chronic HSV ulceration is one of the more common AIDS-defining illnesses in southern Africa and is frequently misdiagnosed.

Antiviral therapy is of very limited benefit in otherwise healthy patients with chickenpox.

In life-threatening HSV or VZV infections intravenous aciclovir is mandatory.

Antiviral therapy must be commenced within 72 hours of onset in immunocompetent patients with shingles.

Antiviral therapy for CMV has virtually no place in the management of primary infection in immunocompetent patients.