Herpes simplex virus I and II: a therapeutic approach

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Abstract

Herpes simplex viruses (HSV) are ubiquitous in humans, and infection with HSV produces a diverse spectrum of disease. The vast majority of HSV infections in adults are easily recognised and relatively benign in their clinical manifestation, but occasionally, life-threatening infections, affecting the viscera and the central nervous system, can occur. Genital herpes simplex virus type II (HSV-II) is the most common sexually transmitted infection worldwide, and increases the risk of human immunodeficiency virus (HIV) infection. Suppressive anti-herpes therapy, despite being effective in reducing genital ulcer recurrence, does not reduce the risk of HIV transmission. Molecular diagnostic tools have revolutionised the ability to diagnose central nervous system infections and disseminated visceral disease accurately, and with the availability of relatively safe and effective antiviral therapy, potentially fatal outcomes can be averted if treatment is instituted early.

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Introduction

The two herpes simplex viruses type I and II (HSV-I and HSV-II) belong to the alphaherpesvirus subfamily, which also includes varicella zoster virus (VZV). They are common infections, afflicting humans worldwide, and by the age of 50, more than 90% of people have serological evidence of infection with HSV-I. HSV-II, a predominantly sexually transmitted virus, is less common, and the prevalence varies between 20-40% in the adult population. Sub-Saharan Africa has the highest HSV-II seroprevalence in the world, sometimes reaching 80% in women and men by 35 years of age.[1]

HSV has two unique biological properties that influence human disease. These are the ability to establish latent infection, and the capacity to invade the central nervous system.[2] Following exposure to HSV of mucosal surfaces, entry of the virus and initiation of viral replication occurs in the epidermis and dermis, manifesting with a vesicular eruption and mucosal ulceration. During primary infection with HSV, the sensory and autonomic nerve endings become infected, and latency is established in nerve cell bodies in ganglia. Orolabial infection, typically caused by HSV-I, establishes latency in the trigeminal ganglion, while sacral nerve root ganglia are the site of latency of genital infection, mostly caused by HSV-II. However, both HSV-I and II can cause infection and disease at either site. HSV-I and II reactivate frequently throughout life, often following known stimuli, e.g. ultraviolet light, immunosuppression, menstruation, and trauma to the skin, which result in local recurrences.

The vast majority of HSV infections are relatively benign, manifesting with mucocutaneous lesions or benign recurrent aseptic meningitis (characteristically with HSV-II), during the lytic phase of infection. Occasionally, patients can present with life-threatening infections that affect the brain or viscera. This review will focus on the diagnosis and treatment of HSV infections, with special emphasis on HIV and HSV co-infection, and the management of severe and life-threatening infections in adults and neonates, where prompt recognition and early institution of antiviral therapy can be lifesaving.

Laboratory diagnosis

The clinical manifestations of patients with mucocutaneous disease are usually easily recognised, and laboratory confirmation is not necessary, usually. Laboratory diagnosis may be required for unusual presentations, such as chronic, non-healing ulcers in an immunocompromised patient; in patients with disseminated HSV infection, where mucocutaneous lesions may be absent; or in patients with disease of the central nervous system. For details of laboratory diagnostics and their clinical utility, refer to Table I.

Table I: Laboratory tests for herpes simplex virus infections

Test type	Clinical utility	Advantages and limitations of the technique
Serology IgG	Evidence of past exposure, and persistent infection	Commercial assays frequently test for a group antigen, and cannot distinguish between herpes simplex virus type I and II. Assays based on viral glycoprotein "gG" are able to distinguish between herpes simplex virus type I and II infections.
IgM	Surrogate marker of active herpes simplex virus replication. High levels are present during primary infections. Variably present during recurrent infections.	False positive reactions are not uncommon, due to technical reasons. Low sensitivity in recurrent disease.
Direct antigen detection in epidermal cells, with labelled anti-herpes simplex virus monoclonal antibodies	Rapid diagnosis of mucocutaneous lesions. Can distinguish between herpes simplex virus type I and II.	Sensitivity depends on good sample collection.
Virus culture	Indicates active virus replication.	Virus grows quickly and easily in cell culture. More sensitive than direct antigen detection. Limited availability. NB: Does not detect virus in all clinical conditions.
Polymerase chain reaction	Generally, but not necessarily, indicates active virus replication. Can distinguish between herpes simplex virus type I and II.	Most sensitive method of virus detection in all clinical sample types. Sensitivity depends on sample volume and polymerase chain reaction methodology.

Antiviral drugs

Acyclovir, an analogue of the nucleoside guanosine, is the prototype antiviral drug that was developed more than three decades ago. It replaced the less effective vidarabine (adenine arabinoside) as the drug of choice for treating HSV. Acyclovir has an excellent therapeutic index, is highly specific for HSV-infected cells, and has become standard therapy for HSV and VZV infections. Selectivity of the compound is based on the fact that it is only phosphorylated in HSV-infected cells. An HSV-encoded enzyme, thymidine kinase (TK), performs the first phosphorylation step. Acyclovir monophosphate is then further activated to di- and triphosphate form by a cellular kinase. In its active triphosphate form, acyclovir inhibits viral replication by acting as a competitive substrate for viral deoxyribonucleic acid (DNA) polymerase, and results in chain termination of the growing viral DNA strand.

Several other nucleoside analogues that inhibit HSV DNA synthesis have been developed since the discovery of acyclovir. Penciclovir and acyclovir have similar antiviral activity, spectrum and safety profiles. Valacyclovir (a prodrug of acyclovir) and famciclovir (a prodrug of penciclovir) are converted to the active compound during first-pass hepatic metabolism, and have greater oral bioavailability than the parent molecules. Another nucleoside analogue, ganciclovir, has activity against HSV, as well as other herpesviruses, such as human cytomegalovirus (CMV) and human herpesvirus type 6 (HHV-6), but has significant myelotoxicity. It is not recommended for the treatment of HSV infections, unless treatment or suppression of both HSV and CMV is required.

Acyclovir has limited oral bioavailability (10-20%), and requires frequent dosing regimens of up to five times a day. Hence the prodrugs, valacyclovir and famciclovir, which have much greater oral bioavailability and more convenient twice-daily dosing regimens, have gained considerable popularity in the management of mucocutaneous HSV infections. Intravenous acyclovir is generally reserved for severe systemic infections, or in situations in which patients are not able to take oral therapy. Reversible renal impairment may result from acyclovir crystallisation in the renal parenchyma, particularly in poorly hydrated patients. This complication can be avoided by slow infusion over one hour, maintaining proper hydration, and adjusting the acyclovir dose in the presence of a reduced glomerular filtration rate. Oral acyclovir therapy, even at doses of 800 mg five times daily, has not been associated with renal dysfunction. Oral treatment with acyclovir, famciclovir and valacyclovir is associated with very few adverse effects, and long-term use is safe, with no cumulative toxicity.[3] The drugs appear to be safe in pregnancy. However, in the absence of well-controlled studies, their use should be restricted to symptomatic HSV infections.

Oral antiviral treatment effectively improves symptoms in people with their first episode of oral or genital herpes, and can be used for treating recurrences. Acyclovir,

Table II: Antiviral therapy for herpes simplex virus infection

Type of infection	Drug	Dosage	Comments
Systemic herpes simplex virus infection in adults			
Herpes simplex virus encephalitis	Acyclovir	10 mg/kg q 8h for 14-21 days intravenously	Infusion over 1 hour. Ensure adequate hydration. Monitor renal function.
Disseminated herpes simplex virus	Acyclovir	5 mg/kg q 8h for 14 days intravenously	Lower dose only if central nervous system disease excluded.
Genital herpes simplex virus			
Primary episode	Acyclovir	400 mg po tid x 7-10 days	
	Valacyclovir	1 000 mg po bid x 7-10 days	
	Famciclovir	250 mg po tid x 5 days	
Recurrent episode Episodic treatment	Acyclovir	800 mg po tid x 2 days, or 400 mg po tid x 5 days	Longer treatment duration for minimum of 5 days, and up to 14 days, is advised in human immunodeficiency virus-positive patients.
	Famciclovir	125 mg po tid x 5 days	
	Valacyclovir	500 mg po bid x 3 days, or 1 g daily x 5 days	
Daily chronic suppressive therapy	Acyclovir	400 mg po bid	Recommended if > 6 recurrences per year. Higher (double) dosages required in human immunodeficiency virus-positive patients.
	Famciclovir	125 mg po bid	
	Valacyclovir	1 g po daily	
Mucocutaneous herpes simplex virus (oral labial, "fever blisters")			
Immunocompetent	Valacyclovir	2 g po bid x 1 day	Immunocompromised patients, or critically ill patients in intensive care unit setting: Acyclovir 5 mg/kg q 8h intravenously, or 400 mg po 5x/day x 7-14 days, or valacyclovir 500 mg bid x 5-7 days
	Acyclovir	400 mg po tid x 5 days	
Neonatal herpes simplex virus			
Disseminated or central nervous system disease	Acyclovir	20 mg/kg q 8h for 21 days intravenously	High rates of relapse reported in children with lower doses and shorter treatment duration.
Skin, eye and mucosal herpes simplex virus disease	Acyclovir	20 mg/kg q 8h for 14 days intravenously	

All dosage recommendations are for adults, unless otherwise indicated, and require adjustment in the presence of renal impairment.
This table was adapted from *The Sanford guide to antimicrobial therapy 2010*.

famciclovir, and valacyclovir are all equally beneficial in reducing the duration of symptoms, lesion healing time, and viral shedding. Daily maintenance treatment with oral antiviral agents decreases the frequency of recurrences and transmission risk, as well as improving quality of life. Physicians, in consultation with the patient, can choose between different treatment strategies. With episodic or patient-initiated therapy, antiviral treatment is started when the patient experiences symptoms that herald an eruption. Single, high doses of antiviral agents provide effective treatment over several days.[4] Another approach is long-term daily suppressive therapy. This is recommended if recurrences are frequent and severe, or if there is concern about person-to-person transmission.

General treatment recommendations for the spectrum of diseases caused by HSV are outlined in Table II.

Drug resistance

With the use of long-term treatment for HSV infections, especially in immunocompromised patients, drug-resistant viral strains may emerge. Drug-resistant HSV occurs most frequently in haematopoietic stem cell transplant patients, but has also been reported in the setting of HIV, and rarely in immunocompetent patients (< 1%). Resistant strains typically have mutations that result in a deficiency or alteration in viral thymidine kinase activity. This results in the loss of activity of all nucleoside analogues that are phosphorylated by the viral TK. Fortunately, TK mutants have impaired neurovirulence, and are unable to establish latency. This means that the virus phenotype reverts to a drug-sensitive one after clearance of the episode. Another less common mechanism of drug resistance is mutations in the viral DNA polymerase gene.

There are two alternative drugs that have activity against herpesviruses, namely foscarnet and cidofovir. They are not analogues of guanosine, and do not require phosphorylation by viral TK. They can be used to treat resistant strains with TK mutations. Unfortunately, both cidofovir and foscarnet are nephrotoxic, and not registered for use in South Africa currently.

Herpes simplex encephalitis

Herpes simplex encephalitis (HSE) is the most common cause of identified sporadic encephalitis worldwide, accounting for 5-10% of all identified cases.[5] All age groups may be affected, and the disease occurs throughout the year. HSV-I causes the majority of infections in adults, while HSV-II is more common in neonates. Approximately one-third of patients with HSE have primary infections, and two-thirds have recurrent infections. The clinical presentation comprises fever, headache, focal neurological symptoms (temporal lobe dysfunction with language, behavioural abnormalities and memory impairment) with, or without, reduced level of consciousness and seizures. The most sensitive and least invasive method to confirm the diagnosis is polymerase chain reaction (PCR) for HSV-I and II on cerebrospinal fluid (CSF). In adults, reported sensitivities and specificities are 96-98% and 95-99%, respectively.[6] Of note, HSV PCR may be negative early in the course of the infection, and repeat testing is advised three to seven days later if the initial PCR result is negative, and clinical suspicion is high.[7] Magnetic resonance imaging (MRI) is the preferred imaging modality, and bilateral implication of the temporal lobes is almost pathognomonic for HSV infection. More than 90% of patients with HSE documented by CSF PCR will have abnormalities detected by MRI.

Antiviral therapy with acyclovir is the treatment of choice in HSE, and significantly reduces mortality from over 70%, to less than 20%. Unfortunately, significant post-treatment morbidity remains, with poor outcomes being observed in older patients (> 30 years), those with a lower Glascow Coma score at initiation of acyclovir, and those with prolonged duration of illness (longer than four days) prior to starting acyclovir therapy.

Initial studies in the early 1980s, comparing vidarabine with acyclovir, demonstrated that acyclovir at 10 mg/kg eight hourly had superior efficacy to vidarabine. It is administered intravenously at a dosage of 10 mg/kg body weight every eight hours, with an infusion time of one hour. The acyclovir dosage requires adaptation in patients with renal impairment. The treatment duration is 14 days. However, some experts recommend treatment for up to 21 days, as shorter treatment courses may be associated with disease relapse. Another approach is to repeat the CSF PCR in patients with an inadequate treatment response at the end of therapy, and continue to treat if the PCR remains positive. Only a few reports of true post-treatment relapse have been described in adults. In one cohort of adult patients with documented treated HSE, 12% of cases developed symptoms and radiological changes up to four months post-treatment. All had a negative HSV PCR, and it is thought that the pathogenic mechanism in relapse is likely to be an immune-mediated process.[8]

The use of adjunctive corticosteroids was assessed in one non-randomised, retrospective study of 45 patients with HSE treated with acyclovir, and showed a worse outcome in those not receiving steroids.[9] A large multicentre randomised clinical trial is currently underway in Europe, evaluating treatment of HSE with acyclovir and adjuvant dexamethasone vs. acyclovir and placebo.[10]

Disseminated herpes simplex virus infections

HSV rarely causes disseminated disease. Viral dissemination to the bloodstream and viscera is typically seen in immunocompromised patients, (e.g. haematological malignancies, transplant recipients, patients taking immunosuppressive medication) and neonates. However, up to 25% of HSV dissemination can occur in apparently immunocompetent individuals, including pregnant patients.[11] The viraemia may be due to primary infection, super-infection with a second HSV strain, or as a result of latent infection reactivation.

Systemic HSV manifestations include oesophagitis, hepatitis, pneumonitis, and HSV encephalitis. Multiple organ involvement is common, and telltale mucocutaneous lesions are often absent. Rapid diagnosis of this rare, and rapidly fatal, condition is essential if antiviral treatment is to be effective. As the presenting symptoms are frequently vague, patients often die before the diagnosis is entertained. HSV PCR on blood is the test of choice, and in the right context, has a very high predictive value for disease. HSV DNA may be detected in patients' blood during primary HSV infection, and also during reactivation in immunocompromised persons with extensive mucocutaneous disease, in the absence of end-organ disease.[12] A positive HSV PCR derived from blood must be interpreted in the light of the patient's clinical condition.

Treatment with intravenous acyclovir is recommended, at a dose of 5-10 mg/kg eight hourly, as soon as this condition is suspected.

Neonatal herpes simplex virus

Neonates have poor and immature cell-mediated immunity, and are therefore at higher risk than other patient groups of developing visceral or CNS infection. More than 90% of neonatal HSV is acquired during delivery, following exposure to HSV in the mother's genital tract. HSV-II is consequently the most common cause, accounting for more than 70% of cases. The risk of transmission is highest in mothers who acquire primary genital HSV infection during late pregnancy (25-50%). This contrasts with the much lower transmission risk of < 1% in patients with longstanding genital HSV, who experience reactivation of HSV at term.[13] In mothers with primary genital herpes at term, Caesarean section delivery is indicated to reduce the risk of transmission to the infant. The value of Caesarean section is less clear in patients with recurrent genital herpes. Here the risk of transmission to the infant is much lower, and trials have failed to show a clear benefit. In this setting, suppressive acyclovir has shown a reduced frequency of genital lesions near term, and lower frequency of Caesarean section delivery. However, there is no data to suggest it reduces the risk of neonatal herpes.[14]

Three different clinical presentations have been described in neonates. These are infection localised to skin, eyes and mucosa (SEM), where cutaneous lesions are typically present; CNS infection manifesting with fever, lethargy, poor feeding and seizures; and disseminated infection, affecting the lungs, brain and liver, which presents with a sepsis-like syndrome. Typical vesicular mucocutaneous lesions are often absent in the latter two presentations, making diagnosis difficult. Demonstration of HSV DNA in the cerebrospinal fluid or blood is the most sensitive laboratory test that can be used to confirm diagnosis.

Visceral infection carries a mortality risk in excess of 80% if left untreated, and less than 50% of patients with CNS disease will experience normal development, despite treatment. Although outcomes are good where the infection remains confined to the skin, eye and mucous membranes, there is a risk of disease progression, and systemic antiviral therapy is strongly recommended. Following randomised controlled trials, acyclovir and vidarabine are the only two antiviral agents to have demonstrated a significant mortality benefit in patients with CNS or disseminated disease.[15] Patient numbers in these early trials were too few to guide duration and dose of antiviral therapy accurately. High-dose intravenous acyclovir (20 mg/kg eight hourly) is currently recommended in all infants with presumptive neonatal HSV infection.[16] Treatment duration is 21 days for disseminated or CNS disease, and 14 days are adequate for infants with SEM disease. By using the above recommendations, there is a substantial survival benefit without excess toxicity, as well as very low relapse rates. The efficacy and role of newer oral antiviral agents with better bioavailability, e.g. valaciclovir, may be adequate for infants with skin, eye or mouth HSV disease, or when treating infants older than six weeks with recurrences, but this still needs to be evaluated.

Herpes simplex virus type II and human immunodeficiency virus

HSV-II is a frequent co-infection in populations with HIV infection, partly because they share the same route of transmission.[17] Infections are usually asymptomatic, but HIV and HSV-II co-infected persons have more frequent genital viral shedding, and higher local HSV-II viral loads, than persons with HSV-II infection alone. HSV infection in HIV-infected persons may go unrecognised, as the lesions can be small and confined to the perianal region, and therefore difficult for patients to detect. In cases of advanced HIV infection, more frequent and persistent anogenital herpetic ulceration occurs. Lesions may become extensive, deeply ulcerated and necrotic.[18] Anogenital herpes was one of the first opportunistic infections described in acquired immune deficiency syndrome (AIDS) patients, and persistent herpetic ulceration is an AIDS-defining illness.

The risk of HIV transmission is also significantly increased in patients with symptomatic genital ulcer disease, of which HSV-II is one of the major causes.[19] This is partly due to inflammation and damage to the epithelium, but HSV-II may play an additional role. Laboratory and epidemiological studies suggest that HSV-II reactivation may increase HIV shedding in genital secretions, thereby increasing the risk of HIV transmission. HIV levels are increased in the blood and genital tract, even in patients with asymptomatic HSV-II reactivation. Disappointingly, although suppression of HSV-II with antiviral therapy reduces the frequency of HSV-II reactivation and lowers HIV levels, it does not appear to reduce HIV transmission. In a recently published randomised placebo-controlled trial of HIV-discordant heterosexual couples, daily acyclovir did not reduce the risk of HIV transmission, despite reducing the occurrence of genital ulcers due to HSV-II by 73%, and reducing the serum HIV viral load.[20]

HSV is the most common cause of mucocutaneous vesicular and ulcerative disease in HIV. However, in the absence of a clinical response to empiric antiviral therapy, other causes, such as CMV, VZV, pustular dermatoses, or non-viral ulcerative sexually transmitted infections, need to be excluded. HSV PCR on clinical material from the lesions has higher sensitivity than viral culture.

Antiviral therapy for HSV infection in the setting of HIV is safe, well tolerated and, most importantly, has no significant

drug-drug interaction with antiretroviral medications. Treatment responses, especially in patients with low cluster of differentiation 4+ cell counts, may be slow, and to allow lesions to heal, higher drug doses and longer treatment duration may be necessary (Table II). Highly active antiretroviral therapy has been shown to decrease the frequency of recurrence, but not the rate of asymptomatic mucosal HSV-II shedding, and therefore, does not reduce HSV-II infectivity.

Conclusion

Infection with HSV produces a diverse spectrum of disease. The vast majority of HSV infections in adults are relatively benign in their clinical manifestations, but they nevertheless cause significant discomfort and anxiety, and impair the quality of life of millions of people. Genital HSV puts individuals at increased risk of acquiring other sexually transmitted infections, including HIV. Relatively non-invasive tests, such as PCR, have greatly improved the ability to diagnose disorders such as HSE and disseminated HSV. Early identification is essential to manage these infections effectively. The development of acyclovir was a landmark in antiviral drug discovery. Acyclovir and its analogues have a remarkable safety profile, and are highly and selectively effective against the alpha-herpesviruses. Their use in clinical practice has transformed the management of both mucocutaneous and disseminated HSV infections.

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