HERPES SIMPLEX VIRUS (HSV) INFECTION OF THE MOUTH

Definition

Herpes viruses are a large family of parasites able to infect humans. All are DNA viruses capable of latency. Among human herperviruses there are two variants - Herpes Simplex Virus type-1 (HSV-1) and type–2 (HSV-2), which can be – as well as other clinical signs and symptoms – responsible for oro-facial disease. Usually HSV-1 infections affect the face and mouth while HSV-2 infections occur genitally. Both viruses may cause recurrent disease.

HSV usually enters humans via the mouth. Oro-genital and penetrative intercourse, contact sports, some high risk occupations and corneal transplant surgery have been associated with HSV transmission.

The first episode of HSV infection in humans who have not previously been exposed to HSV-1 and HSV-2 is called the *primary* infection. Symptoms are not always present during the first infection, and therefore patients may be unaware that they have been exposed to the virus. Following primary infection the virus travels through the nerves that give sensation to the area infected. Once it enters the root of these nerves – the ganglion – it remains there for life. When the virus reactivates, it can cause mucosal or skin lesions in roughly the same area to that where it originally entered the body: these manifestations are defined as *recurrences*.

Epidemiology

HSV-1 and HSV-2 occur worldwide and have no seasonal variation. HSV infection is rarely fatal. Most human beings have been infected and harbour latent virus that can reactivate; hence there is a vast HSV reservoir for transmission to susceptible individuals. Demographic factors affect acquisition of HSV-1 infection. In less developed countries seroconversion happens early in life – at 5 years in around a third of children and in 70-80% by adolescence. In comparison, individuals in more developed countries become infected later on – seroconversion occurs in about 20% of children younger than 5 years; then no substantial rise in frequency happens until an increase to 40-60% at age 20-40 years. In the USA, race also affects acquisition of HSV-1. By age 5 years, more than 35% of African-Amerindians versus 18% of white children are infected with HSV-1. Incidence of infection among university students is around 5-10% annually.

HSV-2 infections are usually sexually transmitted. Most genital HSV infections are caused by HSV-2; however an increasing proportion is attributable to HSV-1. Genital HSV-1 infections are usually less severe and less prone to recur than those caused by HSV-2. HSV-2 seroprevalence rises from about 20-30% at age 15-29 to 35-60% by age 60 years. Factors that affect acquisition of HSV-2 infection include sex (infection is more frequent in women), race (infection is more frequent in Africans Americans than whites), marital status, number of sexual partners, and place of residence (prevalence is higher in city than in suburbs).

As with HSV-1 infection of the mouth, HSV-2 primary, initial or recurrent infection can be symptomless. Recurrence varies between men and women, occurring 2.7 and 1.9 times per 100 days, respectively. Women with initial genital herpes can shed the infection without symptoms; this occurs in 12%, 18% and 23% of primary HSV-1, primary HSV-2 and non-primary-HSV-2 infections respectively.

Clinical presentation

Herpesvirus infections can cause debilitating diseases which, in persons with frequent recurrences, may have psychological and physical sequelae. *Gingivostomatitis and orolabial HSV infection* are expression of trigeminal nerve infection. Gingivostomatitis is a symptomatic primary HSV-1 infection, usually occurring in children and characterized by vesicles and ulcers in and around the oral cavity (Figure 1). Children are often unable to swallow because of the associated pain, and may become dehydrated. In severe cases hospitalization may be required and occasionally autoinoculation can result in conjunctivitis and keratitis. In cases of oral disease, primary infection is usually inside the mouth (gingivostomatitis), whereas recurrent disease is most commonly associated with lesions of the lip (herpes labialis or cold sores) (Figure 2) or cutaneous manifestation (facial herpes). Cold sores are usually preceded by prodromal symptoms as tingling, pain, burning sensation or itching at the site of reactivation. Symptomatic outbreaks of cold sores are estimated to affect 20-40% of adults. Occasionally reactivation may result in irregular oral ulceration in the distribution of the affected nerve (Figure 3).

Reactivation of HSV-1 from the geniculate ganglion has been implicated in the pathogenesis of idiopathic *facial palsy or Bell's palsy*.

Ocular HSV infection is a major cause of corneal scarring and visual loss which is the result of a direct viral cytopathic effect.

Aetiopathogenesis

Herpesviruses have two biologic properties: the ability to invade and replicate in the host nervous system and the ability to establish a site of latent infection. The neurovirulent properties of herpes simplex virus (HSV) enable the virus to cause a disease primarily of the sensory nervous system rather than of the skin. The ability of HSV to infect and cause lyses of cells of the central nervous system (CNS) is illustrated by sporadic cases of potentially fatal HSV encephalitis. In more usual circumstances, however, the main target of the virus is the peripheral nervous system. During primary infection, virus is transported via sensory ganglia to establish a chronic latent infection, most commonly in the trigeminal, cervical or lumbosacral ganglia. Retrograde transport of HSV along nerves and the establishment of latency are not dependent on viral replication in the skin or neurons therefore neurons can be infected in the absence of symptoms.

Periodically HSV may reactivate from its latent state and virus particles then travel along sensory neurons to the skin and other mucosal sites to cause recurrent disease episodes. Recurrent mucocutaneous shedding of HSV can be associated with lesions or asymptomatic shedding and in either scenario is allied with a period when virus can be transmitted to a new host.

Diagnosis

Although acute herpetic gingivostomatitis and recurrent labial and intraoral herpes simplex infection are diagnosed by the clinical history and signs several laboratory techniques may assist in the diagnosis of the difficult case. These include:

- Morphologic studies (Tzanck test) – smear taken from an intact vesicle
- Viral culture, antigen or DNA studies (Immunomorphologic, immunovirologic, molecular virologic methods)
- Serologic – a rising titre of serum antibodies is confirmatory, but gives the diagnosis retrospectively

Treatment

Primary stomatitis

An adequate fluid intake and soft diet must be encouraged. Dehydration especially in children may result in hospital admission. Antipyretic/analgesic agents such as paracetamol (acetoaminophen) relieve pain and fever (aspirin should be avoided in children). Local pain control may be assisted by the use of benzydamine hydrochloride 0.15% mouthwash/spray or lidocaine hydrochloride 1% gel. A 0.2% aqueous chlorhexidine mouthwash (diluted to half strength with warm water if too uncomfortable at full concentration) or tetracycline mouthwash (contents of 250mg capsule of tetracycline or doxycycline dissolved in 15ml warm water and held for 2-3 minutes and expectorated four times daily) may assist in resolution of painful ulceration by decreasing secondary bacterial infection.

Three randomised controlled trials (RCTs) have clearly demonstrated that early aciclovir treatment significantly shortens the duration of all clinical manifestations and infectivity of affected children compared with placebo. Treatment should be started within the first 3 days of disease onset. The proposed therapeutic dose is 15 mg/kg, 5 times daily for 5 to 7 days.

Recurrent herpes labialis

Prevention

Oral antiviral agents . Limited evidence from RCTs suggests that prophylactic oral antiviral agents may reduce the frequency and severity of attacks compared with placebo, but the optimal timing and duration of treatment is uncertain. Long term prophylaxis should be reserved for those subjects who suffer regular severe attacks.

Sunscreen Limited evidence from two small crossover RCTs suggest that ultraviolet sunscreen may reduce herpes recurrence compared with placebo.

Topical antiviral agents There are no RCTs on the effects of topical antiviral agents used as prophylaxis.

Treatment

Oral aciclovir for first attack One small RCT in children found that oral aciclovir reduced the mean duration of pain compared with placebo. Another small RCT in children found that oral aciclovir reduced the median time to healing compared with placebo.

Oral antiviral agents for recurrent attack Two RCTs found that oral aciclovir (if taken early in the attack) marginally reduced the duration of symptoms and pain compared with placebo. More recently valaciclovir has showed similar results.

Topical antiviral agents for recurrent attacks Limited evidence from RCTs suggests that topical 1% penciclovir or aciclovir reduced the duration of pain and symptoms compared with placebo.

Topical anaesthetic agents One small RCT found limited evidence that topical tetracaine reduced the mean time to scab loss compared with placebo. However, the clinical importance of this result is unclear.

Topical antiviral agents for first attack There are no RCTs on the effects of topical antiviral agents.

Zinc oxide cream One small RCT found limited evidence that zinc oxide cream reduced time to healing compared with placebo but found that it increased the risk of skin irritation.

Prognosis

Whilst antiviral agents prevent recurrence, it is most unlikely that HSV is eradicated and therefore, despite therapy, long-term reactivation may be expected.

Complications

Eczema herpeticum

HSV infection is a particularly troublesome complication of atopic eczema and frequently affects the head and neck if associated with autoinnoculation from oro-labial herpes. Eczema herpeticum is a potentially serious and progressive disease from which suppressive therapy with acyclovir is indicated.

Erythema multiforme and Stevens-Johnson syndrome

HSV is a recognised trigger for these mucocutaneous diseases: continuous aciclovir therapy (600mg twice daily for 6 months) can be effective in preventing outbreaks.

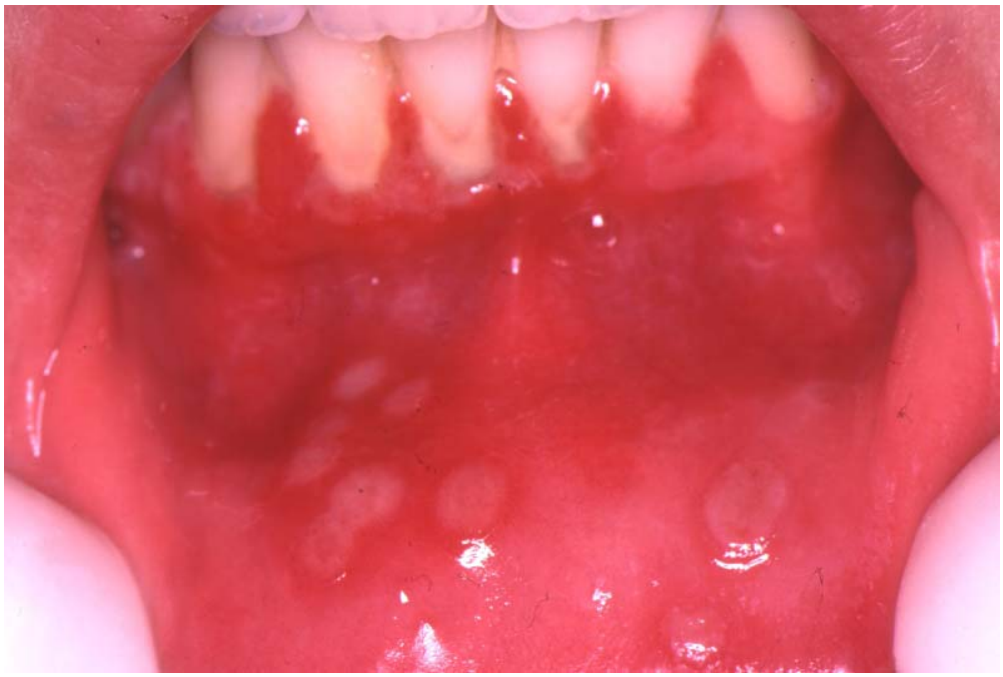

Figure 1 Herpes gingivostomatitis

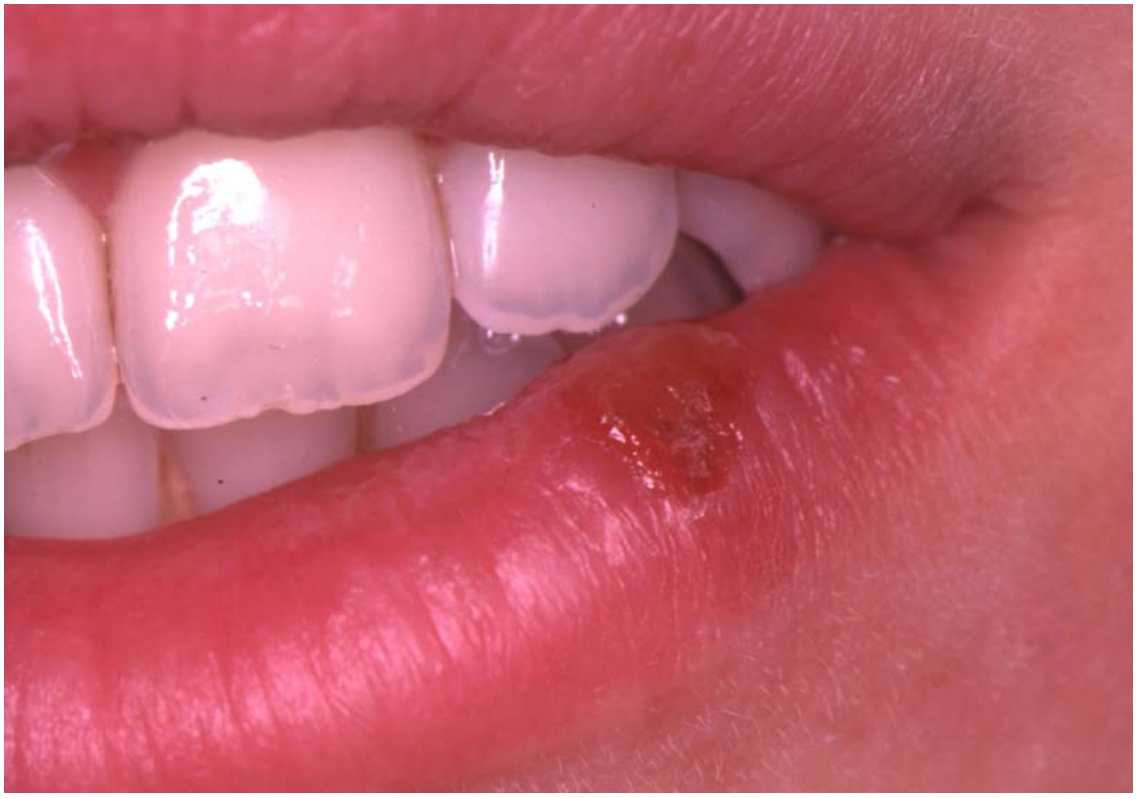

Figure 2. Herpes lesions of the lip (cold sore)

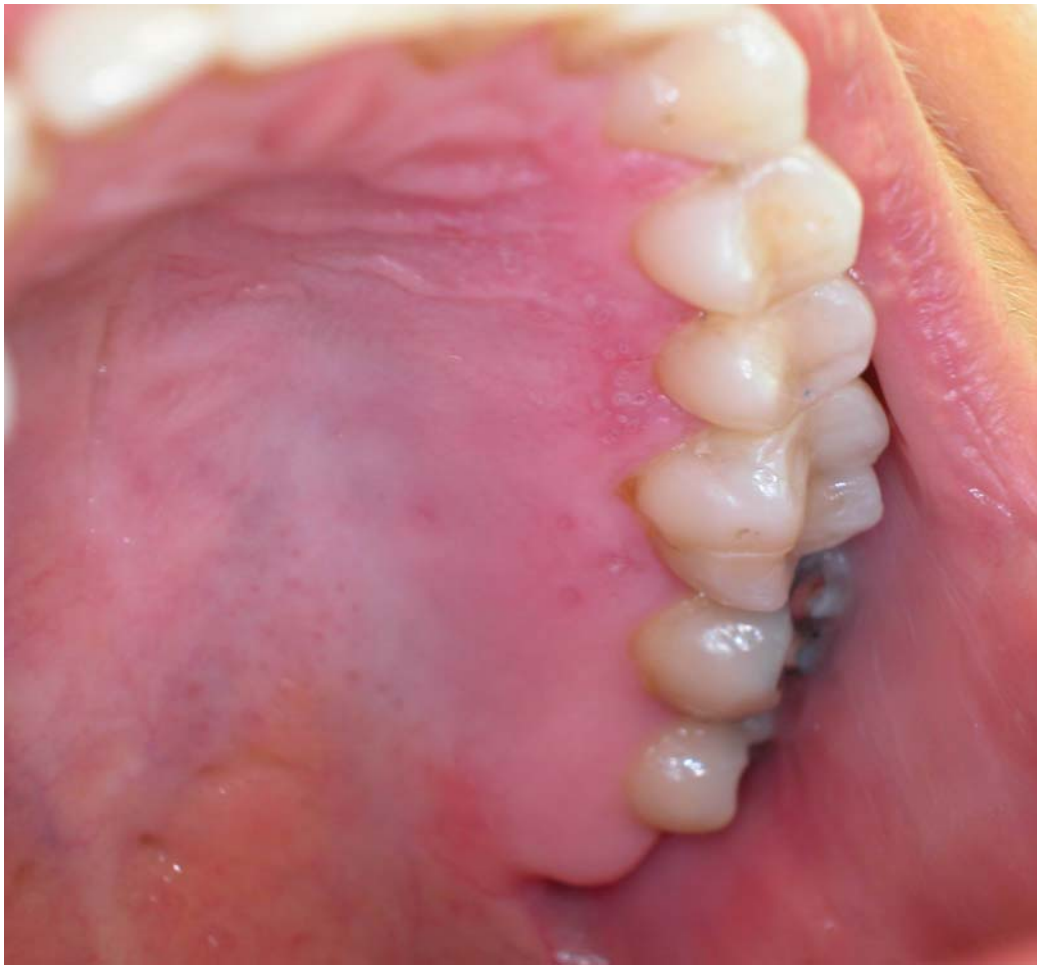

Figure 3. Herpes lesions of the palatal mucosa, recurrence.

Further reading

1 Whitley RJ, Roizman B. Herpes simplex virus infections. Lancet 2001; 357:1513-18.

2 Worrall G. Herpes labialis. Clinical evidence 2002 www.clinicalevidence.org

3 Amir J. Clinical aspects and antiviral therapy in primary herpetic gingivostomatitis. Paediatr Drugs 2001; 3:593-7.

4 Spruance SL, Jones TM, Blatter MM, Vargas-Cortes M, Barber J, Hill J et al. High-dose, short-duration, early valacyclovir therapy for episodic treatment of cold sores: results of two randomized, placebo-controlled, multicenter studies. Antimicrob Agents Chemother 2003; 47:1072-80.

5 Tatnall FM, Schofield JK, Leigh IM. A double-blind, placebo-controlled trial of continuous acyclovir therapy in recurrent erythema multiforme. Br J Dermatol 1995; 132:267-70.

Links

http://www.ihmf.org/

http://www.ahmf.com.au

http://www.herpes-foundation.org/