

# Human herpes simplex labialis

M. Fatahzadeh and R. A. Schwartz\*

Division of Oral Medicine, New Jersey Dental School, Newark, NJ, USA; and \*Department of Dermatology, New Jersey Medical School, Newark, NJ, USA

## Summary

Humans are the natural host for eight of more than 80 known herpes viruses. Infections with herpes simplex virus type 1 (HSV-1) are ubiquitous worldwide and highly transmissible. Herpes simplex labialis (HSL) is the best-recognized recrudescing infection of the lips and perioral tissues caused by HSV-1. Facial lesions of HSL may be unsightly, frequent outbreaks unpleasant, and the infection itself more severe locally and systemically in immunocompromised people. This article highlights the pathogenesis, clinical presentation, diagnostic features and management issues for HSL.

## Introduction

In excess of 80 herpes viruses have been recognized. The Herpesviridae family of viruses includes herpes simplex virus (HSV)-1 and -2, varicella zoster virus, cytomegalovirus, Epstein–Barr virus, human herpes virus (HHV)-6 and -7, and the Kaposi's sarcoma-associated virus HHV-8.<sup>1</sup> Humans are the only natural host in whom these viruses survive for the host's lifetime.<sup>1,2</sup>

## Structure and biology

There are two serotypes of HSV, HSV-1 and HSV-2, both of which contain a linear, double-stranded DNA of nearly 150 kbp contained within a capsid, surrounded by a tegument and an envelope.<sup>1–3</sup> These serotypes share a degree of homology between their DNA but are antigenically different.<sup>1</sup> HSV-1 is mainly implicated in orofacial infections, whereas HSV-2 is predominantly associated with genital lesions.<sup>1,4</sup> Although crossover infections via sexual practices are possible,<sup>1,4–6</sup> transmission of HSV-1 to the genital region occurs more often than transmission of HSV-2 to the orolabial region.<sup>7</sup> In view of the lower rate of clinical recurrence

and subclinical viral shedding associated with HSV-1-induced genital herpes,<sup>8,9</sup> its oral transmission through sexual encounters is probably less likely. Cross-immunity between HSV serotypes is also possible, resulting in milder infection with one serotype if there is a history of prior exposure to the other serotype.<sup>10</sup>

Global serological prevalence of HSV-1 exposure is high, and is influenced by age, race, geographical location, and socioeconomic status.<sup>2,11–14</sup> In less industrialized regions of the world, the rate of HSV-1 seropositivity is higher and seroconversion occurs early in childhood.<sup>2,13,14</sup> In the USA, HSV-1 antibodies are more prevalent in people of sub-Saharan African lineage, older age and poor economic status.<sup>2,11–14</sup> HSV is highly transmissible through contact with active lesions, respiratory droplets, contaminated inanimate objects, and infected exudates or secretions.<sup>1,5,15,16</sup>

Whereas HSV-1 is primarily transmitted by intimate oral contact such as sharing kitchen or bathroom utensils, HSV-2 is spread mainly through genital sexual contact.<sup>1,2</sup> HSV-2 is predominantly asymptomatic. Viral shedding in body secretions contributes to spread of infection to susceptible individuals, but the risk of transmission is highest during symptomatic periods.<sup>1,5,6</sup> Autoinoculation is also a source of viral spread to other body sites.

## Clinical presentation

Primary herpetic gingivostomatitis (PHGS) is the result of initial exposure of a nonimmune individual to HSV-1.<sup>2</sup>

*Correspondence:* Professor Robert A. Schwartz, Head of Dermatology, New Jersey Medical School, Newark, NJ 07103, USA.

E-mail: roschwar@cal.berkeley.edu

Conflict of interest: none declared.

Accepted for publication 2007

PHGS predominantly occurs in young children; most cases are subclinical.<sup>1,4</sup> Symptomatic cases are characterized by a prodromal period of fever, malaise, dysphagia as well as lymphadenopathy, short-lived oral and/or perioral vesicles, widespread oral ulcerations, and generalized marginal gingivitis.<sup>3,11</sup> In healthy individuals, the condition is self-limiting over 7–14 days.<sup>3</sup>

Herpes viruses have the capacity to establish life-long latency in the infected host and to reactivate periodically upon stimulation.<sup>2</sup> Following primary oral infections, HSV-1 migrates centripetally along the nerve tracts from the oral mucosa to the trigeminal ganglion.<sup>1</sup> Although it is unclear how latency is established, it is thought to require an initial viral inoculum of sufficient size to enter and multiply within ganglionic neurones.<sup>2,3,17</sup> The development of latency is probably more influenced by the interaction between host and viral factors than by viral genome expression.<sup>2,3,17</sup> The virus undergoes replication within a minority of ganglionic sensory neurones and forms a genomic reservoir necessary for the persistence of latency throughout the host's lifetime.<sup>2,3,17</sup> Within the ganglion, 4–35% of sensory neurones are reported to be latently infected.<sup>3,17</sup>

Up to 40% of individuals who are HSV-1 seropositive are susceptible to viral reactivation.<sup>4</sup> Several potential outcomes are possible upon interruption of viral latency: asymptomatic viral shedding in the saliva, clinical disease, or rapid viral clearance by the host immune system before either sequela could occur.<sup>1,18,19</sup> In general, viral reactivation leading to asymptomatic viral shedding is referred to as a recurrence, and viral reactivation resulting in clinical disease is known as a recrudescence.<sup>20</sup>

Recrudescence occurs at or near the site of primary infection and is a consequence of centrifugal migration of the reactivated virus from the trigeminal ganglion to the periphery and its local replication.<sup>1,4</sup> Typical internal and external triggers of viral reactivation include stress, physical trauma, operations, menstruation, fever, immunosuppression, corticosteroid administration and ultraviolet (UV) light exposure.<sup>1,3,18,20</sup>

Although recrudescence may present as herpes simplex labialis (HSL) or recurrent intraoral herpes (RIH), HSL is the primary recrudescence disease in healthy individuals.<sup>4</sup> Recrudescence infections generally have few, if any, systemic symptoms. HSL is often preceded by a prodrome of pruritus, tingling, burning or swelling, indicating viral replication at sensory terminals localized to the area of future recrudescence.<sup>1,3–5,12,15,17,18</sup> Viral replication leading

to recrudescence disease primarily occurs in the first 48 h.<sup>18</sup> Nearly 25% of recrudescence lesions abort at the prodromal stage.<sup>15</sup>

Although recrudescence extraoral herpes may affect any site along the involved sensory division of the fifth cranial nerve, the most frequent location is the mucocutaneous junction of the lips (Fig. 1).<sup>1,3,4</sup> Classic lesions are characterized by virally induced epithelial damage and go through different clinical stages.<sup>15</sup> Initially, a transient cluster of microvesicles appears at the site of recrudescence and breaks open to form irregular, superficial erosions that crust over and heal without scarring over a period of 1–2 weeks.<sup>1,3–5,12</sup> Shedding of the virus is often present for several days after resolution of clinical signs and symptoms.<sup>3</sup>

The age, immune status, genetic make-up and site of infection of the host, and the initial dose of viral inoculum and the strain of the virus have been suggested to influence the frequency of recrudescence and asymptomatic viral shedding.<sup>2,8</sup> In total, 5–23% of individuals are reported to experience 12 recrudescences per year and reactivation is less frequent after the age of 35 years.<sup>18,21</sup> Although recrudescence HSL is generally of little consequence in healthy individuals, in whom lesions are limited and minimally painful, frequent episodes may lead to aesthetic concerns, discomfort and stress.<sup>3,17</sup>

Although uncommon in the immunocompetent host, RIH typically presents with a unilateral crop of small vesicles, which break open to leave tiny round ulcers on the palatal mucosa or attached gingiva (Fig. 2,3).<sup>5</sup> The clinical appearance of RIH is often mistaken for recurrent aphthous stomatitis (RAS). Both diseases



**Figure 1** Recurrent herpes labialis in a healthy man. Note crusted lesion affecting the mucocutaneous junction of the lower lip.



**Figure 2** Recurrent intraoral herpes. Note fluid-filled microvesicles on the left palatal mucosa.



**Figure 4** Recurrent aphthous stomatitis. Note multiple, round, superficial ulcers with well-defined erythematous borders affecting the labial and buccal mucosa.



**Figure 3** Recurrent intraoral herpes. Note the superficial erosion resulting from the rupture of small vesicles and coalescing of tiny ulcers on the palatal mucosa.



**Figure 5** Recurrent herpes labialis in an immunocompromised host. Note extensive crusted lesion involving the lower lip vermilion.

have small, well-defined, painful oral ulcerations that resolve spontaneously within 7–10 days. In contrast to RIH, which affects keratinized tissues overlying bone, RAS is not associated with oral vesicles, and predominantly involves movable mucosa (ventral tongue or buccal mucosa) in immunocompetent individuals (Fig. 4).<sup>4</sup> This clinical differentiation is a prerequisite for appropriate therapy and patient counselling.<sup>5</sup> Immunocompromised hosts are at risk for frequent, persistent HSV infections with potential for dissemination and significant morbidity (Fig. 5).<sup>6</sup> These individuals are particularly prone to chronic, severe intraoral herpes affecting both keratinized and non-keratinized tissues.

## Diagnosis

The diagnosis of recrudescing HSL is straightforward based on the reported history, classic location and clinical appearance of lesions.<sup>4</sup> Characteristic HSV-induced viral cytopathy includes intraepithelial vesicles, ballooning degeneration of infected keratinocytes, formation of multinucleated giant cells, eosinophilic viral inclusions, and chromatin margination.<sup>1,5</sup> Laboratory tests such as viral culture, Tzanck smear, direct fluorescent antibody staining, biopsy, and PCR aimed at diagnosis of HSV infection are available, but often reserved for atypical cases and immunocompromised hosts.<sup>2–4</sup>

## Management

HSV infections are highly contagious. Patients should be educated about the infectious nature of herpetic lesions, asymptomatic viral shedding and prevention of viral spread to other sites by autoinoculation or transmission to other individuals.<sup>1,4</sup> Patients should be advised to wash their hands, particularly after application of topical medicaments, to avoid kissing children or partners, and to avoid sharing utensils.<sup>4</sup> A knowledge of potential triggers of viral reactivation such as stress, oral trauma or sun exposure may help patients in avoidance of precipitating factors and pre-emptive application of sunscreens for UV protection or timely application of herpes treatments.<sup>3,4,15</sup>

Essential to a successful therapeutic intervention for HSL is a general assessment of the patient's overall health and the extent of clinical disease.<sup>22</sup> In healthy individuals, recrudescence HSL may be adequately managed by providing symptomatic relief.<sup>3,22</sup> Ice, alcohol, ether, chloroform, lanolin and a variety of over-the-counter products may be used for topical palliation of symptoms.<sup>3,22</sup> Topical medications are best applied gently to the lesions using a cotton-tipped applicator to avoid herpetic infection of the fingers and to prevent increased viral shedding caused by mechanical stimulation.<sup>4,22</sup>

Antiviral agents are indicated for healthy people experiencing frequent, non-aesthetic outbreaks of HSL and for immunocompromised hosts susceptible to severe, persistent recrudescences with potentially morbid outcomes.<sup>3</sup> The available treatments do not cure latent HSV infections but rather palliate symptoms or prevent recurrences. In view of the natural history of HSL and the extent of viral replication in the first 2 days of a recrudescence, timely recognition of clinical disease and early intervention with topical and systemic antivirals are essential for maximum clinical benefit.<sup>15,18</sup>

The drugs used for treatment of HSL are summarized in Table 1. Docosanol 10% cream (Abreva<sup>TM</sup>) and penciclovir 1% cream (Denavir<sup>TM</sup>) are, respectively, over-the-counter and prescription-level topical antivirals used in treatment of HSL in the immunocompetent host.<sup>3,22,23</sup> Docosanol inhibits epithelial cell infection by HSV through its interference with viral attachment.<sup>3,23</sup> In clinical trials, both agents have proven effective in reducing signs and symptoms and time to healing when initiated during the prodrome.<sup>11,23,24</sup> Idoxuridine 15% solution is another topical preparation used early during the onset of symptoms to effectively reduce pain and accelerate

**Table 1** Drugs for recurrent herpes simplex labialis

Topical medications
Docosanol 10% cream* (Abreva <sup>TM</sup> )
Penciclovir 1% cream* (Denavir <sup>TM</sup> )
Aciclovir 5% ointment† (Zovirax <sup>TM</sup> )
Idoxuridine 15% solution*
Cidofovir 1% gel† (Forvade <sup>TM</sup> )
Systemic medications
Valaciclovir 500 mg caplets* (Valtrex <sup>TM</sup> )
Famciclovir 250 mg tablets† (Famvir <sup>TM</sup> )
Intravenous foscarnet† (Foscavir <sup>TM</sup> )
Intravenous cidofovir† (Vistide <sup>TM</sup> )

\*For immunocompetent host; †for immunocompromised host.

resolution of recurrent HSL.<sup>25</sup> Topical and systemic aciclovir in a variety of strengths and dosages, respectively, have been used in the treatment of HSL with variable outcomes.<sup>26</sup> Long-term, prophylactic administration of aciclovir has also proven effective in the prevention of herpetic reactivations in transplant recipients and individuals experiencing herpes-associated erythema multiforme.

Valaciclovir (Valtrex<sup>TM</sup>) and famciclovir (Famvir<sup>TM</sup>) are prodrugs with improved oral absorption compared with their respective active metabolites, aciclovir and penciclovir. The improved bioavailability of these antivirals allows for less frequent dosing and better patient compliance. In clinical trials, both valaciclovir and famciclovir have been efficacious in reducing the duration of an outbreak in immunocompetent and immunocompromised individuals, respectively.<sup>22,27,28</sup>

Foscarnet (Foscavir<sup>TM</sup>) and cidofovir (Vistide<sup>TM</sup>) are administered intravenously. They are known to be highly nephrotoxic and are therefore reserved for treatment of aciclovir-resistant mucocutaneous HSV infections in immunocompromised hosts.<sup>28</sup> A topical preparation of 1% cidofovir gel (Forvade<sup>TM</sup>) has also been found effective against aciclovir-resistant HSV in patients with human immunodeficiency virus.

Experimental and natural treatments such as topical imiquimod 5% cream and systemic ingestion of high-dose lysine or zinc sulphate have also been tried, with limited success, in the management of HSL and its associated symptoms. Clearly, drugs with improved efficacy, more convenient dosing and fewer side-effects are required for managing HSV infections. Helicases are enzymes necessary for viral replication through their action in unwinding the DNA helix.<sup>29</sup> Considerable work on non-nucleoside antivirals such as HSV helicase-primase inhibitors is currently in progress and holds promise for the next generation of anti-HSV drugs with superior efficacy.<sup>29</sup>

### Learning points

- Herpes viruses establish life-long latency in the host.
- Herpes simplex virus (HSV) types 1 and 2 affect orofacial and genital regions, respectively. Cross-over infections are possible.
- Asymptomatic viral shedding contributes to the spread of infection.
- In immunocompetent hosts, intraoral herpes affects the keratinized tissues of the oral cavity.
- Immunocompromised hosts are prone to chronic, severe HSV infections.
- Patient education about the contagious nature of the virus and modes of transmission is essential in the clinical management of herpes simplex labialis (HSL).
- Antiviral agents are typically reserved for healthy individuals experiencing frequent, disfiguring outbreaks of HSL and for immunocompromised hosts.
- Early recognition of signs and symptoms and timely intervention are essential for maximum clinical benefit from antiviral therapy.
- Medications for HSL approved by the US Food and Drugs Administration include topical treatments such as doxycycline and penciclovir creams, and systemic agents such as valaciclovir and famciclovir.

### References

- 1 Blondeau JM, Embil JA. Herpes simplex virus infection: what to look for? What to do! *J Can Dent Assoc* 1990; **56**: 785–7.
- 2 Whitley RJ, Roizman B. Herpes simplex virus infections. *Lancet* 2001; **357**: 1513–8.
- 3 Scubba JJ. Herpes simplex and aphthous: ulcerations, presentation, diagnosis and management. An update. *General Dent* 2003; **51**: 510–16.
- 4 Siegel MA. Diagnosis and management of recurrent herpes simplex infections. *J Am Dent Assoc* 2002; **133**: 1245–9.
- 5 Birek C. Herpes virus-induced diseases: oral manifestations and current treatment options. *J Calif Dent Assoc* 2000; **28**: 911–21.
- 6 Mertz GJ, Benedetti J, Ashley R *et al*. Risk factors for the sexual transmission of genital herpes. *Ann Intern Med* 1992; **116**: 197–202.
- 7 Docherty J, Trimble J, Roman S *et al*. Lack of oral HSV-2 in a college student population. *J Med Virol* 1985; **16**: 283–7.
- 8 Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. *Ann Int Med* 1994; **121**: 847–54.
- 9 Sacks S, Griffiths P, Corey L *et al*. HSV shedding. *Antiviral Res* 2004; **63** (Suppl. 1): S19–S26.
- 10 Ashley RL, Wald A. Genital herpes: review of the epidemic and potential use of type-specific serology. *Clin Microbiol Rev* 1999; **12**: 1–8.
- 11 Whitley RJ, Kimberlin DW, Roizman B. Herpes simplex viruses. *Clin Infect Dis* 1998; **26**: 541–55.
- 12 Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus type 2 and 1: a global review. *J Infect Dis* 2002; **186** (Suppl. 1): S3–S28.
- 13 Nahmias AJ, Lee FK, Beckman-Nahimas S. Sero-epidemiological and sociological patterns of herpes simplex virus infection in the world. *Scan J Infec Dis* 1990; **69** (Suppl.): 19–36.
- 14 Esmann J. The many challenges of facial herpes simplex virus infection. *J Antimicrobial Chem* 2001; **47**: 17–27.
- 15 Turner R, Shehab Z, Osborne K *et al*. Shedding and survival of herpes simplex virus from 'fever blister'. *Pediatrics* 1982; **70**: 547–9.
- 16 Bardell D. Survival of herpes simplex type 1 in saliva and tap water containing some common objects. *Microbios* 1993; **74**: 81–7.
- 17 Sawtell N. comprehensive quantification of herpes simplex virus latency at the single-cell level. *J Virol* 1997; **71**: 5423–31.
- 18 Spruance SL, Overall JC, Kern ER *et al*. The natural history of recurrent herpes simplex labialis: implications for antiviral therapy. *N Engl J Med* 1977; **297**: 69–75.
- 19 Spruance SL. Pathogenesis of herpes simplex labialis: excretion of virus in the oral cavity. *J Clin Microbiol* 1994; **19**: 165–9.
- 20 Norval M. Herpes simplex virus, sunlight and immunosuppression. *Rev Med Microbiol* 1992; **3**: 227–34.
- 21 Straus S, Rooney J, Sever J *et al*. Herpes simplex virus infection: biology, treatment and prevention. *Ann Intern Med* 1985; **103**: 404–19.
- 22 Huber MA. Herpes simplex type-1 virus infection. *Quintessence Int* 2003; **34**: 453–67.
- 23 Sacks SL, Thisted RA, Jones TM *et al*. Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis. A multicenter, randomized, placebo-controlled trial. *J Am Acad Dermatol* 2001; **45**: 222–30.
- 24 Spruance SL, Rea TL, Thoming C *et al*. Penciclovir cream for the treatment of herpes simplex labialis: a randomized, multicenter, double-blind, placebo-controlled trial. *J Am Med Ass* 1997; **277**: 1374–9.
- 25 Spruance SL, Stewart CB, Freeman DJ *et al*. Early application of topical idoxuridine in dimethyl-sulfoxide shortens the course of herpes simplex labialis: a multicenter, placebo-controlled trial. *J Infect Dis* 1990; **161**: 191–7.
- 26 Raborn GW, McGaw WT, Grace M *et al*. Treatment of herpes labialis with acyclovir. Review of three clinical trials. *Am J Med* 1988; **85**: 39–42.

- 27 Spruance S, Jones T, Blatter M *et al.* High-dose, short-duration, early valcyclovir therapy for episodic treatment of cold sores: results of two randomized, placebo-controlled, multicenter studies. *Antimicrob Agents Chemother* 2003; **47**: 1072–80.
- 28 Chilkuri S, Rosen T. Management of acyclovir-resistant herpes simplex virus. *Dermatol Clin* 2003; **21**: 311–20.
- 29 Frick DN. Helicases as antiviral drug targets. *Drug News Perspect* 2003; **16**: 355–62.