Human herpes simplex virus infections: Epidemiology, pathogenesis, symptomatology, diagnosis, and management

Mahnaz Fatahzadeh, DMD,[a] and Robert A. Schwartz, MD, MPH[b]
Newark, New Jersey

Eight of the more than 80 known herpesviruses are human pathogens. Human herpes simplex virus (HSV) is a contagious infection with a large reservoir in the general population. It has a potential for significant complications in the immunocompromised host. In addition, psychological distress caused by the negative stigma associated with genital herpes and visible facial lesions in those experiencing frequent outbreaks renders it a challenging clinical dilemma. This article reviews the epidemiology, pathogenesis, and diagnostic features of HSV infections, providing the clinician with an up-to-date understanding of the available management strategies for mucocutaneous HSV-induced disease. (J Am Acad Dermatol 2007; 57:737-63.)

Learning objectives: At the conclusion of this learning activity, participants should understand the structure and biological properties of human herpesviruses; understand the transmission and epidemiology of human HSV infections; understand the spectrum, pathogenesis, and symptomatology of HSV disease affecting humans; understand the diagnostic features and methodologies employed in clinical practice to diagnose herpes simplex infections; and understand the available management strategies for mucocutaneous HSV-induced disease.

INTRODUCTION

More than 80 herpesviruses have been identified, 8 of which are known human pathogens.[1-3] Herpes simplex viruses belong to the ubiquitous Herpesviridae family of viruses, which comprises herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), varicella zoster virus, cytomegalovirus, Epstein-Barr virus as well as human herpesviruses 6 and 7 and Kaposi's sarcoma–associated herpesvirus (type 8).[4-6] HSV-associated diseases are among the most widespread infections, affecting nearly 60% to 95% of human adults.[7,8] They are incurable and persist during the lifetime of the host, often in latent form. Their clinical manifestations are variable and influenced by the portal of viral entry, degree of host immune competence as well as primary or secondary nature of the disease.[8] Clinical presentations of HSV infection range from asymptomatic infection to mucocutaneous conditions such as orolabial, ocular, and genital herpes, herpetic whitlow, herpes gladiatorum, and eczema herpeticum as well as central nervous complications such as neonatal herpes and herpetic encephalitis and fatal dissemination, a particular threat in the immunosuppressed host.[8-10]

Abbreviations used:

DFA:	direct fluorescent antibody
EM:	erythema multiforme
gG1:	glycoprotein 1
gG2:	glycoprotein 2
HAEM:	herpes-associated erythema multiforme
HSL:	herpes simplex labialis
HSV:	herpes simplex virus
Kbp:	kilo base pair
KVE:	Kaposi's varicelliform eruption
PCR:	polymerase chain reaction
PHGS:	primary herpetic gingivostomatitis
RIH:	recurrent intraoral herpes
TK:	thymidine kinase
TMA:	thrombotic microangiopathy

EPIDEMIOLOGY

Structure and biological properties

All human herpesviruses measure approximately 200 nm in diameter and contain a linear, double-stranded DNA core of approximately 150 kilo base pair (Kbp) enclosed within a protein capsid, covered

From the Departments of Oral Medicine, New Jersey Dental School,[a] and Dermatology & Pathology, New Jersey Medical School.[b]
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Reprint requests: Mahnaz Fatahzadeh, DMD, Assistant Professor of Oral Medicine, New Jersey Dental School, 110 Bergen Street, Newark, NJ 07103. E-mail: fatahza@umdnj.edu.
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by a tegument and a glycoprotein-containing envelope.[4,5,9,11-13] The expressed pattern of alpha, beta, and gamma genes respectively control translation of viral genome, transcription of proteins essential for viral DNA synthesis, and collection/exit of viral particles from the infected cell.[4] HSV 1 and 2 are considered less aggressive than other human herpesviruses on the basis of their virulence potential in tissue culture demonstrated as viral cytopathy.[12] Although HSV-1 and HSV-2 serotypes share similarities in their DNA sequence, they are antigenically distinct because of their different envelope proteins.[3,14,15]

Biological features unique to herpesviruses include latency and reactivation.[4,5,10,11,16,17] Initial exposure to herpesviruses often leads to viral invasion of epithelial cells and intracellular replication at the site of primary exposure. Irrespective of clinical symptomatology, after primary infection, herpesviruses ascend in a retrograde manner through the periaxonal sheath of sensory nerves to the trigeminal, cervical, lumbosacral, or autonomic ganglia of the host nervous system.[11,13,18,19] There, virus replicates, is sequestered from the host immune surveillance, and persists in a dormant state for life.[4,5,9-11,20] The trigeminal and sacral ganglia are the most common location for HSV1 and HSV2 latency, respectively.[20-24]

Chronic latency predisposes the host to recurrent attacks through viral reactivation and increases the potential for viral transmission.[9-11] Recurrent HSV is not a reinfection, but rather is the result of periodic viral reactivation.[20] Once reactivated, virus travels along sensory neurons to the innervated mucocutaneous sites, undergoes replication, and leads to the formation of a cluster of vesicles in the vicinity of the initial anatomic site of exposure.[4,5,11,12,16,17,25-28] HSV reactivation may also lead to asymptomatic viral shedding in the absence of clinical disease.[5,29-33] In general, viral reactivation producing asymptomatic viral shedding is referred to as a recurrence, whereas viral reactivation resulting in clinical disease is known as a recrudescence.[34] Despite the distinction between recurrence and recrudescence in the basic virology literature, most clinicians imprecisely tend to refer to clinical outbreaks as recurrences.

Although spontaneous recurrences are possible, a wide variety of internal and external triggers may lead to transformation of the herpesvirus from a dormant to a proliferative state.[3,9,10,12] These include psychological stress; fatigue; exposure to heat, cold, or sunlight; menstruation; sexual intercourse; fever; immunosuppression; corticosteroid administration; laser surgery; local tissue trauma; nerve damage; and change in antiviral activity of the saliva.[5,9,11-13,25,26,35-38]

Demographics

HSV1 accounts for the majority of nongenital HSV-induced infections in humans,[39] with 45% to 98% of the world population and 40% to 63% of the people in the United States reportedly HSV1 seropositive.[32,40-42] Worldwide HSV1 prevalence varies with age, race, geographic location, and socioeconomic status; a higher rate of seropositivity has been reported for less industrialized countries.[11,26,43-47] By the age of 60, 60% to 85% of adults in the United States demonstrate HSV1 seroconversion.[46,48] Incidence is not seasonal.[11]

In the United States, acquisition of HSV1 infection is strongly influenced by race, with 35% of black 5-year-old children demonstrating HSV1 serum antibodies versus 18% of white 5-year-old children.[11] In the lower socioeconomic populations in the United States, HSV1 affects nearly 33% of children by the age of 5 years and 70% to 80% by late puberty.[11,26,46,49] In contrast, US children living in improved socioeconomic conditions acquire HSV infection later in life with a seroprevalence of only about 20% before 5 years of age and 40% to 60% by early adulthood.[11,46,49,50]

HSV-induced disease, in particular, HSV2 infection, is the most prevalent cause of genital ulcerations of a sexual nature worldwide.[51-54] In the United States, it is estimated that 50 million individuals have genital herpes; half a million new symptomatic cases of genital HSV infections occur annually.[53-56] Over the past 30 years, HSV2 seroprevalence has increased dramatically with 20% to 25% of US adults testing positive for HSV2 antibodies by the age of 40.[7,57]

Risk factors for genital HSV infection include older age, female gender, black race, poor socioeconomic status, low level of education, prior sexually transmitted disease, early age at first intercourse, and a higher number of lifetime sexual partners.[57-59] Prepubertal detection of HSV2 antibodies is rare. Prevalence of HSV2 seropositivity is strongly correlated with sexual maturity and promiscuity.[32,58,59]

Prevalence of HSV2 antibodies is reported to be higher in women.[7,60,61] Antibodies against one type of HSV (eg, HSV1) provide cross-immunity, ameliorating the severity, duration, and frequency of a subsequent infection by a different serotype (eg, HSV2).[3,9,24,26,50,62,63] HSV1-seropositive females have a 5% to 20% lower likelihood of HSV2 seroconversion per year than women who are HSV1 seronegative.[64]

Transmission

The principal mode of acquisition is through direct exposure of mucous membranes or abraded skin to the lesions or mucosal secretions of an

individual with active primary or recurrent infection.[3,5,9,12,16,17,26,36,65-67] Virus can also be transmitted by respiratory droplets or exposure to mucocutaneous secretions of an asymptomatic person shedding the virus in the absence of clinical disease.[3,5,9,12,29-33,64,68]

HSV1 is primarily associated with oral, pharyngeal, facial, ocular, and central nervous system infections and largely transmitted by oral secretions and nongenital contact.[3,5,8,10,11,67,69,70] Sixty-seven percent of those with herpes simplex labialis (HSL) are reported to have HSV1 on their hands, indicating the likelihood of horizontal spread.[29] HSV1 can remain viable on the skin, clothing, or plastic for brief periods, facilitating transmission through close nonsexual contact, such as kissing on the cheeks or sharing common utensils.[15,29,43] HSV2 is frequently involved with anal and genital infections and is mainly transmitted sexually by genital secretions.[3,5,8,10,11,69,70] The risk of HSV2 transmission through oral shedding and intimate nonsexual contact is minimal.[59]

Two types of initial symptomatic presentations are possible for HSV infection.[3] A true primary HSV infection refers to the first episode of herpes in an HSV1- or HSV2-seronegative individual.[3,53,71] A nonprimary infection refers to acquisition of one type of HSV by a person already infected with the other type.[3,24,53,71] True primary infections are more severe, often associated with constitutional signs and symptoms as well as longer duration of viral shedding.[3,24,48,53] Analysis of acute and convalescent sera for anti-HSV antibodies is helpful in the differentiation of primary from nonprimary herpetic infections.[53,69,72] More specifically, high levels of IgM are consistent with a primary infection; while elevated, acute levels of IgG are suggestive of a nonprimary infection.

PATHOGENESIS AND SYMPTOMATOLOGY

Primary herpetic gingivostomatitis

Irrespective of the viral type, HSV primarily affects skin and mucous membranes.[11] Primary herpetic gingivostomatitis (PHGS) is the most common orofacial manifestation of HSV1 infection and is characterized by oral and/or perioral vesiculoulcerative lesions.[8,73] PHGS typically develops after first-time exposure of seronegative individuals or those who have not produced adequate antibody response during a previous infection with either of the two HSVs.[10,11,13] A majority of infections are subclinical.[8] Although PHGS typically affects children between the ages of 1 and 5 years, occasional cases of primary infection affecting adults also occur.[9,16,25,36,74] Infants are passively protected through maternal immunity for the first 6 months of life.[26,69]

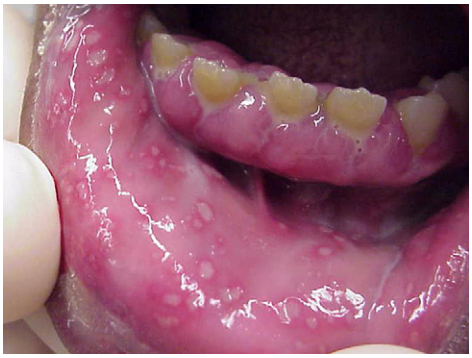

Fig 1. Primary herpetic gingivostomatitis in a young child. Note intense gingival inflammation and multiple round ulcers on labial mucosa.

Although both HSV1 and HSV2 may lead to primary oral infection, nearly all are caused by HSV1.[2,8,75] The majority of HSV1-induced primary orofacial infections are subclinical and, therefore, unrecognized.[16,26,49,69] Symptomatic PHGS is typically preceded or accompanied by a sensation of burning or paresthesia at the site of inoculation, cervical and submandibular lymphadenopathy, fever, malaise, myalgia, loss of appetite, dysphagia, and headache.[9,10,12,13,25,69,72] One or 2 days later, numerous, transient vesicles appear on movable and nonmovable oral mucosa and rapidly rupture to cause painful, superficial ulcerations in and around the oral cavity (Fig 1).[9,12,25,26,69] The most characteristic presentation is acute, generalized, marginal gingivitis with the inflamed gingiva appearing erythematous and edematous.[12,13,25,72] In young adults, pharyngitis and a mononucleosis-like syndrome may herald the onset of primary oral infection with HSV1.[49]

In healthy individuals, primary infection has an excellent prognosis with recovery expected within 10 to 14 days.[12,25] Intraoral viral shedding, however, persists for several weeks after clinical resolution.[12,50,72] HSV1 serum antibodies rise in a few weeks after the exposure, but do not provide protection against viral reactivation.[50]

Recurrent orofacial herpes

After primary infection, latent HSV reactivates periodically, migrating from the sensory ganglia to cause recurrent oral or genital herpes.[17,36,69,76] Although HSV2 may occasionally cause primary oral infection, HSV-2-induced recurrent orofacial disease (recurrent herpes labialis, recurrent intraoral herpes) is rare.[36,75,77,78] Despite the high prevalence of HSV1 in the population, only 15% to 40% of seropositive patients ever experience symptomatic

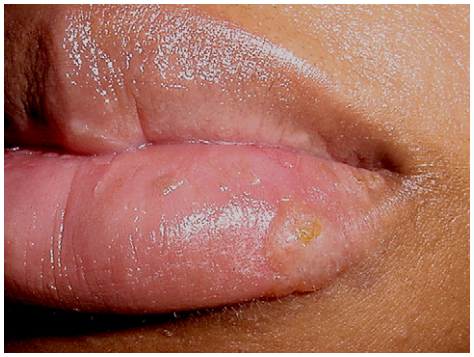

Fig 2. Recurrent herpes labialis in a healthy individual. Note crusted lesion affecting vermilion border.

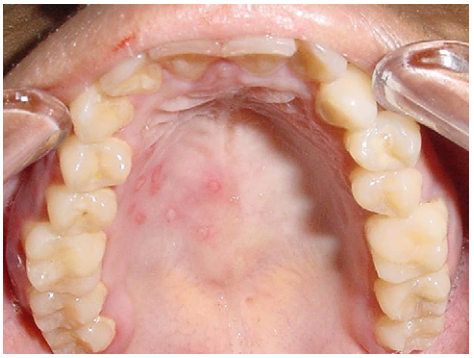

Fig 3. Recurrent intraoral herpes. Note cluster of small, symptomatic ulcers caused by the rupture of transient vesicles on keratinized tissue of the right palate.

mucocutaneous recurrence.[20,21,40,45,68,69,72,78-81] An individual's genetic susceptibility, immune status, age, anatomic site of infection, initial dose of inoculum, and viral subtype appear to influence frequency of recurrence.[5,11,47,75,82] Reactivation appears to become less frequent after the age of 35.[83]

Compared with primary infections, recurrent episodes are milder and shorter in duration with minimal systemic involvement.[9,25,42,50] The severity of recurrent facial herpes infection covers a broad spectrum, ranging from minimal discomfort to extensive, symptomatic, unsightly involvement of the lips, cheeks, nose, and nasal septum.[49,84] In healthy hosts, recurrent lesions remain localized to the mucodermatome of primary infection and often lead to mild discomfort.[12,16,72] Nevertheless, frequent outbreaks are associated with significant morbidity, inconvenience, pain, cosmetic disfigurement, and psychological distress.[5,9,25]

Herpes simplex labialis (HSL), also known as fever blisters or cold sores, is the predominant form of recurrent orofacial herpes.[12,50,79,80,85-87] HSL recurrence is 3 times more frequent in febrile patients than in those without fever.[11] Although most patients suffer two or less attacks per annum, 5% to 10% experience a minimum of 6 outbreaks each year.[85]

HSL typically affects the outer vermilion border and adjacent cutaneous region.[12,63] In as many as 60% of patients, recurrence of herpes labialis is preceded by a prodrome of focal pain, burning, pruritus, or tingling at the site of future lesion development.[9,10,12,15,16,26,36,63,81,87,89,90] Prodromal symptoms last nearly 6 hours and represent early viral replication localized to sensory nerve endings innervating the mucocutaneous dermatomes.[26,36,81,88] Almost one fourth of recurrences abort at the prodromal stage.[36] In classic cases, however, multiple vesicles appear within 24 hours of the prodrome, coalesce, and rupture to form tender superficial erosions which rapidly crust over (Fig 2).[12,25,84] Pain and discomfort are worse during the first few days; lesions heal without scarring in less than 2 weeks.[26,84] Viral shedding, however, continues for 3 to 5 days after the lesions have resolved.[9]

Recurrent herpes infection may also be first evident within the oral cavity, sometimes associated with traumatic dental procedures such as local anesthetic injection or dental extraction.[50,91,92] In an immunocompetent host, recurrent intraoral herpes (RIH) is less common than HSL.[90] RIH typically affects keratinized tissues of the hard palate and attached gingiva innervated by the greater palatine and buccal nerves, respectively.[12] Fragile vesicles often develop unilaterally in the mandibular and maxillary molar and premolar region without crossing the midline.[12,73] Intraoral vesicles quickly rupture to form multiple, small, tender erosions which coalesce into irregular, superficial ulcerations (Fig 3). Prodromal symptoms are less frequently experienced with intraoral recurrences, and intact vesicles are uncommon in the oral cavity.[25]

A less frequent location for intraoral recurrence is the dorsal tongue.[12] RIH may occasionally affect atypical sites such as buccal mucosa or floor of the mouth and mimic a primary infection.[91,93] Intraoral recurrent lesions affecting nonkeratinized tissues are more symptomatic and tend to last longer than those affecting classic sites.[50] In healthy people, the natural history of intraoral HSV follows that of HSL with uneventful resolution of lesions within 2 weeks.[25]

Genital herpes

Genital ulcerations may be caused by either HSV1 or HSV2.[53] Clinical manifestations are variable, ranging from asymptomatic to mild or severe signs and symptoms with potential complications such as

urinary retention, meningitis, and psychological morbidity.[3,37,94,95] Studies reveal that the majority of HSV2 infections are subclinical and unrecognized by those infected.[24,31,57] Classic primary infection is preceded by a prodrome of localized pain, tingling, or burning sensation lasting up to 24 hours.[3] Systemic signs and symptoms, such as headache, fever, malaise, and inguinal lymphadenopathy, are often present.[37] Within a few days of sexual contact, vesicles of varying sizes erupt on the labia minora, introitus, and urethra meatus in women and on the shaft and glans of the penis in men (Fig 4).[3,8] In women, cervical lesions hidden from the view are common during primary infections.[3] Perineum, thighs, and buttocks may also be affected in both sexes.[37] Vesicles gradually rupture to form irregular ulcers and erosions which crust over and heal without scarring.[95]

Involvement of a larger area or facilitation of viral spread over moist female genitalia may predispose women to more severe clinical manifestations.[3] Women also experience more systemic symptoms and are more prone to complications such as aseptic meningitis or dysuria.[3] Meningitis is a serious complication affecting 10% of men and 30% of women with primary HSV infections.[94] Primary HSV lesions heal over 2 to 6 weeks, but viral shedding may persist longer.[3,71,95] Autoinoculation to other anatomic sites are possible, especially during or after a primary genital infection when circulating antibodies are absent or still rising.[3]

Following the initial infection, virus becomes latent in the regional sensory or autonomic ganglia until later reactivation.[3] Reactivation of latent HSV2 may lead to a subclinical recurrence or a symptomatic mucocutaneous outbreak.[24,26] Although recurrences may occur spontaneously, certain stimuli may also trigger viral reactivation.[3,37,38] In contrast to primary infections, recurrent episodes are milder and more localized, and associated viral shedding is less intense and briefer in duration.[3,22] Frequency of HSV2 recurrence and asymptomatic viral shedding vary among different people and within a given person over time.[3,24,96] Symptomatic outbreaks are particularly frequent in people experiencing a severe primary infection.[23] Symptomatic recurrences are more frequent in men,[3,23] which partially explains the greater efficiency of HSV2 transmission from men to women by increasing infectiousness.[23,64]

HSV types 1 and 2 can cause infections in a number of body sites or establish latent infections in sensory ganglia.[8,32] Although primary infections are possible with HSV2 in the oral cavity and HSV1 in the genital region, isolated oral HSV2 infection is rare and oral HSV2 lesions typically manifest in association with clinically symptomatic primary genital herpes.[75,97] HSV2 is the most common cause of genital herpes; however, an increasing number of primary episodes in the genital region has been attributed to HSV1.[48,52,98] The prevalence of HSV1 genital herpes varies geographically, accounting for nearly half of the new cases in some European countries.[52,76,99-103] Primary genital HSV1 infections are more frequent in women[48,52,53] and often symptomatic, leading to a greater awareness of one's infectious status.[104]

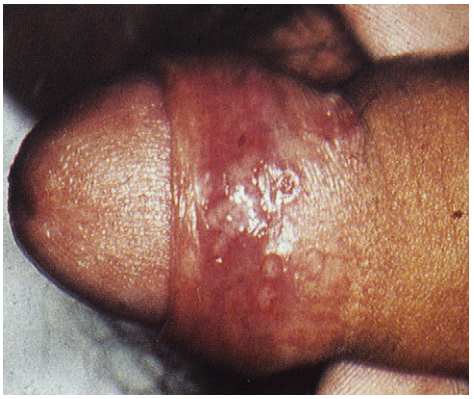

Fig 4. Genital herpes in an immunocompetent male.

It is speculated that improvement in the socioeconomic status, delayed exposure to HSV1, and varying sexual practices may explain the increase in the contribution of HSV1 to primary genital infections in certain geographical settings.[48,52] In other words, oral HSV1 infection during childhood may protect against future genital HSV1 exposure or render its acquisition subclinical.[52] This concept is further supported by the low rate of clinical HSV1-associated genital herpes among US nonwhite minorities, who exhibit a higher rate of oral HSV1 acquisition during childhood.[52] This also suggests that HSV1 seronegative individuals engaged in orogenital sex are at a greater risk for genital HSV1 infection.[52] Silent HSV2 seroconversion occurs more frequently in individuals with prior HSV1 immunity.[52,53,66,105,106]

The clinical presentation of HSV2-induced oral lesions closely resembles those caused by HSV1.[8,68] Similarly, primary HSV1 and HSV2 genital diseases are clinically indistinguishable in appearance, severity, and duration.[8,48,94] These viral subtypes, however, differ in epidemiology, natural history, and propensity for recurrence.[23,67] HSV1-induced genital infections are typically milder and less recurrent compared with those caused by HSV2.[11,24,26,42,52,107] HSV2-induced genital herpes is 6 times more frequent than those caused by HSV1.[95] In contrast, a majority of oral herpes reactivations are

caused by HSV1; HSV2 recurrence in the oral cavity is uncommon.[23,75,94] Studies suggest a greater likelihood for the transmission of HSV1 to the genitals compared with the transmission of HSV2 to the orolabial region.[108]

After the initial infection, infected individuals may periodically shed HSV from multiple anatomic sites irrespective of the clinical symptoms.[60,76] The frequency of symptomatic and subclinical reactivation as well as the magnitude of viral shedding may be affected by the viral strain, initial dose of inoculum, anatomic site of infection, host's genetic make-up, and immune status as well as time since acquisition.[5,60,76,82] The rate of symptomatic recurrence and subclinical viral shedding increases with immunosuppression[76] and decreases with time since the primary infection.[24,76,96,107] Ten years after the acquisition of infection, the risk of shedding is 70% less than the risk during the initial 6 months after infection.[76]

The rate of subclinical HSV2 shedding is not influenced by the history of symptomatic genital reactivation.[76] Asymptomatic viral shedding is of shorter duration in the absence of clinical symptoms than shedding when active lesions are present.[105] Several studies suggest the magnitude of viral shedding and risk of transmission are greater during clinical disease than asymptomatic periods.[9,66,67,109] However, HSV2 detection by polymerase chain reaction (PCR) reveals that the amount of HSV2 DNA shed during symptomatic and subclinical viral reactivation is comparable.[59] The detection of subclinical shedding is influenced by the duration of sampling, viral detection system utilized, and the anatomic areas sampled.[59,105] Studies focused on the relationship between shedding frequency, HSV DNA titer detected by PCR, and transmission have led to conflicting results.[110,111] Clearly, viral shedding contributes to transmission; however, the infectious amount of HSV DNA required for transmission is not yet known.[59,76]

Oral shedding of HSV1 may occur independent of clinical recurrence[112] and may contribute to anogenital HSV1 transmission during oral sex.[105] Asymptomatic shedding of HSV1 in saliva measured by PCR is reported to occur 4.7% of the time.[92] Interestingly, recurrent oral herpes infection may be prevented by both anti-HSV neutralizing properties as well as IgA and IgG antibodies in saliva.[113-119]

Subclinical viral shedding is also a serious concern with genital herpes, increasing the risk of transmission to the uninfected sexual partners.[120] Common genital sites of subclinical viral shedding include penile skin, urethra, and perianal areas in men and vulva, urethra, cervix, and perineum in women.[107] The overall genital HSV2 shedding appears to be equivalent for both sexes.[31] Women with a history of genital herpes are thought to shed HSV2 up to 28% of days.[62] Additionally, HSV2-associated subclinical shedding from the genital tract occurs at a greater rate compared with genital HSV1 infections in men and women.[23,24,76,107] The lower rate of clinical recurrence and asymptomatic shedding for HSV1-associated genital herpes may reflect a serotype-specific pathogenesis.[105]

Asymptomatic viral shedding from nongenital sites is also possible.[107,121] Although infrequent, oral shedding of HSV2 may occur in association with primary or recurrent genital infection and often in the absence of oral lesions.[122] Viral shedding in the absence of clinical symptoms or in people unaware of their infectious status accounts for almost 70% of all genital HSV2 infections.[24,59,64,123] Women are at a greater overall risk of acquiring genital herpes and, in particular, HSV1-induced genital disease compared with men.[48,59,64] Viral transmission is also more than 4 times more likely from male to female than vice versa.[124] These observations may suggest men and women differ in anatomic susceptibility for HSV transmission.[60]

Primary and possibly recurrent HSV1 infections may spread to the face, nasal, ocular, and genital mucosa, or digits by dissemination or autoinoculation.[36,125] "Autoinoculation" refers to the process of self-infection by a virus already present in the affected individual, leading to the involvement of peripheral nerve endings at the site of infection and retrograde transport of the virus to the involved ganglia.[125] Autoinoculation occurs via a portal of entry in the healthy skin and subsequent clinical disease resembles that of a typical herpetic outbreak.[125] The likelihood of autoinoculation is far greater with primary than a recurrent HSV1 infection.[36,125]

Eczema herpeticum

Dissemination of oral or perioral HSV infection may complicate a cutaneous burn, preexisting atopic dermatitis, or cosmetic procedures in the head and neck region, giving rise to a serious, progressive condition known as eczema herpeticum or Kaposi's varicelliform eruption (KVE).[9,36,125-128] KVE has an acute onset of extensive, unsightly, vesiculoulcerative nodules and plaques clinically resembling impetigo.[9,16] Monomorphic vesicles and pustules coalesce into large superficial erosions which are susceptible to superinfection by cutaneous bacteria.[9,125] Patients may also experience fever, malaise, and other constitutional symptoms.[125] In KVE, herpetic lesions directly spread to a diseased or irritated cutaneous region, bypassing the nerve endings and

ganglion.[125] As dissemination is not true inoculation, viral latency, periodic reactivation, and clinical recurrence are not expected sequelae.[125] Crusting and healing occurs in about 1 month.[9]

Herpes gladiatorum

Inoculation of HSV1 through abraded skin of athletes engaged in contact sports such as wrestling, rugby, and soccer may precipitate herpes gladiatorum or wrestler's herpes.[5,9,36,129,130] The latter is characterized by cutaneous eruptions on the face, ears, and neck within 2 weeks of direct skin-to-skin contact.[9,16] Ocular and systemic manifestations may be seen, as may cutaneous recurrence.[5,9,16,129,130] Outbreaks of herpes gladiatorum may lead to exclusion of athletes from sports events and necessitate prophylactic antiviral therapy throughout the sport season.[8,131]

Herpetic whitlow

Herpetic whitlow refers to the cutaneous herpetic infection of the pulp of the hand's distal phalanx often affecting healthcare workers, children with primary oral herpes (Fig 5) and adults with genital HSV infection.[5,9,32,127,132,133] It results from direct inoculation of the involved digit through the abraded skin by either HSV1 or HSV2.[127,132,133]

In young children, herpetic whitlow is often associated with HSV1 autoinoculation through finger or thumb sucking during primary herpetic gingivostomatitis.[8,133] Affected children are usually 1 to 3 years of age; a typical outbreak lasts a few weeks.[16,133,134] In adolescents and the general population, herpetic whitlow is frequently associated with digital-genital contact.[133,135,136,137]

Herpetic whitlow has been predominantly a problem of healthcare workers.[36,138] In health professionals, herpetic whitlow is often the result of exposure of a digit on the dominant hand to the patient's active oral or genital lesions or infected secretions in asymptomatic carriers.[5,8,50,69,132,133,139-141] Although primary exogenous inoculation with HSV1 is a frequent cause of herpetic whitlow in healthcare professionals,[135,136,142] the routine use of disposable gloves has altered the epidemiology of herpetic whitlow from HSV1 to HSV2.[32,143] Herpetic whitlow is now more commonly associated with HSV2 exposure from digital/genital contact.[32,136]

Herpetic whitlow is clinically associated with swelling, erythema, nonpurulent vesicular eruptions, shallow erosions, and severe local pain in the affected dermatome.[9,132,133] Symptomatic neuritis in the affected finger and forearm is also possible.[16] Herpetic whitlow should be differentiated from bacterial felon or paronychia.[133] It is a self-limiting condition for which surgical intervention is not necessary.[8,132,133] Although usually not necessary, antiviral therapy may benefit patients with extensive disease.[8] Herpetic infections of digits typically heal over 3 to 4 weeks but may recur.[16] A majority of recurrent episodes involve adults 20 to 40 years of age.[139] Their frequency of recurrence is less compared with orolabial and genital herpes.[139] Most recurrences may be triggered by stimuli and are often preceded by prodromal symptoms.[139] A female-to-male predominance with respect to recurrent herpetic whitlow has been described and may reflect a greater predisposition to infection or help-seeking behavior in women.[94,133,137,139]

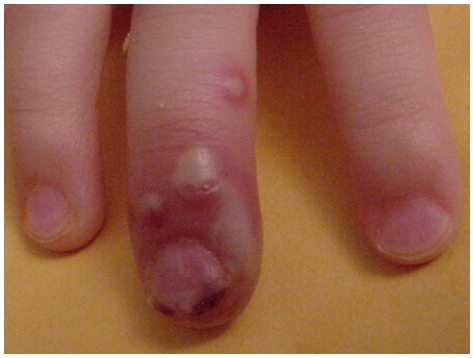

Fig 5. Primary herpetic whitlow on middle finger of a 2-year-old child with concurrent primary oral herpes. Note erythema, vesicular eruptions, and crusted ulceration on affected digit.

Ocular herpes

Ocular HSV infection is a predominant cause of corneal blindness in the United States.[2,8,75] Studies report that 22% of patients with ocular herpes have concurrent primary oral HSV infection and nearly 58% report a prior history of primary herpes in the oral cavity.[36,144] Ocular HSV inoculation may lead to unilateral or bilateral keratoconjunctivitis, recurrent ocular ulcerations, and sight impairment necessitating prompt antiviral therapy.[5,8,9,11,50,145,146]

Other potential complications of HSV infection include neonatal herpes, fatal meningoencephalitis, or disseminated disease in the immunocompromised person.[5,10,11,74,147]

Neonatal herpes

Neonatal herpes is a devastating and often fatal consequence of vertical transmission of HSV to neonates.[8,123] HSV-infected infants are often premature and of low birth weight.[148] Neonates may acquire HSV infections in utero, intrapartum, or

postnatally; of these, intrapartum transmission is predominant.[8,11,16,50,148]

Neonatal infections may arise from direct exposure of the baby to maternal lesions or secretions infected by asymptomatic viral shedding during vaginal birth.[8,9,16,26,149] HSV transmission to neonates may also occur transplacentally or through contact with infected healthcare workers or family members in the postpartum period.[8,9,36,148] Nearly 10% of infections are attributed to postnatal HSV exposure.[150]

Congenital HSV infection is rare[11] and may lead to microcephaly, hydrocephalus, retinitis, and cutaneous vesicular eruptions.[151] Natally acquired HSV infections are often symptomatic and cover an spectrum of manifestations with different prognoses.[11,16,152-154] These include neonatal disease limited to the skin, eyes, mouth; neonatal encephalitis; and disseminated disease involving liver, lung, and other vital organs.[11,16,152-154]

The initial signs and symptoms of presentation of neonatal herpes are often nonspecific.[148] Even with therapy, mortality rates are high in neonates with HSV encephalitis or disseminated disease,[148] and surviving infants are often neurodevelopmentally disabled.[154] Therefore immediate and intense therapeutic interventions with antivirals are highly indicated.[155,156]

An increased risk for both acquisition and transmission of HSV infections between patients and providers of oral health care has been documented.[40,138,143,157] A particular concern is the potential for HSV1 transmission from the healthcare provider to neonates or immunocompromised patients.[36] Education of the health professionals about the modes of transmission and implementation of universal precautions and effective hygiene guidelines may reduce the risk of HSV-induced mucocutaneous infections.[5,36] The American Academy of Pediatrics recommends that healthcare professionals with clinically visible facial lesions should refrain from patient contact.[158] However, the issue of avoiding HSV transmission during periods of asymptomatic shedding remains unresolved.[36]

Neonatal transmission is of less concern if infection is acquired in the first or second trimesters.[159] Pregnant females contracting primary genital HSV late in term are at a greater risk for the transfer of infection to the baby than those having recurrent disease.[52,160-162] Cesarean deliveries are considered when a mother experiences primary genital herpes or symptomatic outbreaks near or at the time of delivery.[163,164] It has been argued that in the absence of active lesions of recurrent genital herpes and in the presence of protective, maternal transplacental antibodies, the risk of viral transmission to neonate is minimal, not justifying caesarean delivery.[9,165]

Twenty percent of pregnant women are reported to be HSV2 seropositive, with only 5% verifying a symptomatic episode by history.[166] A challenging issue is the propensity for transmission during subclinical viral shedding from the uterine cervix in the absence of clinical disease.[16,149] Studies report that HSV2 accounts for nearly 70% of cases of neonatal herpes,[123] a majority of which are due to intrapartum asymptomatic viral shedding in mothers without any signs or symptoms of genital herpes.[8,49,104,105,150,167] Asymptomatic primary genital herpes accounts for viral shedding during early labor in about 30% of women whose infants are are also 10x more at risk for neonatal herpes compared to those with HSV reactivation in the absence of clinical disease.[161]

The risk of neonatal transmission is higher in younger females, maternal HSV seronegativity, genital HSV1 infection, premature delivery before 38 weeks of gestation, and viral shedding from the cervix.[162,168] Neonatal HSV1 transmission occurs with high efficiency and may explain the increasing incidence of HSV1-induced neonatal infections.[168]

The type of HSV involved and the neonatal disease classification may influence the outcome of neonatal infection.[162] Babies with HSV1-associated cutaneous, ocular, and oral disease fare better than those with HSV2-associated cutaneous involvement.[162] Similarly, infants with HSV1-associated encephalitis suffer less neurological morbidity compared with those with HSV2 infection.[162] In contrast, HSV1-induced disseminated disease leads to more significant sequelae than HSV2.[162]

Although not evaluated in large clinical trials, several preventive strategies have been recommended to reduce the risk of neonatal transmission:

1. Identification of those at risk for neonatal HSV transmission by thorough questioning of the pregnant female and her partner about their HSV history at the first prenatal visit[148]
2. Recommendation of sexual abstinence, protective condoms, or prophylactic antivirals in the context of a sexual relationship between an HSV2-seropositive male and an HSV2-seronegative female[53,123]
3. Suppression of HSV reactivation with antivirals from 36 weeks of gestation in HSV2-seropositive pregnant females at high risk for an active HSV outbreak at the time of labor[169]
4. Antiviral treatment of pregnant females with an active primary or recurrent genital outbreak near or at the time of delivery[148,169,170]

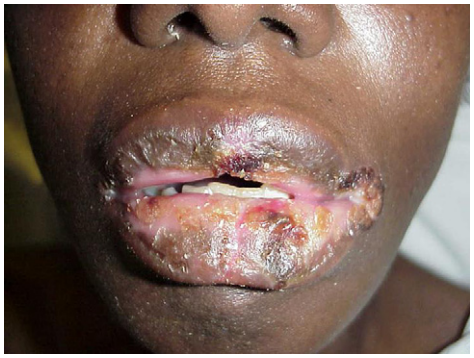

Fig 6. Recurrent herpes labialis in an immunocompromised host. Note extensive disease affecting the vermilion border of upper and lower lip.

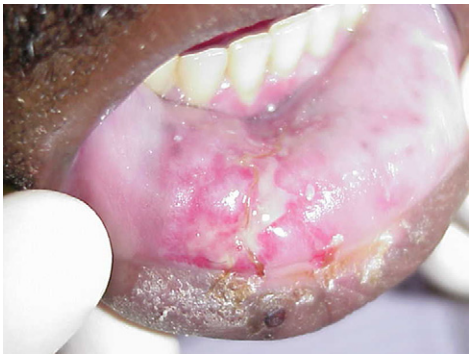

Fig 7. Recurrent intraoral herpes in an immunocompromised host. Note crusted lesion on vermilion border extending onto nonkeratinized labial mucosa as an asymmetric, superficial ulcer covered with yellowish pseudomembrane.

5. Abstinence from oral sex between an HSV1-seronegative female and an HSV1- seropositive male or a male partner with active oral lesions during the last trimester[53]
6. A thorough interview regarding potential symptoms of herpetic infections at the time of labor and a follow-up speculoscopy for suspected cases[148]
7. Administration of occlusive coverage to nongenital HSV lesions prior to vaginal delivery[148]
8. Elective cesarean delivery if active HSV lesions are present or the risk of HSV2 transmission is high within 2 weeks of labor and avoidance of iatrogenic trauma to fetal skin by forceps or scalp electrodes during the delivery[53,148,169]

HSV is the predominant infectious agent responsible for sporadic encephalitis worldwide.[11,75,171] HSV encephalitis has a mortality rate above 70% and is often associated with neurological impairment despite therapy.[8,11,26,175] It is often caused by reactivation rather than primary HSV infection.[8] Encephalitis is a serious complication of HSV infection in more than one third of neonates.[172] Although HSV2 is the most common cause of HSV encephalitis in neonates, HSV1 most frequently leads to encephalitis in children and adults.[8,173] Timely diagnosis and therapeutic intervention are the key elements in the successful management of HSV encephalitis.[8]

HSV infection in the immunocompromised patient

Recurrent HSV infection is a major cause of morbidity and occasional mortality in the immunosuppressed patient, who experience frequent, persistent, and severe recurrences of HSV1 (Fig 6) and HSV2 infections.[8,10,12,24,25,69,72,124,174,175] Mucocutaneous recurrences are often protracted, more symptomatic, poorly responsive to therapy, associated with longer duration of shedding, involving multiple sites, and at risk for viremic dissemination.[8,12,72,98] Intraoral lesions are often extensive, surrounded by a white, elevated border, and involve both keratinized and nonkeratinized mucosa, mimicking primary HSV infection (Fig 7).[12,25,72,176] Oral HSV2 reactivation and viral shedding are also more frequent among HIV-infected individuals.[59,177-179]

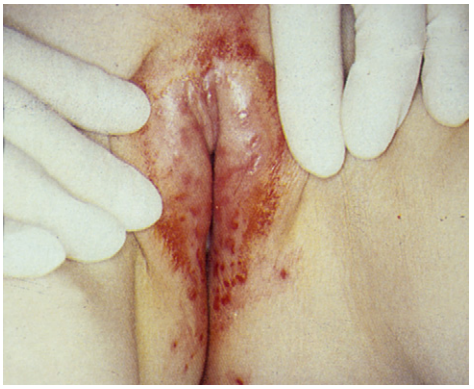

Fig 8. Genital herpes in an immunocompromised host.

In immunocompromised patients, we and others have seen anogenital HSV infections evident as atypical lesions, in particular as painful verrucous nodules and as persistent ulcers (Fig 8).[180,181] HSV types 1 and 2 may cause verrucous lesions simulating condyloma acuminatum or verrucous carcinoma. Confluent verrucous papules and nodules may occur on the penis, scrotum, vulva, intergluteal cleft, and other skin and mucosal sites may also be involved. Recurrent vegetations were described covering the entire vulva in a pregnant patient with common variable immunodeficiency.[182] Verrucous varicella also occurs in immunosuppressed patients, most

Table I. Differential diagnosis of primary oral HSV infection in immunocompetent individuals

Differential diagnosis	Clinical features
Primary herpetic gingivostomatitis	• Transient vesicles • Generalized acute, multiple, round, superficial ulcers • Affects movable and nonmovable mucosa • Intense marginal gingivitis • Systemic signs and symptoms
Hand-foot-mouth disease	• Acute multiple ulcers • Primarily affecting anterior oral cavity • Accompanied by characteristic lesions on hands and feet
Herpangina	• Acute, multiple ulcers • Affecting posterior oral cavity • Mild systemic symptoms • Seasonal prevalence
Erythema multiforme	• Explosive onset • Widespread, irregular ulcers • Deep, hemorrhagic lesions • Often spares gingiva • Blood-crusted lips • With or without cutaneous target lesions
Pemphigus vulgaris	• Vesicular eruptions • Generalized, irregular, superficial ulcers • With or without cutaneous lesions
Acute necrotizing ulcerative gingivitis	• Intensely erythematous gingival inflammation • Papillary necrosis, halitosis, and perfuse drooling • Systemic signs and symptoms

commonly in those with HIV/AIDS.[183] Discrimination between HSV and herpes zoster can be challenging in this context. Genital herpes also predisposes those infected to a greater risk for acquisition and transmission of HIV.[52,122,184,185]

DIAGNOSIS

The mode of onset, classic constitutional symptoms, appearance and distribution of lesions, absence of prior herpetic episodes on history, and reported exposure to HSV1 often establish the diagnosis of primary herpetic gingivostomatitis.[9,12,25,72,73] The presence of multiple, round, superficial oral ulcerations as well as acute, generalized marginal gingivitis on clinical examination are especially helpful in diagnosis.[72] Occasionally, diagnosis of primary HSV infections poses a challenge, particularly in adults with less typical presentation.[5,12,72] In these settings, mucocutaneous conditions such as erythema multiforme (EM) or pemphigus vulgaris, which require different management strategies, should be considered.[12,72,186] The presence of generalized prodromal symptoms prior to appearance of lesions in HSV helps differentiate it from allergic stomatitis, in which systemic symptoms often accompany local lesions.[72]

Herpes-associated erythema multiforme

Interestingly, nearly 80% of recurrent EM cases are thought to be associated with HSV reactivation.[187-191] Recurrent EM refers to an infrequent variant of this disease characterized by multiple outbreaks of EM often associated with herpes reactivation.[11,72,124,187,191-199] Asymptomatic viral shedding in the absence of clinical herpes may also precipitate herpes-associated erythema multiforme (HAEM).[188,193,200]

Using PCR, presence of viral DNA in HAEM lesions have been demonstrated.[188,193,201,202] Faster resolution of HAEM outbreaks with transient HSV gene expression compared with those with prolonged HSV gene expression supports an etiologic role for HSV in HAEM.[201,203] It is proposed that in these patients, HSV fragments trapped within CD34-positive cells are transported to the skin during an acute herpetic outbreak.[204] Pathogenesis may represent a delayed-type hypersensitivity reaction[193,204] involving HSV superantigens in the tissue, infiltration of dermis by inflammatory cells,[203] cytokine production, and immune responses culminating in cell-mediated epithelial cell death.[191,205]

Patients with HAEM typically experience an average of 6 attacks annually, with each episode lasting nearly 2 weeks[196] for a mean duration of 9.5 years.[187] HAEM has an acute onset with numerous target lesions on the acral exterimities[204] within 10 days of an oral or genital herpetic reactivation.[11,192] Systemic symptoms are absent or minimal.[204] This condition is self-limited; patients experience no mucocutaneous involvement between outbreaks.[196]

Differential diagnosis

PHGS may also be mistaken clinically for impetigo, particularly when lesions are limited to the lips and facial skin and do not involve the oral cavity.[25,72] Table I provides differentiating features of PHGS and other clinically similar conditions presenting with acute multiple oral ulcerations.

Aphthous stomatitis, the most common oral ulcerative condition, is often confused with recurrent intraoral herpes.[41] Both multiple minor aphthous ulcers and herpetiform aphthous ulcers clinically resemble intraoral herpes (Figs 9 and 10). However, the site distribution of lesions and absence or presence of a vesicular stage are helpful clues in

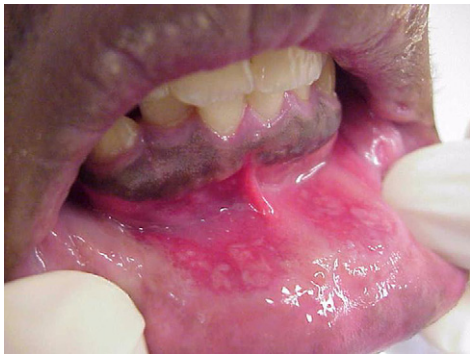

Fig 9. Herpetiform aphthous ulcer. Note multiple small, shallow, coalescing ulcers with brisk erythematous halo affecting nonkeratinized labial mucosa.

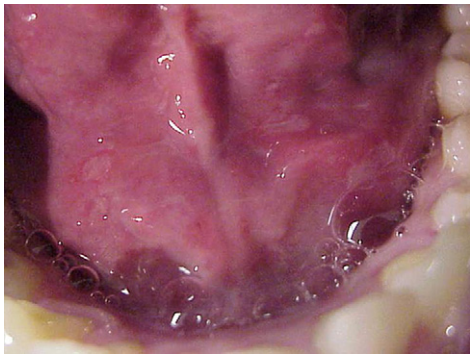

Fig 10. Herpetiform aphthous ulcer. Note multiple, shallow erosions with surrounding erythema affecting nonkeratinized tissues of ventral aspect of the tongue and floor of the mouth.

Table II. Differential diagnosis of recurrent intraoral herpes in immunocompetent individuals

Differential diagnosis	Clinical and histologic features
Recurrent intraoral herpes	• Acute, multiple, round ulcers or superficial erosions • Preceded by transient vesicles • Affecting keratinized tissues • Infrequent prodromal symptoms • Viral cytopathy on biopsy • Positive viral culture
Intraoral herpes zoster	• Acute, multiple ulcers • Unilaterally distributed on keratinized tissues • With or without cutaneous eruptions • Preceded by transient vesicles • Intensely symptomatic • Viral cytopathy on biopsy • Positive viral culture
Recurrent minor/herpetiform aphthous ulcers	• Acute, multiple, small ulcers with brisk erythematous halo • Affecting nonkeratinized mucosa • No vesicular stage • No prodrome • No systemic signs and symptoms • No inflammation of marginal gingivae • No viral cytopathy on biopsy • Negative viral culture

establishing the clinical diagnosis.[12] Table II provides the differentiating features of recurrent aphthous stomatitis and intraoral herpes.

Most HSV2-seropositive people do not have the classic signs and symptoms of genital herpes, making history and clinical presentation insufficient for diagnosis.[7,23,24,59,99,123] In addition, conditions such as erosive lichen planus, atopic dermatitis, or urethritis may resemble genital herpes.[123,206] Therefore, we and others recommend laboratory testing as a method to confirm clinical impressions of genital herpes.[56]

Laboratory diagnosis

Clinicians may wish to utilize laboratory tests to establish definitive diagnosis when clinical presentation of HSV infection is atypical.[5,9,12,69,72] These include viral isolation in culture, cytological smear/Tzanck preparation of vesicular content, direct fluorescent antibody (DFA) studies, tissue biopsy, viral DNA detection by PCR and serological assays.[9,11,12,25,165,207-209] Viral identification tests, such as viral culture with typing and nucleic acid amplification testing, are typically used for undiagnosed patients with fresh primary or recurrent genital lesions.[53]

The most rapid, inexpensive, and frequently used diagnostic tool is a cytological smear (Tzanck smear) taken from the base of a freshly opened vesicle.[69,72,73,165,210,211] The collected specimen is typically stained with Giemsa, Wright's or Papanicolaou stain and examined for virally-induced cytopathological features by light microscopy.[13,69,72,212] Although the Tzanck test confirms herpes simplex or herpes zoster infection as the etiology, it cannot differentiate between them.[13,25,69] These viral infections share similar cytopathological features, necessitating immunohistochemical or DFA studies to type the virus.[69,165,213,214]

The diagnostic "gold standard" for HSV is viral isolation in tissue culture,[8,13,48,123,165,213,215] reserved for patients with active lesions.[24,53] This procedure involves collection of fluid from the base of an intact

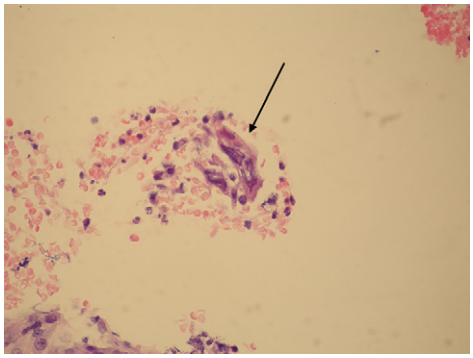

Fig 11. HSV1 viral cytopathy. Note desquamated epithelial cells (*arrow*) with intranuclear viral inclusions. (Hematoxylin-eosin stain; original magnification: ×100.)

vesicle by vigorous swabbing, its transfer to a suitable media, transportation on ice and inoculation onto an appropriate cell culture.[3,11,13,73,216] Characteristic cytopathological features of HSV such as multinucleated giant cells, syncytium, and ballooning degeneration may be detectable 1 or 2 days after viral inoculation (Fig 11).[11,69,72]

The purpose of this technique is to detect virally induced degenerative changes in cells inoculated with the virus and to classify the virus as part of the herpesvirus family (see Fig 9).[13] In general, 2 to 7 days are required to achieve maximum sensitivity for observing cytopathological changes.[3,8] DFA testing or immunohistochemistry may also be used to detect viral antigens and type the virus collected in a lesional smear or isolated in tissue culture.[8,13] DFA is a fast, sensitive, specific, and inexpensive method for labeling HSV antigens with monoclonal antibodies and viral typing.[217]

A negative viral culture does not rule out herpes.[53,91] The sensitivity of viral culture is lower for dried, crusted, aged lesions, improperly handled specimens as well as in subjects with recurrent rather than primary infections.[3,66,75,123,214] In recurrent episodes, viral cultures may prove negative in more than 50% of cases with genital herpes.[218] A positive HSV culture does not always confirm HSV as the etiology because the inoculum may have been isolated from concurrent lesions contaminated by HSV-infected secretion in asymptomatic carriers.[69,72] Despite high sensitivity and specificity, the substantial cost and diagnostic delay discourage routine use of viral culture in clinical practice.[73,213,215] These drawbacks, however, should not preclude the application of viral culture, particularly when diagnosis is uncertain.

Nucleic acid amplification tests such as polymerase chain reaction for detection of HSV DNA antigen and viral typing in suspect lesions are faster and more sensitive than viral culture but are also expensive, labor intensive, and not readily available.[3,8,13,66,173,218-220] In addition, false-positive results may occur because of contamination of nonherpetic lesions by distant HSV shedding.[53,89] Nevertheless, PCR is the preferred test reserved for diagnosis of herpes encephalitis.[56,171]

A punch, shave, or wedge biopsy specimen from a lesion edge may also be used to detect the typical degenerative changes associated with HSV infections.[13,221] As these histologic features are also shared by varicella-zoster viral infections, histologic examination of a biopsy specimen cannot differentiate between HSV1, HSV2, and varicella-zoster virus. Biopsy technique may be helpful for confirmation of HSV etiology in old, atypical lesions and in exclusion of disorders with similar clinical presentation.[91] In addition, application of immunocytochemistry or in-situ hybridization to biopsy specimens may overcome the drawback of false-positive results for nonherpetic specimens contaminated by HSV.[89]

Serologic assays are indicated when virologic techniques such as culture, antigen detection, or PCR are impractical or nondiagnostic, as in patients with recurrent infections, healing lesions, or in the absence of active lesions.[24,53] When interpreted appropriately, serologic assays directed at anti-HSV immunoglobulins confirm a primary HSV infection and rule out prior viral exposure.[11,69,72] Acute and convalescent sera are obtained within the initial 3 to 4 days and several weeks after the onset of symptoms, respectively.[24,53,69,72] Because of delayed humoral response, HSV antibodies are absent from specimens taken during acute onset of HSV infection but gradually appear; increase over the subsequent weeks; and remain for life.[13,56,145]

The absence of HSV antibodies in acute serum specimen, appearance of HSV-specific IgM and/or a 4-fold increase in IgG antibody titer during convalescence (as well as viral isolation in tissue culture, if active lesions present) provide conclusive diagnostic evidence for primary HSV infection.[9,25,69,72,93] It is, therefore, essential to examine the acute serum for the presence of both IgM and IgG antibodies.

The presence of anti-HSV IgG in the acute serum, the appearance of HSV-specific IgM, and an increasing anti-HSV IgG during convalescence (as well as viral isolation, when possible) are diagnostic of a recurrent HSV infection.[72,93] Usefulness of serology for this purpose, however, has been questioned because only a small percentage of patients with recurrent infection demonstrate a significant rise in the HSV antibody titer.[72,87,211,222] Because of

diagnostic delay, serology is not routinely used in clinical practice.[69,72] The most frequent use of serology is to determine whether partners of persons with clinical herpes infection are at risk. Serology may also assist in the detection of individuals (eg, immunocompromised, organ transplant recipients) predisposed to chronic and severe HSV infection as well as in diagnostic confirmation of atypical cases.[13,69]

Unlike conventional serology, new type-specific assays discriminate between HSV1 and HSV2 antibodies with a high degree of sensitivity and specificity.[7,123,207,215,223] These enzyme-linked immunosorbent assays are inexpensive, rapid, and based on antigenic subtype differences such as glycoprotein G1 (gG1) and G2 (gG2) capable of inducing specific IgG antibodies.[7,24,123,216,224]

Drawbacks of enzyme-linked immunosorbent assay include low purity of the recombinant or glycoprotein G and the potential for cross-reactivity between glycoproteins G1 and G2, all of which may affect specificity.[7,24] A 38% sequence similarity between gG1 and gG2 proteins has been demonstrated in homology studies.[7] False-negative results may also occur in new infections because of the delayed appearance of HSV IgG antibodies and lower sensitivity.[7,24,53,123] As IgM antibodies appear first, confirmation of seroconversion may be established faster by detecting IgM rather than IgG antibodies.[7]

False-negative results should be verified clinically or a repeat serology performed at a later date if seroconversion is suspected.[53,123] Serological assays in low-risk populations may lead to false-positive results, necessitating confirmation by a Western blot assay.[53,123] The latter relies on detection of antibodies to a battery of viral proteins for differentiating HSV1 from HSV2 and is considered the epidemiologic "gold standard" for HSV.[123,225,226] Western blot assay is, however, expensive, time-consuming, and not readily available.[24,225]

Serologic assays cannot differentiate between antibodies generated in response to a genital versus an oral HSV infection and as such cannot confirm the site of infection.[52,53,56,123] This is particularly relevant when diagnosing genital herpes, as the viral subtype influences the potential for recurrence, disease prognosis, and follow-up counseling.[23,227] Because of the predominance of sexual transmission, HSV2 seropositivity is generally consistent with an anogenital infection.[3,52] However, because of an increasing prevalence of genital HSV1 infections in certain countries, it is difficult to interpret whether a positive HSV1 serology indicates an oral or a genital infection.[7,52,123] Serologic findings in patients with AIDS and other types of immunosuppression may be challenging.

MANAGEMENT

In general, management of HSV infections starts with prevention. Examples of appropriate preventive strategies include education of the public regarding the contagious nature of the disease, its potential for autoinoculation, efficacy of barrier techniques such as condoms in preventing viral transmission, asymptomatic viral shedding, triggers, and prophylactic antiviral therapy.[2,9,12,36,69,72,73,90,228]

An overall evaluation of the clinical signs, symptoms, and general health of the patient is essential to the success of therapeutic interventions for HSV infection.[8,73] Other factors influencing treatment selection include the site of infection and the primary or recurrent status.[8]

Current management approach to HSV infection does not target viral eradication, but rather the prevention of transmission, suppression of recurrence, attenuation of clinical course, viral shedding and complications, as well as palliation and promotion of healing.[2,9,10,70,73] Antiviral agents do not cure HSV infections, but rather modify the clinical course of the disease through the inhibition of viral replication and subsequent epithelial damage.[5,10] In view of the natural history of herpes infection and the extent of viral replication which occurs in the first 48 hours of a recurrence, rapid access to the sites of viral replication is critical to therapeutic efficacy in preventing a clinical recurrence.[5,16,36,81]

Topical, oral, or intravenous antiviral agents may be used in the management of HSV infections.[11,36] The effectiveness of topical agents is determined by their penetrability through the epithelium and availability at the sensory nerve endings, where viral replication occurs.[36] In general, topical therapy is less effective than other modes of intervention, partially due to problems with reaching inaccessible lesions.[11,36] For lesions affecting the nasal septum, internal ear, a hairy scalp, or internal genitalia, systemic antivirals are the indicated choice.[36]

Compared with topical agents, oral antivirals allow systemic drug exposure, faster access to the sites of viral replication, greater bioavailability, less frequent dosing, and improved patient compliance.[36,77,229-231] Oral antivirals also provide a practical and appropriate route for long-term suppressive therapy in patients with frequent, severe outbreaks of herpes infection.[16,36] In addition, intervention with systemic antivirals is indicated for eczema herpeticum, neonatal herpes, HSV encephalitis,

ocular herpes, and HSV infections in the immunocompromised patient.[8,16,36,148,156]

Antiviral agents

Docosanol 10% cream (Abreva, Bausch & Lomb, Tampa, Fla) is an over-the-counter product with indirect antiviral activity approved for topical treatment of recurrent HSL.[12,73,87] This 22-carbon primary alcohol interferes with the attachment of epithelial cell membrane receptors and proteins coating the viral envelope, ultimately blocking the virus from infecting cells.[12,87,232] Topical docosanol reduced signs and symptoms of recurrent HSL in clinical trials when administered early during the prodrome.[12,233]

Penciclovir 1% cream (Denavir, Novartis Pharma GmbH, Wehr, Germany) and acyclovir 5% cream (Zovirax, Glaxo SmithKline, Research Triangle Park, NC) are topical prescription-level antivirals approved for treatment of recurrent HSL in immunocompetent individuals and mucocutaneous HSV infections in immunocompromised hosts, respectively.[8,12,73,124] In a controlled clinical trial, topical penciclovir has also been shown to reduce time to healing by nearly 1 day when initiated during the prodromal phase.[77]

Acyclovir is also available in oral and injectable formulations, has a good safety profile, and is well tolerated by patients.[8-10,70,124] A rare side effect associated with rapid intravenous administration of high-dose acyclovir is reversible crystalline nephropathy.[11,98] A drawback of oral acyclovir is, however, its poor bioavailability (10%-20%) and short plasma half-life, necessitating frequent dosing.[9,62,124] Although systemic acyclovir is not approved for either primary or recurrent oral herpes infection, many clinical studies have tested its off-label use in both immunocompetent and immunocompromised patients and have reported varying degrees of efficacy.[73]

Acyclovir, valacyclovir, and penciclovir are all acyclic guanosine analogues which target viral polymerase and viral DNA replication.[4,8] These medications must undergo sequential phosphorylation by virally-induced thymidine kinase (TK) and host cellular kinases in order to convert to the biologically active triphosphate form.[2,4,8,124] As the first step in the phosphorylation cascade necessitates viral enzymes, the adverse effects of guanosine analogues on host cells are attenuated.[98]

The primary mode of action of acyclovir and valacyclovir triphosphates is selective inhibition of DNA polymerase and subsequent incorporation into the replicating viral DNA chain, irreversibly terminating its further elongation.[124,234,235] Compared with acyclovir, penciclovir has a longer half-life and a higher intracellular concentration within HSV-infected cells, but is 100 to 160 times less potent in inhibiting viral DNA polymerase.[8,236,237] Penciclovir halts viral DNA synthesis through irreversible, competitive inhibition of DNA polymerase rather than DNA chain termination.[2,98,124,238]

Valacyclovir (Valtrex, Glaxo SmithKline, Research Triangle Park, NC) is a systemic antiviral agent approved for treatment of recurrent HSL.[73] It is the valine ester prodrug of acyclovir, which is more readily absorbed and fully metabolized to acyclovir and L-valine in the liver and intestine.[2,8,9,70,124,234,239] Valacyclovir has up to 5 times greater bioavailability, allowing less frequent oral dosing and improved patient compliance.[9,234,239]

The most frequently reported side effect in both healthy and HIV-infected individuals is headache.[234] A serious and potentially fatal adverse effect of long-term, high-dose valacyclovir (8 g daily) therapy in immunocompromised patients is thrombotic microangiopathy (TMA).[234,240] This has little practical implications for the management of HSV infections in HIV-seropositive patients because no direct cause-and-effect relationship between valacyclovir and TMA has been demonstrated.[234] In addition, control of HSV infections in HIV-seropositive patients without profound immunosuppression requires lower doses of valacyclovir than reported in TMA complications.[241] Nevertheless, patients with advanced HIV disease receiving high doses of valacyclovir should be closely monitored for signs and symptoms of TMA.[234] Valacyclovir is approved by the Food and Drug Administration (FDA) for the management of HSV infection in patients with HIV disease.

Famciclovir (Famvir, Novartis Pharmaceuticals Corporation, East Hanover, NJ) is a systemic antiviral medication approved for the treatment of orolabial herpes in immunocompromised hosts[70,73]; it is a diacetyl ester prodrug of penciclovir and is rapidly absorbed from the gastrointestinal tract and converted to it after ingestion.[2,8,9,124,242] Famciclovir has improved oral absorption, greater bioavailability, and longer dosing intervals compared with penciclovir in treatment of HSV disease.[9,124] Famciclovir shares the same mechanism of action with acyclovir by inhibiting DNA polymerase but does cause DNA chain termination.[2,238]

Foscarnet (Foscavir, Hopsira, Lake Fort, Ill) is an intravenous antiviral medication approved for the treatment of acyclovir-resistant HSV in immunocompromised hosts.[8,73,124] Resistance to acyclovir is uncommon in healthy individuals.[234,241,243] Although acyclovir resistance may be attributed to alteration in DNA polymerase, it is most frequently

caused by the deficiency of or mutations in the TK gene.[10,244-246]

Foscarnet is a pyrophosphate analog with a mechanism of action independent of phosphorylation by viral or cellular kinases.[2,124,245,247,248] It competitively blocks pyrophosphate binding sites on the viral DNA polymerase, directly inhibiting its activity.[98,124,242,248] Serious adverse effects of foscarnet include renal toxicity, mandating close follow-up of serum creatinine throughout therapy.[69,124] Sufficient hydration before and during infusions and avoidance of other nephrotoxic medications may help prevent or minimize renal impairment.[69,124] Resistance to foscarnet is uncommon and may be caused by point mutations in HSV DNA polymerase.[249]

Cidofovir (Vistide, Gilead Sciences, Inc, Foster City, Calif) is an acyclic nucleoside 5-monophosphate which upon phosphorylation by host kinases selectively inhibits the viral DNA polymerase.[248] It is highly nephrotoxic and is reserved by the Centers for Disease Control and Prevention for treatment of HSV disease resistant to acyclovir and foscarnet.[12] As cidofovir does not require TK for activation, it is also effective on TK-deficient HSV.[8,248] Cidofovir has a long half-life and is administered once weekly by intravenous route.[8] A 1% cidofovir gel may be compounded from intravenous cidofovir into a safe topical preparation (Forvade, Gilead Sciences, Inc) effective against acyclovir-resistant HSV infection.[98,250] Mutations in viral DNA polymerase may lead to cidofovir resistance.[8]

Treatment of primary herpetic infections

Subclinical PHGS is frequently undiagnosed and therefore untreated.[8] In healthy people, symptomatic primary oral herpes is often managed by supportive and symptomatic interventions.[25] Palliative care may be provided by oral preparations containing a topical anesthetic such as lidocaine, diphenhydramine, or dyclonine and a mucosal coating agent such as Milk of Magnesia, Maalox (Novartis Consumer Health, Inc, Fremont, Mich), or Kaopectate used to rinse the mouth before meals.[25,73] In view of the risk of aspiration during the intake of food or fluids, patients should be educated about the potential for a reduced gag reflex secondary to rinsing with preparations containing topical anesthetics.[90] Nutritional supplements may also be necessary when oral pain impacts on the intake of liquids and foods.[90]

PHGS may occasionally become a serious problem in children who are unable to maintain hydration and nutrition due to dysphagia and oral pain.[8,25,36,72,251] Affected infants may benefit from administration of antipyretic/analgesic agents that alleviate fever and oral pain.[12,73] If ice chips and frozen popsicles are not sufficiently soothing to allow oral intake of fluids, electrolytes, and nutrients, referral for evaluation and supportive care may be necessary.[16,25,49,72] Because of an increased risk of seizures, the use of topical lidocaine preparations in pediatric patients is not recommended.[252]

Initiation of oral acyclovir suspension, 15 mg/kg, within 3 days of symptoms and continuing 5 times a day for 1 week has been shown to accelerate healing of lesions, to reduce viral shedding, and to improve oral intake of food or drinks in pediatric patients with PHGS.[251] In contrast to immunocompromised hosts, the indications for and efficacy of systemic antiviral agents for PHGS in healthy adults is not clearly defined.[73,253-255] Nevertheless, an off-label course of acyclovir at the same dosage and schedule indicated for primary genital herpes (200 mg, 5 times daily or 400 mg, 3 times daily for 7-10 days) may be used to manage severe primary oral outbreaks in adults.

Patients with suspected or proven primary genital herpes should be treated promptly with antiviral agents to minimize discomfort, to prevent neurologic complications, and to facilitate recovery.[3,8,256,257] The therapeutic intervention is particularly important when constitutional symptoms are present or the patient is immunocompromised.[258]

Acyclovir, famciclovir, and valacyclovir are safe and efficacious oral antiviral agents available for treatment of primary genital herpes.[8,53,56,98,257,259] All 3 agents reduce severity of symptoms, duration of viral shedding, and hasten healing of lesions.[260,261] Famciclovir and valacyclovir offer more convenient dosing than acyclovir with 5 times a day dosing but are more expensive.[257,259,262] Reduction of viral shedding and time to crusting of genital lesions is also achieved with topical acyclovir but to a lesser degree than with oral or intravenous acyclovir.[26] Although duration of therapy is usually 5 to 10 days, treatment may be extended beyond the standard recommendation when patients are still suffering from symptoms.[257,259] Treatment of first-episode genital herpes with these antivirals does not influence the frequency or severity of future recurrences.[259,262,263]

Palliative measures such as loose-fitting cotton underwear, cold compresses, and saline bathing of the affected area are often soothing.[3,53,257] Maintaining lesions clean and dry help to reduce the risk of both superinfection and adhesion development.[257] Other beneficial measures for genital herpes include topical application of zinc as well as creams containing licorice root as well as oral intake of 1000 mg of L-lysine 3 times daily.[264-266]

Treatment of recurrent herpetic infections

In immunocompetent individuals, recurrent HSL and intraoral herpes generally cause limited disease and transient discomfort, necessitating only palliative intervention.[8,12,72,73,91] Symptomatic relief for recurrent HSL may be provided by topical application of ice, alcohol, ether, chloroform, local anesthetics, various over-the-counter occlusive preparations (eg, Zilactin [Blairex Laboratories, Inc, Columbus, Ind], Orabase [Colgate-Palmolive Company, New York, NY], Anbesol [Wyeth Consumer Healthcare, Richmond, Va], Orajel [Del Laboratories, Rocky Point, NC]), lip balms (eg, cocoa butter, lanolin, or petrolatum-based products).[25,73,90]

Patients with orofacial herpes should be advised to wash their hands, particularly after application of topical medicaments, to avoid kissing anyone, and not to share kitchen or bathroom utensils.[90] Topical medications are best applied gently with a cotton-tipped applicator to prevent increased viral shedding caused by mechanical stimulation and to minimize the risk of herpetic whitlow and viral autoinoculation to other anatomical sites.[25,90] The probability of autoinoculation is greater for primary as compared with recurrent episodes and especially within 1 month of the primary infection.[36,125]

Therapeutic decisions for optimal management of recurrences should involve both the clinician and the patient.[257] It is essential to consider the patient's opinion, specific circumstances, personal impact of outbreaks, sexual relationships, and the cost of treatment when individualizing the management program.[257,259,262] Therapeutic strategies may also need to be modified as the individual's symptoms and personal circumstances change.[257,259]

In recurrent orofacial herpes, antiviral agents are typically reserved for patients who experience frequent attacks, disfiguring lesions, persistent outbreaks, or considerable anxiety.[9,72] These include individuals with predictable recurrences due to high-risk activities such as high-altitude skiing or rejuvenating facial procedures.[12,72] However, while some patients opt not to treat their frequent outbreaks, others find even mild or infrequent episodes obtrusive enough to warrant therapeutic intervention.[259,262]

Efficacy in treatment of recurrent facial herpes has been demonstrated for both topical and systemic antiviral agents.[36] Therapies approved by the FDA include topical preparations such as penciclovir and docosanol as well as oral valacyclovir.[8] However, topical and oral acyclovir as well as systemic famciclovir have been used to treat HSL, although the former two agents are not FDA approved for this purpose.

Maximal clinical benefit with antivirals requires timely recognition of signs, symptoms, and precipitating factors of the disease as well as the optimal use of the available agents for episodic or suppressive therapy depending on the individual patient's situation.[5,8,16,36,81,91,98] Episodic therapy is appropriate for patients with mild and infrequent outbreaks[36,267] preceded by a well-defined prodrome and having minimal impact on their daily life or when subclinical shedding is not a concern.[53,259]

The purpose is to abort lesions, to minimize clinical manifestations, and to reduce infectivity during attacks rather than the number of outbreaks.[3,230,259,262] As episodic therapy depends on the presence of prodrome, patients must be vigilant in the recognition of early signs and symptoms and timely initiation of therapy at the prodrome or within 1 day of the outbreak.[36,56,124,259,267] In a recent study of HSL in adults, oral intake of 2 g of valcyclovir twice a day for 1 day, started during the prodrome, aborted some lesions and reduced the duration of an outbreak by 1 day.[229] Initiation of therapeutic antiviral agents during resolution when vesicles dry out leads to marginal improvement, if any.[53] Timely intervention dictates that susceptible individuals have a prescription or a supply of medications available for unpredictable outbreaks.[56,257,259]

Options other than antiviral agents are available for episodic treatment of HSL. Topical application of a mixture of L-lysine, botanicals, and other nutrients has also shown benefit in reducing symptoms of orofacial herpes.[268] Several studies advocate ingestion of a large amount (2-3 g) of lysine in single or multiple doses for ameliorating outbreaks of HSL.[269,270] Intake of lysine should be started at the onset of prodromal symptoms and continued until complete resolution of lesions.[270]

Outbreaks of genital herpes are generally mild and infrequent, with the majority of those persons affected not requesting treatment.[262] In randomized controlled trials, acyclovir, valacyclovir, and famciclovir have been demonstrated to be clinically efficacious in aborting development of lesions, reducing viral shedding, and speeding the healing of lesions when initiated early during the prodrome for episodic treatment of genital herpes.[257,259,271-273] The choice of therapy among the approved antivirals may depend on the convenience of dosing regimen and the patient's compliance.[257,259]

Compared with intermittent episodic therapy, suppressive therapy is effective in the prevention of future outbreaks, reduction of HSV excretion, and potentially reducing viral transmission.[8,24,48,76,98,105,124,255] A knowledge of potential triggers of viral reactivation, such as stress, oral trauma, or sun exposure, may

Table III. Therapeutic strategies for recurrent herpes simplex labialis*

Topical medications	Systemic medications
Penciclovir, 1% cream (Denavir)†	Valacyclovir, 500 mg caplets (Valtrex)†
Apply to affected area starting at prodrome and every 2 hours (while awake) for 4 days	2 g p.o. at first prodrome and 2 g p.o. 12 hours later
Acyclovir, 5% ointment (Zovirax)‡	Famciclovir, 250 mg tablets (Famvir)‡
Apply to affected area starting at prodrome and every 3 hours, 6 times/d, for 7 days	500 mg at first prodrome 2 times/d for 5 to 10 days
Docosanol, 10% cream (Abreva)§	Foscarnet (Foscavir)‡
Apply to affected area starting at prodrome, 5 times/d, until healed	40 mg/kg every 8 hours for 2-3 weeks (if intolerant or resistant to acyclovir)
	Cidofovir (Vistide)‖
	5 mg/kg once a week for 2 wk followed by 5 mg/kg every other week (for acyclovir- and foscarnet-resistant HSV)

p.o., By mouth.
*Compiled from Brady and Bernstein[8] and Huber.[73]
†Approved by the FDA for immunocompetent host with mucocutaneous HSV infection.
‡Approved by the FDA for immunocompromised host with mucocutaneous HSV infection.
§Approved by the FDA as an over-the-counter medication.
‖Not approved by the FDA but recommended by the Centers for Disease Control and Prevention.

help in the avoidance of precipitating factors and preemptive application of therapeutics.[12,36,72,90,274] Short-term prophylactic therapy a few hours to days before an event known to precipitate a recurrence may reduce the frequency and severity of a herpetic outbreak.[36,275]

Evidence for preemptive therapy in the prevention of facial herpes remains equivocal.[36] Application of sunscreen before ultraviolet light exposure has proven protective against solar damage to the perioral region, herpetic Photoactivation, and HSL recurrence in susceptible patients.[86] In another study, no benefit for topical application of sunscreen prior to sun exposure in the prevention of HSL recurrence in susceptible skiers was demonstrated.[276]

In a study of 147 skiers, subjects taking 400 mg acyclovir twice daily, starting 12 hours before sun exposure and continuing up to 7 days, developed considerably fewer recurrences compared with control subjects (7% of subjects vs 26% of controls).[275] In another study of skiers, intake of 800 mg acyclovir twice daily started half a day to 1 day before sun exposure provided no significant protection against HSL recurrence compared with placebo.[277] Despite conflicting studies, preemptive therapy with topical or systemic antivirals should be offered to patients with known triggers who are at risk for recurrent HSL as a result of a transient stressful event or short-term exposure to intense sun (such as high-altitude skiing or beach vacation).[36]

HSV reactivation in the mucodermatome of the fifth cranial nerve may lead to serious sequelae when local mucocutaneous protection is compromised.[16] For instance, HSV1 reactivation in seropositive individuals undergoing facial procedures predispose them to postoperative eruptions, poor healing, and severe scarring in the trigeminal nerve dermatome.[16,278] Studies demonstrate a high HSV1 seroprevalence among the adult population[46] and a poor correlation between one's serologic status and recollection of previous HSL episodes.[279] In one study, nearly 40% of patients with HSV1 antibodies did not remember any prior HSV-related outbreak.[280]

Considering the efficacy and safety profile of available antiviral agents, their prophylactic administration in patients receiving laser resurfacing is routinely indicated, irrespective of a positive or negative history for orofacial HSV1 outbreaks.[278,279] In a recent study, administration of oral Famciclovir, 250 mg twice daily, starting the day before the procedure and continued for 2 weeks, effectively suppressed facial HSV recurrences after the procedure.[278] In another study, prophylaxis with valacyclovir, 500 mg twice a day, initiated 1 day before or on the day of the procedure and continued during the 2 postoperative weeks, was highly efficacious in suppressing procedure-induced HSV reactivation.[280] Further controlled studies are necessary to establish the optimal dosage, duration, and start time of prophylactic antiviral therapy for this indication.[279]

With regard to management of EM, episodic administration of oral acyclovir appears to offer no benefits once the disease has occurred.[281] However, long-term therapy with acyclovir (400 mg twice daily for 6 months) or other antiherpes drugs (eg, famciclovir or valacyclovir) is the first-line

Table IV. Therapeutic strategies for primary and recurrent genital herpes*

Condition	Immunocompetent	Immunocompromised
Primary genital herpes	Acyclovir 200 mg p.o. 5 times/d for 7-10 days[8,56,98] Acyclovir 400 mg 3 times/d for 7-10 days[8,56] Valacyclovir 1 g p.o. twice a day for 7-10 days[8,56,98] Famciclovir 250 mg p.o. 3 times/d for 7-10 days[8,56,98]	
Recurrent genital herpes (episodic therapy)	Acyclovir 200 mg p.o. 5 times/d for 5 days[8,98]	Acyclovir 200 mg p.o. 5 times/d for 5-10 days[56]
	Acyclovir 400 mg p.o. 3 times/d for 5 days[8,56,98]	Acyclovir 400 mg p.o. 3 times/d for 5-10 days[56]
	Acyclovir 800 mg p.o. 2 times/d for 5 days[8,56]	Valacyclovir 1 g p.o. twice a day for 5-10 days[8,98]
	Valacyclovir 500 mg p.o. twice a day for 3-5 days[8,56,98]	Famciclovir 500 mg p.o. for 5-10 days[8,98]
	Valacyclovir 1 g p.o. once a day for 5 days[8,56]	
	Famciclovir 125 mg p.o. twice a day for 5 days[8,56,98]	
Recurrent genital herpes (long-term suppressive therapy)	Acyclovir 400 mg p.o. twice a day[8,56,98]	Acyclovir 400-800 mg p.o. twice a day or 3 times/d[8]
	Valacyclovir 500 mg p.o. once a day[8,56,98]	Valacyclovir 500 mg p.o. twice a day[8,98]
	Valacyclovir 1 g p.o. once a day[8,56,98]	Valacyclovir 1 g p.o. once a day[98]
	Famciclovir 250 mg twice a day[8,56,98]	Famciclovir 500 mg p.o. twice a day[8]

p.o., By mouth.
*Information in this table has been compiled from the following references: Brady and Bernstein,[8] Centers for Disease Control and Prevention,[56] and Chakrabarty et al.[98]

treatment for suppression of HSV and HAEM recurrences.[72,187,188,193,282] Lack of response with acyclovir may be attributed to poor patient compliance or subtherapeutic tissue concentrations.[188,200,283] Oral steroid use partially ameliorates HAEM attacks but often prolongs recurrences.[194] Other empirical protocols for HAEM therapy include azathioprine, cyclosporine, antimalarials, and thalidomide.[187,193] In view of the prolonged therapy, necessity for follow-up, and undesirable side effects, these therapeutics do not offer an appealing strategy for a disease with episodic outbreaks.[284]

Long-term suppressive therapy is primarily directed against the frequency of herpetic outbreaks.[36] Other potential effects of suppressive therapy include reducing severity of symptoms, psychosexual complications, and the risk of transmission to sexual partners and babies of infected mothers.[257,259,262,285] Independent of the presence of triggers or risk factors, long-term antiviral prophylaxis may be started at any time and continued for an unspecified duration.[36] Issues of importance in long-term suppression include frequency and severity of outbreaks, level of interference with one's quality of life, absence of a well-defined prodrome, patient's immune status, and the risk of transmission to a seronegative partner.[7,8,43,53,257]

In a recent study, administration of valacyclovir, 500 mg, daily over a 4-month period effectively prevented outbreaks of recurrent HSL.[274] In addition, administration of 500 or 1000 mg valacyclovir once or twice daily throughout the sport season has proved to be effective in preventing recurrence of herpes gladiatorum in wrestlers.[131] Management of ocular herpes involves prompt referral to an ophthalmologist for diagnosis and treatment with antiviral ophthalmic drops such as trifluridine or vidarabine.[8,146] Long-term suppression of ocular herpes is preferable to episodic therapy and may be achieved with systemic antivirals.[16]

Nearly 20% of patients experience more than 6 episodes of genital herpes annually and those with primary episodes lasting beyond 34 days are more predisposed to frequent outbreaks.[23,259] In view of the cost and inconvenience associated with daily therapy, long-term suppression is typically considered for patients suffering from frequent or severe outbreaks of facial herpes as well as individuals with 6 or more annual outbreaks of genital herpes.[8,36,262] Nevertheless, long-term suppression may be

considered for patients with less severe or fewer outbreaks if the patient requests it.[257]

Prior to the advent of highly active antiretroviral therapy, long-term HSV suppression was the main strategy for control of genital recurrences in immunocompromised patients.[257]

A number of controlled randomized trials have indicated that acyclovir, valacyclovir, and famciclovir are efficacious in suppression of recurrent genital herpes, although the latter two agents offer more convenient dosing regimens.[257,286,287] In a recent study comparing quality-of-life measures, 72% of patients chose suppressive therapy over episodic treatment in the management of recurrent genital outbreaks.[288] Long-term suppression is reported to reduce clinical outbreaks of genital herpes and subclinical shedding by 80% and 95%, respectively.[3,98,289] The protective effect of suppressive therapy with 500 mg valacyclovir daily in reducing the risk of genital herpes transmission among heterosexual HSV2-discordant couples through reduction of asymptomatic viral shedding has also been demonstrated.[62,290,291]

Although long-term suppression will not alter the natural history of HSV disease, extended suppressive therapy (eg, beyond 5 years) will result in fewer genital recurrences after cessation of therapy.[257] Some individuals may experience herpetic outbreaks while receiving suppressive therapy.[257] Breakthrough episodes may indicate the patient's poor compliance, a need to adjust therapy, resistance to antiviral medications (although unlikely in immunocompetent individuals), or misdiagnosis of the condition.[257,259,292] Episodic intervention may be used to manage breakthrough outbreaks during long-term suppressive therapy.[257]

Effective suppression requires continuous daily intake of antivirals, which is costly and dependent on the patient's compliance.[98] In general, a minimum of 3 months of daily treatment is required before beneficial effects are observed.[2] Although duration of suppressive therapy varies on the basis of individual needs,[53] in the absence of adverse effects daily treatment should continue for a minimum of 1 year.[2] Occasionally, patients desire short-term suppression of genital herpes during special events of less than 1 month's duration.[257] Under these circumstances, therapy for 5 days or more is necessary to achieve a reliable suppressive effect.[257]

A yearly evaluation is necessary to assess the therapeutic outcome, review the patient's lifestyle and needs, and discuss cessation of suppressive therapy (ie, drug holiday) in those with well-controlled disease.[53,56,257]

Tables III and IV provide a summary of available therapeutic strategies for recurrent HSL and genital herpes, respectively.

In view of the highly selective and specific mechanism of action for currently available antiviral agents, combination or multidrug therapy has also been tried in resistant HSV disease and immunosuppressed hosts to achieve additive or synergistic anti-HSV effects.[12,98,293,294] Many investigations have focused on development of HSV vaccines to control epidemic spread of this disease.[295] This has proven to be challenging, as latent viruses are able to reactivate despite humoral or cell-mediated immunity.[296] In a recent phase II study, an HSV2 vaccine constructed from a glycoprotein-D subunit and a lipid A adjuvant provided 74% protection against acquisition of genital herpes in HSV seronegative women who are seronegative for both simplex viruses, but had no efficacy in other women or men regardless of their HSV serology.[76,98,295] Interestingly, genital HSV2 disease was not prevented by HSV1 seropositivity.[76] Differential protection against genital disease afforded by this vaccine may be attributed to potential sex-specific differences in pathogenesis of genital herpes or induction of anti-HSV immune responses between genders.[76,295] In female patients, vaginal and cervical mucosae through which HSV transmission occurs are not lined by a protective stratum corneum.[295] In addition, these mucosal surfaces are continually washed out by secretions containing antibodies and phagocytic cells, providing a local immunologic barrier to subsequent infection.[295] Among HSV1-seropositive female patients, the vaccine was not protective against genital HSV2 infection perhaps because they were already protected by their existing HSV1 antibodies.[124,295,297]

Helicase-primase inhibitors are new non-nucleoside antivirals, which target the helicase-primase complex critically involved in HSV DNA replication.[98] Safety and efficacy of these orally administered agents against both herpes simplex viruses have been demonstrated in animal models.[98] Evaluation of helicase-primase inhibitors in controlled clinical trials involving humans is the next step in development of new generation of anti-HSV drugs with improved efficacy, less toxicity, better cost-effectiveness and more convenient administration.[98]

CONCLUSION

Mucocutaneous infections caused by HSVs are common in the general population. Although not a major concern in most healthy individuals, frequent outbreaks are often associated with inconvenience, cosmetic concerns, and psychological distress. Such

infections may also lead to significant morbidity or mortality in those unable to mount sufficient immune response. Although recent scientific advances have dramatically improved our understanding of the HSV pathogenesis, diagnosis, and treatment, a cure is not available. Current management strategies encompass prevention, palliation, and antiviral therapy based on clinical severity and the general health of the patient. As with all herpesviruses, infection persists for the life of the host.

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