TREATMENT OF RECURRENT GENITAL AND LABIAL HERPES

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Abstract

Herpes simplex viruses (HSV) present one of the most frequent groups of viruses in the human population. Herpes simplex infections manifest through varying symptoms and lesions of the orofacial or genital tract. The peak of viral titers occurs within the first 24 h in both genital herpes and herpes labialis infections. Due to the rapid viral replication and subsequent progression of lesions in both *Herpes labialis* (HL) and *Herpes genitalis* (HG), the therapeutic window for treating HSV infections with antiviral drugs is narrow. It is important to recognize prodromal symptoms in patients and subsequently (self-) administer appropriate therapy. Clinical trials have shown that the shorter duration of higher doses of antiviral drugs, the more suitable and equally or even more effective results are obtained. According to the analyzed literature, Acyclovir remains the most effective choice of treatment for the majority of patients. In some cases, other similar antiviral drugs could be effective when the treatment with Acyclovir fails to give the expected results.

Keywords: *Herpes genitalis*, *Herpes labialis*, treatment, Acyclovir, reoccurrence

Introduction

Herpes simplex viruses are among the most common pathogens affecting the human population worldwide, with a prevalence rate of approximately 67% for HSV1 and 13% for HSV2[1]. Infections caused by HSV manifest through various symptoms, ranging from painful self-limiting lesions of the orofacial or genital tract to severe eye infections and life-threatening disseminated infections[2]. There are two types of HSV viruses: HSV1, which is associated with infections above the waist, specifically the eyes and mouth (Whitley, 2018), and exhibits tropism for the trigeminal nerve ganglia, and HSV2, which typically affects the region below the waist and have tropism for the sacral nerve ganglia[3, 4]. Transmission of HSV1, as well as HSV2, occurs through close contact and results in lifelong infection (Zhu, 2021)[1]. HSV1 infection typically occurs in early childhood. Once the virus enters the body, it remains in the corresponding ganglion in its latent form until the next reactivation. HSV2 infection occurs later in life, usually through sexual transmission. However, in modern contexts, the epidemiology of HSV is changing[2]. There is significant overlap in clinical manifestations, where an increasing number of cases of genital herpes are caused by HSV1, as well as cases of oral herpes caused by HSV2[4].

The clinical manifestations and treatment

The clinical manifestations of HSV1 and HSV2 infections can range from asymptomatic to mild or life-threatening, but in the majority of immunocompetent individuals, they result in a mild illness that may not require treatment and often resolves spontaneously. Diseases caused by HSV include oral herpes, genital herpes, *eczema herpeticum*, herpetic stromal keratitis, disseminated neonatal disease, meningitis, and *herpes simplex encephalitis*[1].

HSV1 infection typically occurs 3-10 days after initial contact with the virus and most commonly presents as *herpes simplex orofacialis*. It begins with the appearance of multiple vesicles that, upon rupture, leave painful erosions on the mucous membranes of the oral cavity and throat, as well as on the cornea and conjunctiva. Following the primary infection, several infected individuals will experience recurrent infections, often in the form of herpes labialis[5]. HSV2 infection occurs 2 to 21 days after initial contact with the virus and clinically presents as multiple small vesicles that quickly become painful erosions. The infection can then manifest as balanitis, vulvovaginitis, cervicitis, urethritis, and anal inflammation. Other symptoms related to this condition are mild, but recurrent infection in the form of genital herpes is common[5].

For the treatment of HSV infections, there are currently three classes of licensed antiviral agents, all of which target viral DNA (Deoxyribonucleic acid). These include acyclic guanosine analogs - acyclovir, ganciclovir, and penciclovir, as well as analogs of acyclic nucleotides, such as cidofovir and the pyrophosphate analog foscarnet[2]. Nucleoside analogs directly target viral DNA polymerases in their active form,

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leading to the inhibition of viral DNA replication and halting the formation of infectious virions[6].

Acyclovir is one of the most commonly used antiviral drugs for herpes infections and acts as a competitive inhibitor of viral thymidine kinase (TK), inhibiting the activity of both TK and DNA polymerase. By stopping the complete replication of the viral genome through DNA polymerase inactivation, the formation of mature virions is also prevented[6]. In the treatment of primary infections in immunocompetent patients, acyclovir is administered at doses of 200-400 mg, five times a day for 5 to 7 days. Suppressive or prophylactic therapy is also recommended for cases of frequent recurrent infections and patients with compromised immune systems. In these cases, the dose of acyclovir is 400 mg, taken twice a day for several months[5].

Recurrent herpes labialis

Recurrent labial herpes (Images 1 and 2) is a mucocutaneous disorder that affects 10-30% of the adult population, with a recurrence rate ranging from episodic events to monthly recurrences[3]. It is always preceded by painful prodromal symptoms such as tingling, paresthesia, and a burning sensation in the affected area. These symptoms usually occur a few hours or 1 to 2 days before the clinical manifestation. A cluster of small vesicles appears on the erythematous and edematous surface of the lips, which then form crusts and heal without leaving scars. Although the exact cause of these recurrent episodes is still unknown, several contributing factors have been identified so far (Table 1). These factors can be physical, such as dental and neurosurgical interventions, various dermo-cosmetic procedures on the face, as well as UV radiation and local traumas. Hormonal factors like menstruation, pregnancy, and psychogenic factors such as severe stress may also play a role in its occurrence[3].

Dermocosmetic procedures as potential triggers

Patients undergoing dermo-cosmetic facial procedures, including chemical peels, dermabrasion, laser treatments, and filler procedures, are at a higher risk of recurrent herpes simplex oropharyngeal infection[3]. Although reactivation of herpes after hyaluronic acid injection is rare, most cosmetic practitioners lack awareness of prevention, diagnosis, or treatment due to a lack of experience. Mechanisms that can lead to herpes reactivation and outbreaks after hyaluronic acid injections may include local trauma (such as direct axonal damage by the needle and tissue manipulation after filler injection), inflammatory reaction following filler rejection, systemic stress, or immunosuppression. Reactivation of the virus typically occurs at the injection site, mainly in the perioral region and nasolabial folds. Changes are usually observed within 24 to 48 hours after the procedure[7]. When it comes to the reactivation of herpes after hyaluronic acid filler injections, the diagnostic criteria include: a history of recent hyaluronic acid injection into the face (within the 48 hours preceding the examination), skin lesions consistent with herpes appearance or neurological symptoms of encephalitis, even if there is no prior history of herpes, and experimental testing that yields positive results[7].

Image 1. Recurrent *herpes labialis*

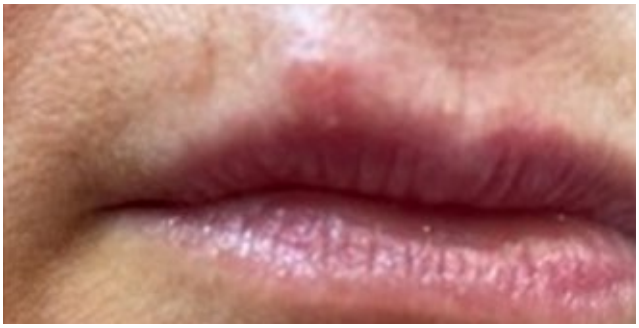


Image 2. Recurrent *herpes labialis*

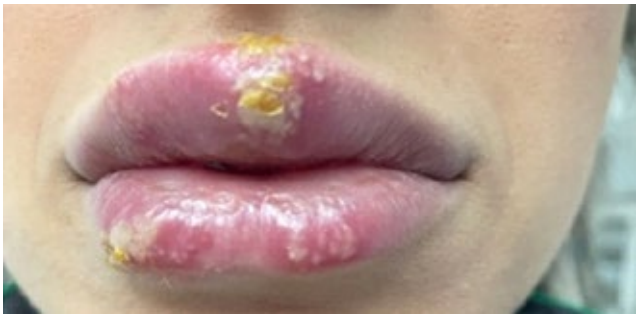


Table 1. Factors contributing to the occurrence of recurrent labial herpes[3]

	Systemic factors
Fever	Herpes
Hormonal	Menstruation (*catamenial herpes*), pregnancy
Infectious	Influenza, erysipelas, meningitis, pneumonia, etc.
Immunosuppression	Iatrogenic, cancer, chemotherapy, medications used for organ transplantation, etc.
Psychological	Stress, fatigue, psychological factors.
Physically	Ultraviolet radiation (*solar herpes*).
Traumatic	Direct contact (*herpes gladiatorum*), burns, cuts.
Surgical	Neurosurgical procedures, dental and cosmetic procedures.

Table 2. Presents studies on cases of HSV reactivation after hyaluronic acid injection[7]

Study	Age	Gender	Location	Symptoms	Duration	Test (Result)	Therapy
Dougherty et al, 2011.	Unknown	Female	Mouth	Swelling resembling angioedema, erythema, pain, crusting	12 h	Bacterial and viral cultures (HSV1+)	Valacyclovir
Gazzola et al, 2012.	34	Female	Mouth	Vesicles	2 days	Unknown	Acyclovir
Khoo et al, 2018.	27	Female	Nose	Headaches and seizures	5 weeks	Cerebrospinal fluid (HSV1+)	Acyclovir
Kim et al, 2013.	Unknown	Female	Mouth	Swelling, crusts	Unknown	Unknown	Acyclovir

Recurrent herpes genitalis

Recurrent genital herpes is much more common, occurring approximately 3 to 4 times a year. The first recurrence usually happens about four months after the primary infection, with subsequent reactivations occurring every 6 to 8 weeks. Clinical manifestations are typically preceded by a prodromal stage of tingling and/or itching 12 to 48 hours before the appearance of lesions. Skin changes manifest as multiple vesicles in the genital area, accompanied by severe pain and itching, and can last for 8 to 12 days, ending with healing without scarring (Images 3, 4, 5, and 6).

Image 3. Recurrent *herpes genitalis*

Image 4. Recurrent *herpes genitalis*

The therapy for genital and labial herpes

The peak of viral titers occurs within the first 24 hours in cases of genital and labial herpes infections. Within 48 hours of a labial herpes infection, lesions progress from the vesicular stage to the ulcer or soft crust stage. In the case of genital lesions, the progression depends on the condition of the skin surface, ranging from the 3rd to 4th day when the surface is dry, to the 8th or 9th day when the surface is moist. Due to the rapid replication of the virus and subsequent lesion progression in both cases, the therapeutic window for treating HSV infections with antiviral drugs is very narrow.

Image 5. Recurrent *herpes genitalis*

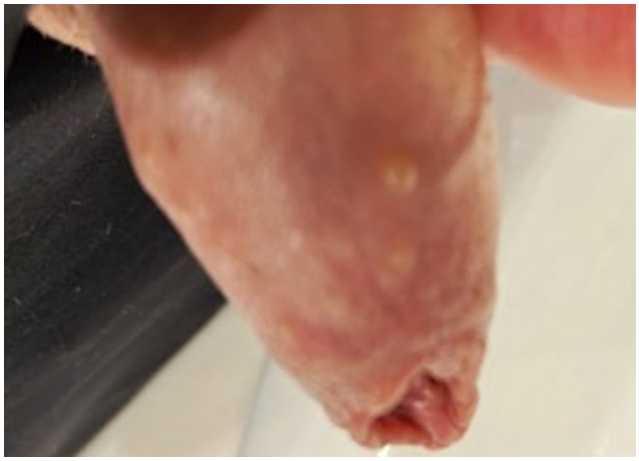
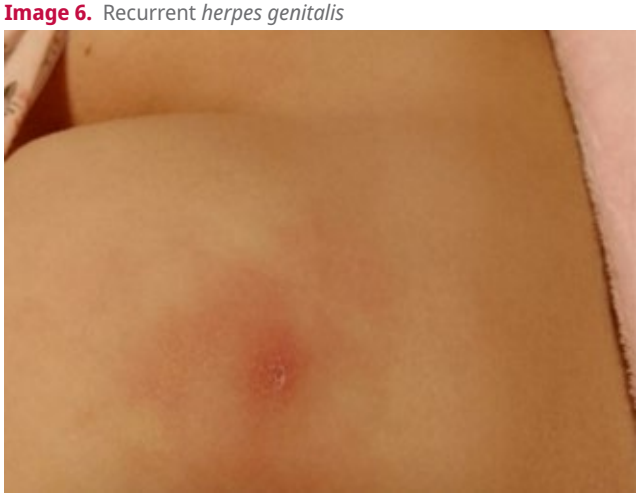


Image 6. Recurrent *herpes genitalis*



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Effectively treating recurrent HSV outbreaks is therefore quite challenging. However, since many patients will experience prodromal symptoms before the appearance of skin lesions, these patients need to be able to recognize them and self-administer appropriate therapy accordingly. This practice can be extremely beneficial for HSV treatment. Given that the viral replication period is early and short, many recent or newer clinical trials suggest that shorter-duration treatment with higher doses of antiviral drugs may be more suitable and equally or potentially even more effective. This practice would also reduce the likelihood of treatment resistance and the occurrence of unwanted side effects.

One of the recent studies was a placebo-controlled trial of a two-day acyclovir therapy conducted by Wang et al[7]. This study investigated the effect of shorter-duration acyclovir therapy on recurrent genital herpes in 84 patients who had experienced three or more recurrences of genital herpes in the previous 12 months (Table 3). The patients were randomly assigned to receive either 800 mg of acyclovir three times a day for two days or a corresponding placebo. Patients were instructed to initiate the appropriate treatment within 12 hours of the first symptom. The result of this short-duration acyclovir therapy was a reduction in healing time (P=0.001) and episode duration (P < 0.001) by 2 days compared to the placebo. Additionally, an increase in the number of patients with aborted lesions compared to the placebo was demonstrated (27% *vs* 11%; P=0.029)[7].

Similar studies have demonstrated the effectiveness of short-duration high-dose oral antiviral therapy compared to three-day and five-day valacyclovir therapy, as well as one-day famciclovir therapy (Table 4). The clinical trial of valacyclovir included 800 participants randomly assigned to receive either 500 mg of valacyclovir for three days or 500 mg of the same drug for five days, initiated within the first 24 hours of symptom onset. This study showed that the three-day valacyclovir therapy had a similar effect to the five-day therapy in terms of time to lesion healing, episode duration, and the number of patients with aborted lesions. The famciclovir trial tested the effect of one-day therapy with 1.000 mg of famciclovir taken twice daily, to be administered within the first 6 hours of symptom onset. This one-day treatment resulted in a shorter time to lesion healing by two days (P < 0.001), as well as a higher number of patients without full outbreak of lesions (23% *vs* 13%; P=0.003). Short-term famciclovir therapy showed significant results in the treatment of recurrent herpes labialis in a placebo-controlled trial

Table 3. Effects of Short-Term OAV Therapy on Genital Herpes Treatment[8]

Medicine	Duration of therapy	Dose	Control	Meantime (days) (therapy *vs* control)	Mean episode duration (days) (therapy *vs* control)	Patients with interrupted episodes (%) (therapy *vs* control)
Valacyclovir	3 days	500 mg, 2 times a day	Valacyclovir 500 mg, 2 times a day, during the next 5 days	4.4 *vs* 4.7 (P=NS)	4.3 *vs* 4.4 (P=NS)	25 *vs* 27 (P=NS)
Acyclovir	2 days	800 mg, 3 times a day	Placebo	4.0 *vs* 6.0 (P=0,001)	4.0 *vs* 6.0 (P=0,001)	27 *vs* 11 (P=0.029)
Famciclovir	1 day	1.000 mg, 2 times a day	Placebo	4.3 *vs* 6.1 (P < 0.001)	3.5 *vs* 5.0 (P < 0.001)	23 *vs* 13 (P=0.003)

Note: The healing time of lesions measures the duration of a subset of severe or classic herpetic outbreaks, characterized by the formation of vesicles, ulcers, or crusts (also papules in some studies). The endpoint is lesion reepithelialization/crust loss. Episodes with only prodromal symptoms, erythema, and/or papule formation (or only symptoms and/or erythema in some studies) are considered "aborted" or prevented lesion occurrences. The occurrence of these favorable outcome episodes is described as a percentage of all episodes. Episode duration, sometimes referred to as the time to heal all lesions or the time to return to a state of normal skin, is the time for the resolution of all episodes, regardless of lesion severity. The definition of normal skin varies in different studies.
Legend: NS - Not significant.

Table 4. Effects of Short-Term Antiviral Therapy on Recurrent Herpes Labialis Treatment[8]

Medicine	Duration of therapy	Dose	Comparative Therapy	Control	Mean Duration (days) (treatment-control)	Mean Episode Duration (days) (treatment-control)	Patients with Interrupted Episodes (%) (treatment-control)
Valacyclovir	1 day	2.000 mg, 2 times a day	Valacyclovir 2.000 mg, 2 times a day first day; 1.000 mg, 2 times a day, during the second day	Placebo	Study 1 4.3 *vs* 4.3 *vs* 5.1 Study 2 4.8 *vs* 4.6 *vs* 5.4	Study 1 4.0 *vs* 4.5 *vs* 5.0 Study 2 5.0 *vs* 5.0 *vs* 5.5	Study 1 44 *vs* 46 *vs* 38 Study 2 43 *vs* 43 *vs* 35
Famciclovir	1 dose	1.500 mg	Famciclovir 750 mg, 2 times a day, during one day	Placebo	4.4 *vs* 4.0 *vs* 6.2	4.5 *vs* 5.7 *vs* 7.0	33 *vs* 29 *vs* 34

Note: The healing time of lesions measures the duration of a subset of severe or classic herpetic outbreaks, characterized by the formation of vesicles, ulcers, or crusts (also papules in some studies). The endpoint is lesion reepithelialization/crust loss. Episodes in which only prodromal symptoms, erythema, and/or papule formation existed (or only symptoms and/or erythema in some studies) are considered "aborted" or prevented lesion occurrences. The occurrence of these favorable episode outcomes is described as a percentage of all episodes. Episode duration, sometimes referred to as the time for healing of all lesions or the time to return to normal skin state, is the time for resolution of all episodes, regardless of lesion severity. The definition of normal skin varies in different studies.
*****All values of lesion healing time and episode duration for active treatment groups in both studies were statistically significantly different from placebo, except for famciclovir 750 mg twice daily for one day.
† None of the frequency of aborted lesions in active therapeutic groups in either study differed significantly from placebo.

using both single-dose and one-day famciclovir therapy, comparing the effect of 1.500 mg (single dose) versus 750 mg twice daily (one-day doses) of famciclovir. The drug was administered within the first hour of symptom onset, before the appearance of skin lesions. The results of this study demonstrated a significantly reduced time for primary lesion healing with both of these doses compared to placebo, but only the single dose of famciclovir showed a noticeable reduction in time to pain resolution and return of skin to normal state[8].

Conclusion

Based on the analyzed literature and considering our own experience in the clinical prevention and treatment of recurrent labial and genital herpes, acyclovir remains the most effective treatment choice for the majority of patients. In some cases, other similar antiviral drugs may be effective when treatment with acyclovir does not yield the expected results. Timely prescription of acyclovir for patients with recurrent herpes would be the proper approach to avoid the manifestation of clinical disease that may accompany each new episode or recurring herpes triggered by medical or cosmetic procedures.

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