

Recurrent Herpes Labialis in Adults: New Tricks for an Old Dog

Ted Rosen MD
Baylor College of Medicine, Houston, TX

ABSTRACT

Herpes labialis remains a common worldwide affliction. Recent advances in understanding the basic pathogenesis have led to new therapeutic intervention, both on-label and off-label. Aside from reducing the duration and symptomatology of acute outbreaks, another goal of treatment is to decrease the frequency of future episodes. Oral and topical acyclovir and its analogues are the mainstay of both chronic suppressive and episodic therapy. A new muco-adhesive formulation of acyclovir provides a decrease in outbreaks, probably due to a diminution of herpesvirus load in all reservoir sites. Acyclovir-resistant strains are rare in immunocompetent hosts; parenteral foscarnet and cidofovir are administered in this situation. Parenteral acyclovir is the drug of choice for eczema herpeticum, which may begin as herpes labialis in an atopic dermatitis patient. Thermotherapy may be beneficial, and a certified device to deliver heat is available outside the United States.

J Drugs Dermatol. 2017;16(3 Suppl):s49-53.

INTRODUCTION

The prevalence of common herpes viruses varies greatly by continent, country, and even region within a country, as well as by population subgroup (such as age, gender, and immune status). However, based upon recent evidence, HSV-1 is rather ubiquitous worldwide, typically reaching about 40% seroprevalence by age 15 and then rising to a seroprevalence of 60-90% among older adults.[1,2] While some HSV-1 infections cause genital herpes, this virus is predominantly responsible for oro-labial disease, commonly referred to as "cold sores" or "fever blisters." This disorder is most common in Caucasian women, although it certainly can affect both genders and individuals from any ethnic group.

Oro-labial herpes may occur as a singular event, or it may become a periodically recurrent disorder. Recurrent HSV-1 outbreaks are generally associated with mild morbidity, notably a low risk of scarring. However, outbreaks are also quite variable in both frequency and severity.[3] For those who experience frequently recurrent oro-labial herpes, these often painful and usually unsightly lesions engender considerable stress and anxiety.[4] It can be estimated that between 15-40% of those infected with HSV-1 involving the peri-oral region will develop bothersome recurrences.[5-7] Factors that can lead to recurrences include, but are not limited to: emotional stress or physical fatigue, infection (most often upper respiratory), exposure to ultraviolet light, local trauma (including medical procedures in close proximity to the mouth), menses, and immunosuppression.[8] On the other hand, some recurrences occur without any appreciable precipitating event. Interestingly, smoking tobacco products has been associated with both less frequent and less severe HSV-1, although it is doubtful that any healthcare provider would offer this as a therapeutic intervention.[9]

Rationale for Treatment

It is certainly worth a short discussion about whether such a common and relatively banal disease warrants any treatment at all. The opinion of this author is that therapy is justified for many disparate reasons. Treatment may shorten the duration of an attack, thereby reducing the duration of cosmetically distressing lesions and associated emotional upset. In fact, "cold sore" sufferers' emotional upset is actually quite justified. A recent survey study disclosed that oro-labial herpes simplex infections are among the two most stigmatizing of all cutaneous disorders; so much so, that a majority of those surveyed would be ashamed if they themselves had herpes labialis, would find another person unattractive if they had herpes labialis, and wouldn't want to touch or share food/drink with someone afflicted with HSV-1.[10] Treatment may also decrease the duration of pain (or discomfort) attendant to an outbreak. Therapy may encourage or hasten healing, which normally takes 12-17 days from the onset of the associated prodrome. Despite an overall low inherent risk, treatment should reduce the potential for residual scarring. As discussed below, select treatments may even alter the natural disease history by reducing the frequency of future recurrences. A more theoretical rationale for treatment is to reduce the ongoing asymptomatic shedding of virus, which occurs on the oral mucosa about 20-25% of days of the year.[11] Moreover, considering the high degree of safety of the current anti-viral therapeutic armamentarium directed toward HSV-1 infection, it appears that treatment is clearly warranted, especially if the patient desires therapy.

TABLE 1.

Treatments for Primary Oro-labial HSV-1		
Anti-viral drug	**Dose**	**FDA Approved?**
Acyclovir	15 mg/kg 5x daily for 7 days	Not for age < 12
Valacyclovir	1.0 g BID for 7 days	Not for age < 12
Famciclovir	500 mg BID for 7 days	Not for age < 12

Adopted from reference 12 and package inserts

Primary Herpetic Gingivo-Stomatitis

Although discussion of this entity, most often seen in the pediatric population, is beyond the scope and purpose of this paper, the typical treatment options are shown in Table 1. Please note that the safety and efficacy of the commonly used oral anti-herpes drugs (acyclovir and its analogues) have not been established in the population under 12 years of age; therefore, formal FDA approval does not exist.[12]

Recurrent Oro-Labial Herpes: Suppressive Therapy

In managing recurrent HSV-1, there are several key decisions. Most importantly, the clinician must decide between episodic treatment (only administered during an outbreak) or chronic suppressive treatment. Episodic therapy can be accomplished via topical, systemic, and mucosal routes of drug administration, whereas chronic suppressive therapy is primarily accomplished by oral anti-viral drug administration. Some possible reasons to choose episodic or suppressive therapy are enumerated in Table 2, with the caveats that therapeutic choices must always be individualized and selected by the healthcare provider following thorough discussion with the patient. Anti-viral drug dosages frequently utilized in chronic suppression are shown in Table 3. However, none of these regimens are FDA approved, and chronic anti-viral drug suppression of HSV-1 with resultant reduction in clinical outbreaks is much more difficult to successfully achieve than with HSV-2-related genital herpes.[12,13] As aptly summarized in a recent Cochrane Systematic Review: "The current evidence demonstrates that long-term use of oral antiviral agents can prevent HSL (herpes simplex labialis), but the clinical benefit is small."[14] Acyclovir has also been associated with several different forms of nephrotoxicity; this problem is discussed below. A host of other potential interventions designed to prevent herpes labialis outbreaks (such as oral lysine, ingestion of various food supplements, low-level laser therapy, administration of gamma globulin, or yellow fever vaccine) have not proven successful.[14] The use of topical imiqumod, when applied directly to the lesion as an attempt to meaningfully suppress herpes labialis, has largely been abandoned due to the potential for a severe local reaction.[15] However, an intriguing case report detailed the once daily occlusive application of ¼ a standard sachet of 5% imiquimod to a distant skin site for three weeks, with the treatment starting during an active outbreak.[16] This method resulted in a massive polarized Th-1 immune response with interferon-γ release, and notable clinical suppression: namely, a remission of one and a half years duration.[16] Unfortunately, there have been no confirmatory or follow-up reports regarding this method of attaining disease suppression.

TABLE 2.

Episodic versus Suppressive Therapy	
Episodic Therapy if….	**Suppressive Therapy if….**
Infrequent outbreaks	Frequent outbreaks
Mild-Moderate disease	Severe disease
Patient preference	Patient preference
No erythema multiforme	Associated with erythema multiforme
No eczema	Patient has eczema
Clearly defined prodrome	No prodrome
Suppression fails	Suppression works well

Recurrent Oro-Labial Herpes: Episodic Therapy

As noted previously, there exists a plethora of therapeutic choices for the episodic management of oro-labial herpes. It should be noted that all episodic interventions demonstrate optimal benefit when administered immediately upon onset of the outbreak prodrome. Topical therapies are listed in Table 4. Why might topical therapy be preferred by select patients? Some reasons include: few real or potential side effects in the short-term and no long-term health concerns; no drug-drug interactions to consider; easy portability and rapid initiation; application right to the site of cutaneous pathology giving the patient a feeling of empowerment; and cost-effectiveness. However, even a cursory glance at Table 4 shows that

TABLE 3.

Chronic Suppression of HSV-1 Oro-labial Herpes			
Agent/Dose	**Maximum decrease in number overt outbreaks**	**Time studied**	**FDA Approval**
Acyclovir 400 mg BID-QID	53%	4 months	No
Valacyclovir 500-1000 mg daily or 500 mg BID	50%	4-6 months	No
Famciclovir 500 mg BID	Uncertain data	Very short term	No

Adopted from reference 12

TABLE 4.

Topical Episodic Therapies for Herpes Labialis			
Agent	**Decrease in resolution time**	**Decrease in pain duration**	**Miscellaneous**
Acyclovir 5% Cream	0.5 – 2.0 days	Minimal	Ointment not as effective
Penciclovir 1% Cream	0.7-1.2 days	0.6-1.0 day	May be applied after the prodrome
Docosanol 10% Cream	0.75-1.6 days	0.5-0.6 day	Over-the-counter Increased aborted attacks
Acyclovir 5% Hydrocortisone 1% Cream	1.4 days	1.0 day	Fewer lesions progress to frank erosion

Adopted from reference 12 and package inserts

the clinical benefits from episodic topical therapy are modest. While topical drugs are quite safe, such agents are also very inconvenient, as they are require frequent and prolonged application. Acyclovir cream approved use is five times daily for four days; penciclovir cream is to be applied every two hours while awake for four days; docosanol cream is five times daily "until healed"; and acyclovir-hydrocortisone cream indicated dosage is 5 times daily for 5 days. The newest of the approved topical agents, acyclovir 5%-hydrocortisone 1% cream, was first introduced in 2009, and theoretically uniquely addresses both symptomatic relief and healing by concurrently reducing inflammation while exerting direct anti-viral effects.[17] Two unique benefits related to this agent compared to placebo are smaller ultimate mean lesional size and fewer outbreaks progressing to overt erosion.[17]

An interesting adaptation of the aforementioned steroid/anti-viral combination as episodic therapy was tested on 42 patients, wherein a placebo-placebo group was compared to subjects who received valacyclovir (2 g orally BID for 1 day) and topical clobetasol gel 0.05% (BID for 3 days applied to the affected area).[18] Patients who received the combination therapy experienced more aborted lesions (50% versus 15.8%), a reduced the mean maximum lesion size (9.7 versus 54 mm) and most strikingly a lower mean healing time of classical lesions (5.8 versus 9.3 days).[18] This regimen, while proving quite effective in a small randomized and controlled study, did not alter the long-term natural disease history. A different, similarly sized (n=49) study compared oral famciclovir 500 mg and topical fluocinonide .05% gel, administered three times daily for five days, to oral famciclovir and gel vehicle dosed in the same manner. In this steroid/anti-viral comparison to an active anti-viral agent plus placebo, addition of the steroid proved beneficial on some efficacy parameters; namely, the topical steroid/oral anti-viral subjects experienced: more aborted lesions, reduced maximum lesion size, and non-statistically significant reduced duration of pain and reduced healing time.[19] Based on just a few studies, it appears that the addition of a topical corticosteroid to antiviral therapy produces improvements in the clinical course of herpes labialis, compared to antiviral agent monotherapy, and that such combination therapy shows an even greater degree of benefit compared to no treatment.

What about episodic oral anti-viral therapy? The most typically utilized oral therapies are summarized in Table 5. For all these regimens to be successful, drug is best taken within one hour of the onset of a prodrome. In patients lacking a definable prodrome, drug should be taken within 48 hours of the onset of any sign or symptom (eg, erythema, papule, or vesicle formation). As is true of topical therapy, episodic treatment with oral anti-viral drugs provides modest improvements in time to lesion healing and duration of pain. It should be noted that acyclovir is relatively insoluble in urine, is rapidly filtered by glomeruli and secreted by renal tubules, thereby producing high urinary concentrations, especially in patients with pre-existing renal impairment.[20] In turn, this may lead to direct renal tubular toxicity, acute interstitial nephritis and/or crystal nephropathy.[21] While the absolute risk is certainly small (<0.5%) and discontinuation

TABLE 5.

Oral Episodic Therapies for Herpes Labialis				
Agent	**Decrease in resolution time**	**Decrease in duration of pain**	**Increase in aborted episodes**	**Miscellaneous**
Acyclovir 400mg 5 times daily for 5 days	1.0 day	1.3 days	14%	Oral suspension available Not FDA approved
Valacyclovir 2.0 grams twice, 12 hours apart	1.0 day	0.5 day	10-22%	FDA approved
Famciclovir 1.5 grams once or 750 mg BID	2.0 day	1.2 days	2.4-15.4%	FDA approved

Adopted from reference 12 and package inserts

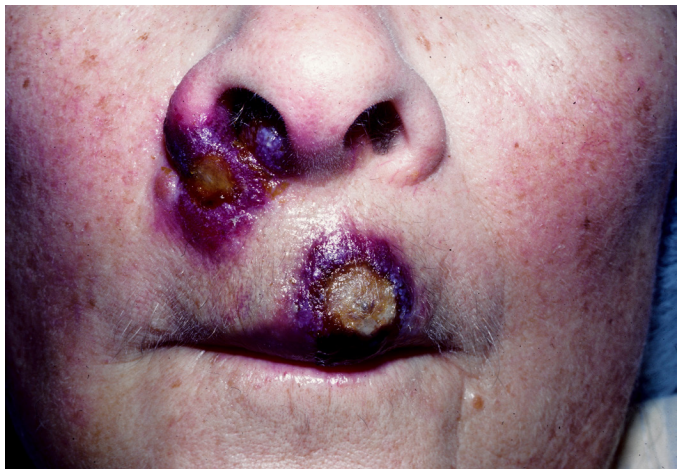
of the offending drug usually results in a rapid return to normal renal function, oral acyclovir (or valacyclovir) may induce acute nephrotoxicity.[22] This may be a realistic consideration – both during high dose episodic and chronic suppressive therapy - in those individuals with diabetes, hypertension, or any other reason for decreased creatinine clearance. Famciclovir is apparently not similarly linked to kidney damage.

A recent (approved April, 2013) innovation in herpes labialis treatment is a muco-adhesive buccal tablet containing 50 mg of acyclovir. Large multinational pivotal trials included well over 700 patients. A milk derived protein functions as an adhesive that allows the tablet to stick to the ipsilateral upper canine fossa for the requisite 6 hours until dissolution. During the time the intact tablet adheres to the buccal mucosa and gradually dissolves, eating and drinking are permitted. If applied as studied (within one hour of prodrome onset), the drug hastens episode resolution by one day, reduces time to healing by about a half day, and leads to a greater number of aborted attacks (35%) compared to placebo.[23] What is rather unique about this drug is that it has been shown to actually reduce the number of future outbreaks and increase the time between subsequent outbreaks; muco-adhesive acyclovir tablets increased the time to next recurrence by 40 days (median) to 105 days (mean).[23] "Real world" utilization may lead to even better performance in this regard.[24] In short, acyclovir buccal tablet is the first antiviral drug that has demonstrated reduction in the number of fever blister outbreaks following an episodic treatment. Why can a single 50 mg tablet provide such benefit? Despite very low acyclovir plasma concentration, the buccal adhesive tablet provides extremely high concentrations in saliva and both oral and labial tissue.[25] In this manner, the overall viral load is likely reduced by addressing all the likely HSV-1 reservoirs, not only in the trigeminal ganglia but also within the peripheral nerves and oral soft tissues. The simple course of therapy (one tablet), a lack of significant plasma concentration, and the ability to alter the natural course of the disease all make this an exciting new modality for those with frequently recurrent herpes.

Role of Parenteral Acyclovir

Acyclovir Sodium Injection is a sterile, aqueous solution for intravenous infusion, containing 50 mg acyclovir per mL. This formulation is indicated for the following HSV-1 infections: herpetic encephalitis, neonatal herpes infection, and both initial and recurrent mucosal and cutaneous herpes simplex in immunocompromised patients. The standard dose is 5 mg/kg infused over one hour, every eight hours; higher doses may be utilized for encephalitis, in neonates, and for eczema herpeticum. Adequate hydration is essential and dosage adjustments are mandatory in the face of reduced renal function. Because herpes labialis in immunocompromised and immunosuppressed individuals can be devastating (Figure 1), parenteral acyclovir is often used. However, at least one meta-analysis suggested that intravenous acyclovir and oral valacyclovir (1 gram BID) might well be equipotent.[26]

FIGURE 1. Severe HSV-1 associated with leukemia chemotherapy.



Acyclovir Resistance

HSV-1 acyclovir resistance is rare in clinical isolates obtained from the general population (<1%), but is common among clinical isolates obtained from immunosuppressed and immunocompromised individuals (between 2.5% and 10.9%)[27] Acyclovir resistance is due to genetic mutations producing polymorphisms in the thymidine kinase and/or DNA polymerase genes. Luckily, many acyclovir-resistant mutants exhibit a reduction in their capacity to establish latency and to reactivate. Intravenous foscarnet or cidofovir are usually utilized. Details can be found elsewhere.[27,28]

Thermotherapy

Short application of intense heat may be of benefit. A certified medical device which delivers a four second burst of 50-51^{0}C heat through a small portal is in wide use in England, Europe, Canada, and Australia. When applied one to two times during the day of prodrome onset, the process may be aborted (no vesicles or erosions). If used on already active lesions, it may shorten the time to resolution by up to eight days. This device is not approved in the United States but is readily available on foreign versions of Amazon.

DISCLOSURES

Attendee and Facilitator, Advisory Boards, Cipher (formerly Innocutis) Pharmaceuticals.

REFERENCES

1. Smith JS, Robinson NJ. Age-specific prevalence of infection with herpes simplex virus types 2 and 1: A global review. *J Infect Dis*. 2002;186(suppl1):S3–S28.
2. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA*. 2006;296:964-73.
3. Spruance SL, Kriesel JD. Treatment of herpes simplex labialis. *Herpes*. 2002;9:64-9.

4. Logan HL, Lutgendorf S, Hartwig A, et al. Immune, stress, and mood markers related to recurrent oral herpes outbreaks. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1998;86:48-54.
5. Embil JA, Stephens RG, Manuel FR. Prevalence of recurrent herpes labialis and aphthous ulcers among young adults on six continents. *Can Med Assoc J.* 1975;113:627-30.
6. Nikkels AF, Pièrard GE. Treatment of mucocutaneous presentations of herpes simplex virus infections. *Am J Clin Dermatol.* 2002;3:475-87.
7. Fatahzadeh M1, Schwartz RA. Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management. *J Am Acad Dermatol.* 2007;57:737-63.
8. Yeung-Yue KA, Brentjens MH, Lee PC, et al. Herpes simplex viruses 1 and 2. *Dermatol Clin.*2002;20:249-66.
9. Wolf R, Wolf D, Ruocco V. The benefits of smoking in skin diseases. *Clin Dermatol.* 1998;16:641-7.
10. Donigan J, Pascoe V, Kimball A. Psoriasis and herpes simplex virus are highly stigmatizing compared with other common dermatologic conditions: A survey-based study. *J Am Acad Dermatol.* 2015;73:525-526.
11. Ramchandani M, Kong M, Tronstein E, et al. Herpes Simplex Virus Type 1 Shedding in Tears and Nasal and Oral Mucosa of Healthy Adults. *Sex Transm Dis.* 2016;43:756-760.
12. Cernik C, Gallina K, Brodell RT. The treatment of herpes simplex infections: an evidence-based review. *Arch Intern Med.* 2008;168:1137-44.
13. Rahimi H, Mara T, Costella J. Effectiveness of antiviral agents for the prevention of recurrent herpes labialis: a systematic review and meta-analysis. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2012;113:618-27.
14. Chi CC, Wang SH, Delamere FM, et al. Interventions for prevention of herpes simplex labialis (cold sores on the lips). *Cochrane Database Syst Rev.* 2015 Aug 7;(8):CD010095.
15. Bernstein DI, Spruance SL, Arora SS, et al. Evaluation of imiquimod 5% cream to modify the natural history of herpes labialis: a pilot study. *Clin Infect Dis.* 2005;41:808-14.
16. Tsambaos D, Rodi M, Pasmatzi E, et al. Long-term remission of recurrent herpes labialis following topical imiquimod application on distant healthy skin: a clinical and immunological study. *Antivir Ther.* 2011;16:863-9.
17. Hull CM, Harmenberg J, Arlander E, et al. Early treatment of cold sores with topical ME-609 decreases the frequency of ulcerative lesions: a randomized, double-blind, placebo-controlled, patient-initiated clinical trial. *J Am Acad Dermatol.* 2011;64:696.e1-11.
18. Hull CM, McKeough M, Sebastian K, et al. Valacyclovir and topical clobetasol gel for the episodic treatment of herpes labialis: a patient-initiated, double-blind, placebo-controlled pilot trial. *J Eur Acad Dermatol Venereol.* 2009;23:263-67.
19. Spruance SL, McKeough MB. Combination treatment with famciclovir and a topical corticosteroid gel versus famciclovir alone for experimental ultraviolet radiation-induced herpes simplex labialis: a pilot study *J Infect Dis.* 2000;181:1906-10.
20. Yarlagadda SG, Perazella MA. Drug-induced crystal nephropathy: an update. *Expert Opin Drug Saf .* 2008;7:147–158.
21. Izzedine H, Launay-Vacher V, Deray G. Antiviral drug-induced nephrotoxicity. *Am J Kidney Dis.* 2005;45:804–817.
22. Lam NN, Weir MA, Yao Z, et al. Risk of acute kidney injury from oral acyclovir: a population-based study. *Am J Kidney Dis.* 2013;61:723–729.
23. Bieber T, Chosidow O, Bodsworth N, et al. Efficacy and safety of acyclovir mucoadhesive buccal tablet in immunocompetent patients with labial herpes (LIP Trial): A double-blind, placebo-controlled, self-initiated trial. *J Drugs Dermatol.* 2014;13:791-798.
24. Rosen T. Pragmatic and Profound Benefits of Acyclovir Buccal Adhesive Tablets.*J Drugs Dermatol.* 2016;15:775-7.
25. Lemarchand C, Singlas E, Costantini D, et al. Plasma, saliva and labial mucosa pharmacokinetics and pharmacodynamics of acyclovir Lauriad® mucoadhesive buccal tablet in healthy volunteers. *J Clin Pharmacol Clin Pharmacokin.* 2014;1 (1).
26. Glenny AM, Fernandez Mauleffinch LM, Pavitt S, et al. Interventions for the prevention and treatment of herpes simplex virus in patients being treated for cancer. *Cochrane Database Syst Rev.* 2009 Jan 21;(1):CD006706.
27. Piret J, Boivin G. Resistance of herpes simplex viruses to nucleoside analogues: mechanisms, prevalence, and management. *Antimicrob Agents Chemother.* 2011;55:459-72.
28. Chilukuri S, Rosen T. Management of acyclovir-resistant herpes simplex virus.*Dermatol Clin.* 2003;21:311-20.
29. Schlippe G, Voss W, Bayer M, et al. Neue Behandlungsmethode bei einem Herpes-labialis-Rezidiv. [New method of treatment for a herpes labialis recurrence]. *Derm Praktische Dermatologie.* 2011;17:340–342.[Article in German]

AUTHOR CORRESPONDENCE

Ted Rosen MD

E-mail:..... vampireted@aol.com