How to manage recurrent orofacial herpes simplex virus-1 lesions

Recurrent herpes labialis can cause significant inconvenience, pain, embarrassment and distress. **Gerd Gross**, **Keith Harding**, **Tonny Karlsmark**, **Robert S. Kirsner**, **Michael Lewis**, **Arjen Nikkels** and **Leslie N. Schechter** review the presentation, prevention and treatment of this disease and also focus on a novel therapeutic approach using occlusive hydrocolloid patches

Recurrent herpes labialis (RHL), or cold sores, represents the most frequent presentation of orofacial human herpes simplex virus-1 (HSV-1) infection. A common infection, RHL can cause significant inconvenience, pain, embarrassment, psychological distress and potential disfigurement.[1] Frequent episodes can significantly reduce sufferers' quality of life.[2,3]

Although most individuals with a history of RHL experience no more than two episodes per year, up to 10 per cent experience at least six.[4]

RHL accounts for 1 per cent of primary care consultations in the UK.[5] However, many individuals with RHL prefer to seek advice from community pharmacists. In Canada, 30 per cent of surveyed pharmacists reported receiving frequent enquiries related to RHL (at least 10 times per month), compared with 2 per cent of physicians.[1] Therefore, community pharmacists are ideally positioned to advise patients on avoidance and over-the-counter treatment of cold sores, and to refer patients to a GP when necessary.

This article evaluates current treatment approaches and advances in the management of RHL, including a novel therapeutic approach using an occlusive hydrocolloid patch.

Causes

HSV-1 infection is nearly ubiquitous. Forty-five to 98 per cent of individuals show serological evidence of infection, with this seroprevalence rising with age.[6,7] The primary oral infection with HSV-1 typically occurs during childhood or adolescence through non-sexual contact and is characteristically asymptomatic.[7,8]

HSV-1 infection is highly contagious and primarily transmitted via saliva. The virus can be shed in the mouth and hence transmitted even when there are no active cold sores.[9] Immunocompromised patients and people undergoing oral surgery are particularly likely to shed HSV-1.[7] The virus can remain viable on the skin, clothing or plastic for brief periods, increasing the risk for transmission.[4] Pharmacists can play an important role in preventing RHL by explaining how the spread of HSV-1 could be minimised (see Panel 1).[10]

After the primary infection, HSV becomes persistent in a latent state, primarily in the trigeminal ganglion.[7,11] On reactivation, newly generated HSV-1 spreads along nerve fibres to mucocutaneous sites, yielding the symptoms of RHL. Thus, RHL occurs in 15 to 40 per cent of HSV-1 seropositive individuals, with the highest risk among women and young adults.[2,4,7,12] Factors that can trigger HSV-1 reactivation include trauma, fatigue, ultraviolet light exposure, menstruation and stress.[4,8,13]

Clinical presentation

Symptoms of primary HSV-1 infection are usually relatively mild and consist of small blisters that rapidly collapse and coalesce to form shallow, painful, irregular ulcers covered by a yellowish-grey membrane-like structure and surrounded by an erythematous halo.[7] These manifestations may occasionally be accompanied by fever, lethargy, loss of appetite, irritability and hypersalivation. In non-immunocompromised individuals, all signs and symptoms resolve within 10 days.

HSV-1 reactivation classically manifests as RHL (ie, cold sores), which presents as a well localised cluster of vesicles along the vermillion border of the lips (Figure 1).[4,7,8] RHL can be graded as simple or severe:

Figure 1: Recurrent herpes labialis outbreak in a healthy individual

- **Simple RHL** Up to three grouped vesicles.
- **Severe RHL** more than three grouped vesicles that are multifocal and associated with large, oedematous blisters or even eczema herpeticatum. Severe herpetic lesions may occasionally be accompanied by fever.[14]

The seven stages of RHL development have been outlined (see Panel 2).[12] Up to 60 per cent of sufferers experience prodromal symptoms,

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Panel 1: Advice on minimising the spread of cold sores[10]

- Avoid touching cold sores, unless you are applying a cream. Creams should be dabbed on gently (rather than rubbed in) to minimise skin damage
- Wash your hands before and after applying the cream, and after touching the affected area
- Do not share creams or other medicines with others
- Do not share items that come into contact with the affected area (eg, lipsticks or cutlery)
- Avoid kissing and oral sex until your cold sores have completely healed
- If you have a cold sore, be particularly careful around newborn babies, pregnant women and people with a low immune system, such as those undergoing chemotherapy or those with HIV

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Panel 2: Developmental stages of RHL*

Stage	Name	Average duration (days)	Description
1	Prodrome	1	Skin appears normal, but a tingling, burning pain or itching sensation is present; virus can be cultured from skin; systemic viral-like symptoms may be present
2	Erythema	1–2	Redness
3	Papule	1–2	Papules and swelling
4	Vesicle	1–2	Small fluid-filled blisters on an erythematous base that collapse or break open
5	Ulcer	1–3	Shallow grey ulcer or sore with bright red edge; most painful stage; weeping fluid is highly infectious
6	Crust	4–14	Amber-coloured crust develops into a hard, dark scab
7	Completion of skin re-epithelisation	4–14	Loss of crust; there may be some skin flaking, residual redness and swelling, and asymmetry; lesion is technically healed; skin pain may persist

*Adapted from Barbarash[12]

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which may include pain, burning, tenderness and tingling at the site of reactivation.[4,7] Approximately 25 per cent of RHL cases do not proceed beyond this stage. The prodromal stage is usually followed within 24 hours by the emergence of erythematous maculopapular lesions that quickly develop into small blisters, with single clusters varying in size from 0.5 to 1.5cm.[12] The vesicles subsequently collapse and form ulcers that crust over. Healing occurs over seven to 10 days.

Treatment

General approaches Simple remedies, such as the topical application of ice or alcohol, may help relieve some symptoms of RHL.[4] In addition, some natural treatments may reduce the pain associated with RHL and speed recovery, although opinion on their benefit remains divided. Natural approaches for which there is some published evidence of efficacy include lemon balm (*Melissa officinalis*),[15] lysine,[16] resveratrol,[17] vitamin C (with water-soluble flavonoids),[18] topical zinc,[19,20] and topical vitamin E.[21,22]

Various palliative cold sore treatments are available in the UK (Panel 3). These may relieve some RHL symptoms including pain, dryness and itching. Active ingredients, such as phenol, lidocaine and benzocaine, provide topical anaesthetic activity. These formulations also include some type of petroleum ointment to moisturise and protect the lesions.[12]

Antiviral agents Antiviral agents are typically reserved for the treatment of RHL episodes that are frequent, potentially disfiguring and anxiety inducing.[4] Simple RHL can be treated topically, while severe cases require oral treatment.[14]

Topical Antivirals creams are the most commonly recommended RHL treatments.[1] In the UK, creams containing aciclovir 5 per cent (Zovirax, Clearsore, Cymex Ultra, Lypsyl Cold Sore Cream, Soothelip, Soroway and Virasorb) and penciclovir (Fenistil and Vectavir) are available over-the-counter to treat RHL. When used promptly at the first sign of a lesion, aciclovir and penciclovir creams appear similarly effective in speeding healing time (by about one day) and reducing discomfort.[23–27]

Topical antivirals are most effective when used during the prodromal stage of RHL. Therefore, patients and pharmacists need to recognise the early signs of RHL and to begin topical treatment promptly. Antiviral creams have several limitations. The need for frequent application — five times daily for aciclovir and every two hours for penciclovir — is inconvenient and may affect adherence. Moreover, these preparations do not protect the lesion or prevent scab formation, and hence do not aid the healing of the lesion or mask its appearance.[28]

Oral Systemic antiviral treatment is necessary if cold sores recur frequently or for infections in the mouth.[29] Aciclovir and valaciclovir (a prodrug of aciclovir) are licensed for oral use for RHL in the UK.

Oral aciclovir has shown mixed results. In one small, randomised, double-blind study in patients with frequent RHL, aciclovir (400mg twice daily for four months) significantly lengthened the time to lesion recurrence and reduced the number of RHL episodes as compared with placebo.[30] However, a larger double-blind, randomised study in Canadian skiers with a history of RHL triggered by sun exposure showed that aciclovir (800mg twice daily 12 to 24 hours before sun exposure) provided no significant benefit in terms of prevention or healing rate versus placebo.[31]

Controversial evidence suggests that RHL induced by ultraviolet light may present as two types: "immediate" lesions that develop within 48 hours, and "delayed" lesions that occur after three to seven days.[13] Immediate lesions may result secondary to activation of herpes viruses dormant in the skin around the mouth and in the ganglion of the trigeminal nerve. These lesions, which comprise about a third of all lesions, may not respond satisfactorily to oral aciclovir. By contrast, prophylactic oral aciclovir may be more effective against delayed lesions.[32]

Two randomised studies have demonstrated the efficacy of oral valaciclovir in the treatment and prevention of RHL. In one study, valaciclovir (500mg daily for 16 weeks) delayed RHL recurrence in individuals with a history of more than four recurrent lesions in the previous year.[33] In the other study, valaciclovir (500mg twice daily) was 100 per cent effective in preventing RHL reactivation after facial resurfacing procedures, circumventing the associated problems of severe outbreaks, delayed re-epithelisation and scarring in this patient population.[34]

Famciclovir, a prodrug of penciclovir, has shown some efficacy in RHL,[35,36] but is not licensed for this indication in the UK.

RHL as a partial-thickness wound A novel approach to RHL therapy treats the cold sore lesion as a partial-thickness wound that may benefit from an occlusive dressing. By definition, a partial-thickness wound extends through the epidermis into, but not through, the dermis.[37,38] HSV-1 infection triggers an inflammatory process that penetrates through the epidermis into the dermis (Figure 2), although the virus itself may be restricted to the epidermis.[39]

The wound healing process involves stages of coagulation, inflammation, cell proliferation and tissue remodelling.[40] Attention has focused on the inflammatory phase since disruption or prolongation of this phase can affect healing.[37] For instance, during the inflammatory phase, neutrophils remove wound debris while macrophages ingest debris and secrete growth factors essential for wound repair. Moreover, in response to specific chemoattractants, leukocytes infiltrate the wound and, once activated, release growth factors that promote tissue formation.[41]

Occlusive dressings and wound healing Wounds exposed to the air dry out, forcing re-epithelialisation to occur beneath the scab.[42] Occlusive or semi-occlusive dressings substantially accelerate wound healing, as compared with standard dry dressings or air exposure.[42–48] Occlusive dressings may provide superior wound healing for a variety of reasons. They maintain a moist environment that allows the epidermis to move rapidly over the wound surface and which thereby aids re-epithelialisation. They may also sustain the electrical gradient that appears critical for wound healing, and promote wound matrix molecule deposition.[37,49] Fluid from acute wounds stimulates the proliferation of fibroblasts, keratinocytes and endothelial cells essential for wound healing. Occlusive dressings may also extend the inflammatory healing
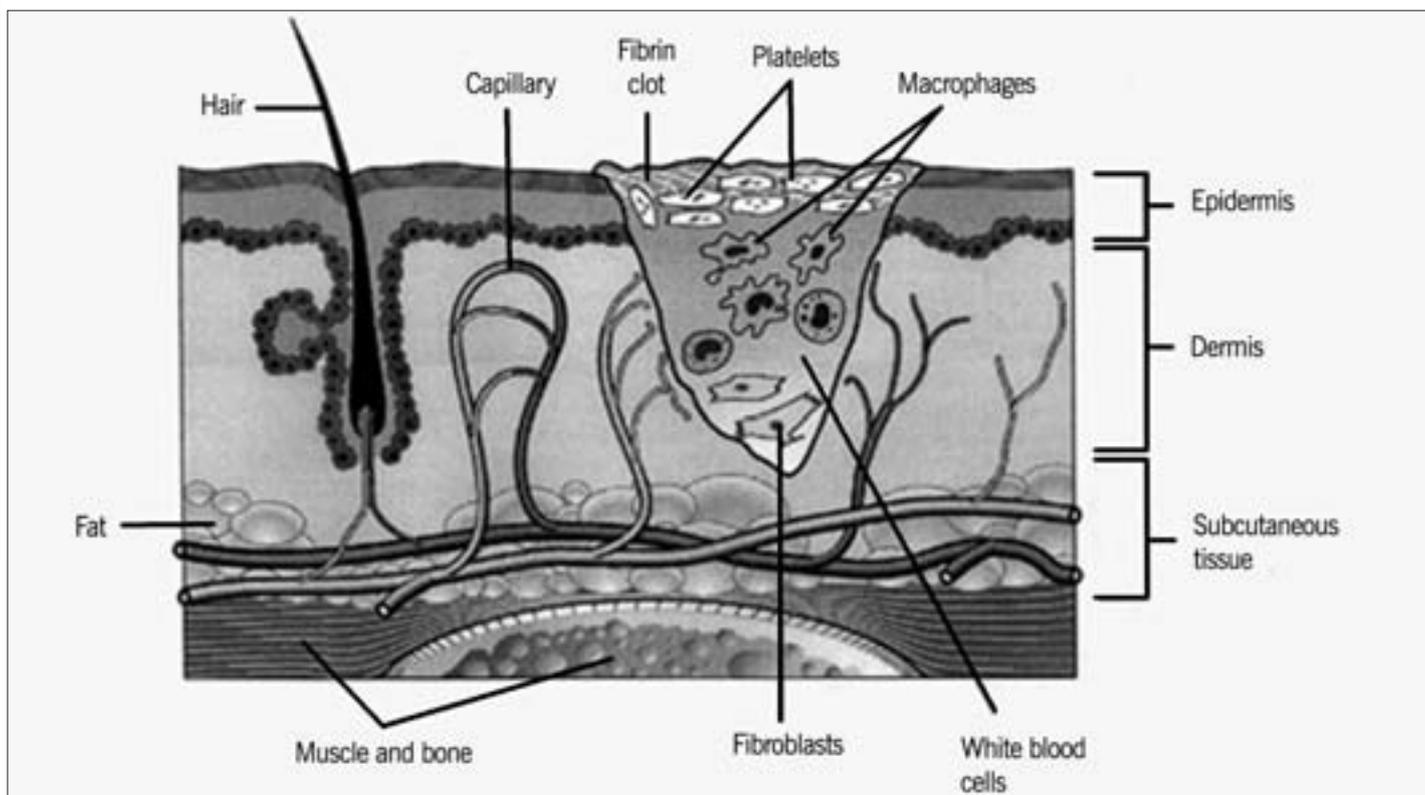
Figure 2: Recurrent herpes labialis — inflammatory healing phase

phase and the associated activity of growth factors, thereby accelerating re-epithelialisation.[49]

Occlusive dressings must be applied within two hours of wounding to achieve rapid re-epithelialisation.[49,50] Dressings may be removed between 24 and 48 hours later without jeopardising the rapid re-epithelialisation process, suggesting that their benefits may be sustained.

Moreover, occlusive dressings do not increase the risk of infection and may actually be protective in this regard.[51] They can also help to reduce wound pain.[49]

Occlusive dressings and RHL treatment

The use of occlusive hydrocolloid patches for RHL lesions has recently been evaluated. Hydrocolloids comprise adhesive, absorbent and elastometric ingredients.[52] Hydrocolloids adhere to either dry or moist skin, minimising scab formation and maintaining an aqueous wound environment with abundant growth factors, characteristics that should promote healing in the treatment of RHL. Their use during the epithelialisation stage of acute wounds was recently advocated by a consensus panel sponsored by the French National Authority for Health.[53]

So far, only one published clinical study has tested a hydrocolloid cold sore patch.[28] This study randomised adults with RHL to treatment with Compeed — a semiocclusive, transparent, hydrocolloid, non-medicated cold sore patch approximately 15mm in diameter — or aciclovir cream 5 per cent. Treatment was started within one hour of the onset of RHL. A total of 351 subjects experienced a cold sore and received treat-

ment. The primary outcome endpoint was the subject's global assessment of therapy (SGAT), rated on a scale of zero (no response) to 10 (excellent response).

The cold sore patch and aciclovir cream showed similar efficacy, with statistically indistinguishable mean SGAT ratings of 7.9 and 8.0, respectively, and with no significant inter-group differences in blinded clinician assessments of global response or median healing time (7.6 and 7.0 days, respectively). The patch was associated with significantly better patient-reported scores for lesion protection and hygiene ($P<0.05$), discretion (ie, lesions) were less noticeable ($P<0.05$), and relief of social embarrassment and anxiety ($P=0.002$). Although application site reactions were more

common with the patch treatment, both treatments were generally well tolerated.[28]

The use of local therapies, including hydrocolloid dressings, is not advisable in severe RHL or disseminated facial herpes virus infection.[14] These circumstances require the use of a systemic antiviral agent and specialist advice. Systemic antiviral therapy is also mandatory for eczema herpeticum, a potentially life-threatening herpes superinfection of a pre-existing skin disease.[54]

Conclusions

Community pharmacists can play an important advisory role in the prevention, identification and over-the-counter treatment of RHL. To fulfil this role, they need to maintain up-to-date

Panel 3: Palliative treatments for RHL in the UK

Product	Active ingredients
Blistex Relief Cream (formerly Blisteze)	Aromatic ammonia solution (6.04 per cent), strong ammonia solution (0.1 per cent), liquefied phenol (0.494 per cent)
Bonjela gel	Cetalkonium chloride (0.01 per cent), choline salicylate (8.714 per cent)
Carmex lip balm	Menthol (0.7 per cent), camphor (1.7 per cent), phenol (0.4 per cent), salicylic acid
Colsor lotion/cream	Menthol (0.5 per cent), phenol (0.5 per cent), tannic acid (5 per cent)
Cymex cream	Urea (1 per cent), dimethicone 350 (9 per cent), cetrimide (0.5 per cent), chlorocresol (0.1 per cent)
Lypsyl cold sore gel	Lidocaine (2 per cent), zinc sulphate (1 per cent), cetrimide (0.5 per cent)

knowledge of various treatment options for RHL.

Accumulating data suggest that non-medicated occlusive dressings may be as effective as topical antiviral creams and may also help protect and mask unsightly cold sores. These benefits may bolster patient satisfaction with treatment and perhaps improve treatment adherence. These dressings may also protect against bacterial contamination of the lesion and limit viral shedding. However, further research is required to assess their effects on pain and RHL recurrence. In conclusion, evidence suggests that occlusive hydrocolloid dressings deserve consideration as a part of the armamentarium for the treatment of RHL.

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