

## Practical Management Measures for Patients with Recurrent Herpes Labialis

S. A. St. Pierre, MD; B. L. Bartlett, MD; B. J. Schlosser, MD, PhD

Department of Dermatology, Northwestern University, Chicago, IL, USA

### ABSTRACT

*Recurrent herpes labialis (RHL) is a common condition associated with the formation of vesicles around the mouth, often preceded by prodromal symptoms including tingling and burning. Treatment is targeted toward individual episodes, but in severe cases, suppressive therapy may be indicated. At present, no cure exists for this troublesome condition. The purpose of this article is to serve as a practical guide in the management of RHL by summarizing current treatments and discussing potential new therapies.*

**Key words:** recurrent herpes labialis

Recurrent herpes labialis (RHL) occurs in a subset of patients infected with the herpes simplex virus (HSV). HSV type 1 is most commonly associated with oral blisters, and its seroprevalence in the US is 57.7% in those aged 14-49.<sup>1</sup> Most patients with RHL experience less than 2 episodes per year, but 5%-10% experience  $\geq 6$  occurrences per year.<sup>2</sup> After the virus ascends the dorsal root ganglion during primary infection, it lies dormant until reactivated, often by triggers such as sunlight, stress, menses, or trauma to the area. This reactivation leads to what are commonly known as "cold sores" or "fever blisters." In those with RHL, the pain, discomfort, and temporary disfigurement of these lesions can be reduced by using one of several therapies shown to hasten healing and decrease progression of disease. In episodic therapy, it is essential that patients recognize prodromal symptoms for immediate self-medication.

Treatment for RHL can be episodic or suppressive, depending upon the frequency and severity of episodes. There are no specific recommendations regarding when to start suppressive therapy, however, consideration may be given when a patient has  $\geq 6$  episodes of RHL in 1 year. Therapy may lead to decreased potential for the rare complication of perioral scarring, although this phenomenon has not been described in the literature. Depigmentation after healing of lesional areas is extremely rare.<sup>3</sup>

### **Intermittent Episodic Therapy**

When utilizing episodic therapy, patient-initiated administration of therapy at the first sign of prodromal symptoms is key to reducing healing time and lesion pain. Prodromal symptoms include burning, tingling, and itching.

### **Topical Antiviral Agents**

#### **Acyclovir 5% Cream or Ointment**

An FDA-approved antiviral treatment for RHL, acyclovir cream has been shown to reduce lesion healing time by 0.5-0.6 days and the duration of pain by 0.3-0.4 days.<sup>4</sup> An ointment-based formulation is approved for use in immunocompromised patients.

#### **Docosanol 10% Cream**

N-docosanol, a 22-carbon alcohol that has been FDA-approved for over the counter (OTC) use against RHL, has shown efficacy in reducing healing time based on 1 study. This report described 2 identical randomized placebo-controlled multicenter studies that looked at docosanol 10%, applied 5 times daily until resolution of lesions, vs. polyethylene glycol placebo. Treatment was initiated in the prodrome or erythema stage of an episode. The authors noted an 18 hour decrease in healing time of lesions in the treatment vs. the control group ( $p=0.008$ ).<sup>5</sup>

#### **Penciclovir 1% Cream**

Penciclovir is an FDA-approved topical antiviral used to treat RHL. It has been shown to decrease healing time and duration of pain when compared with placebo. Two placebo-controlled, randomized trials demonstrated a reduction in median healing time by 0.7 days and by 2 days, respectively, when compared with placebo controls.<sup>6,7</sup> When compared with topical acyclovir in a randomized controlled trial with 124 subjects in each treatment group, topical penciclovir showed no significant difference in the clinical cure rate, side-effects, or time to resolution.<sup>8</sup>

## Oral Systemic Antiviral Agents

### Acyclovir

Several studies have demonstrated the efficacy of oral acyclovir for the treatment of RHL. Dosages between 200mg-400mg 5 times daily decreased healing time by 1 to 1.5 days when compared with placebo.<sup>9,10</sup> Although this regimen is not US FDA-approved for RHL, it is widely used off-label in clinical practice.

### Valacyclovir

Valacyclovir, the prodrug of acyclovir, is FDA-approved for use in RHL; it shows 3 to 5 times the bioavailability of acyclovir. In 2 large identical randomized controlled trials, Spruance et al. studied 2 groups taking high-dose, short course valacyclovir: The first group self-initiated treatment with 2000mg 2 times daily for 1 day while the second group took 2000mg 2 times daily the first day in addition to 1000mg 2 times daily for a second day. In both studies, each group saw improved healing time compared with the placebo group (0.5 to 1 day reduction) and decreased duration of pain when compared with the placebo group (0.5 to 0.7 day reduction). There was no difference in duration of episode when treating for 1 day vs. 2 days.<sup>11</sup> In contrast, a smaller non-randomized double-blind study of 3 treatment groups – taking either a single dose of 500mg, 1000mg, or 2000mg within 2 hours of initiation of the prodromal period – showed no statistically significant difference in aborting lesion formation when comparing the different doses.<sup>12</sup>

### Famciclovir

The oral prodrug of penciclovir, famciclovir is FDA-approved for RHL in immunocompetent patients; it demonstrates efficacy in addition to a more convenient dosing regimen. Famciclovir also has an FDA-approved indication for use in episodic therapy of RHL in immunosuppressed patients. In 1 double-blind study of 102 subjects with a history of sun-induced herpes labialis, subjects were administered 1 of 4 treatments within 48 hours of ultraviolet (UV) exposure of the lips: 125mg, 250mg, or 500mg of famciclovir, or placebo 3 times daily for 5 days. There was a statistically significant dose-proportionate decrease in lesion size, as well as a reduction in healing time as assessed by the patient (decreased by 2 days,  $p=0.01$ ) and investigator (decreased by 2.8 days,  $p=0.008$ ).<sup>13</sup> In a larger randomized controlled trial, subjects were assigned to 1 of 3 groups: famciclovir single dose 150mg, famciclovir 750mg twice a day for 1 day, or placebo. Patients were instructed to initiate treatment within 1 hour of prodromal symptom onset. The study found a median healing time of primary vesicular lesions to be decreased by about 2 days in both treatment groups when compared with placebo. There was no statistically significant difference in healing time between the 2 treatment groups. In addition, the time to resolution of pain was decreased in the single-dose group compared with placebo group (median decrease of 1.2 days,  $p=0.046$ ).<sup>14</sup>

Although oral antivirals for the treatment of RHL have not been directly compared with each other in any study, some

patients may find single-dose therapy to be more convenient while providing similar efficacy to other oral antivirals.<sup>15</sup>

## Combination Therapies

An area of developing study is the combination of a topical or systemic antiviral agent with a topical steroid.

### Acyclovir 5% + Hydrocortisone 1% Cream

In August 2009, the FDA approved a new antiviral/steroidal combination therapy of acyclovir 5% and hydrocortisone 1% for the treatment of RHL. Regulatory approval was based on a randomized controlled trial in 2002 in which 380 immunocompetent adults with a history of herpes labialis were exposed to experimental UV radiation to induce outbreaks. On day 2, prior to the appearance of the majority of lesions, subjects were randomized at a 1:1 ratio to receive active medication or vehicle control 6 times per day for 5 days. Overall, 120 of 380 subjects developed delayed classical lesions. Of these 120 subjects with lesions, 50 (26% of the treatment group) received the treatment cream and 70 (37% of the placebo group) had received the placebo vehicle. Observed differences in healing time were statistically significant: 9 days for those on the treatment regimen and 10.1 days for control subjects ( $p=0.04$ ). There was no statistically significant effect on pain.<sup>16</sup>

### Other Experimental Combination Therapies

Oral valacyclovir used with topical clobetasol gel may be an additional potential combination therapy. A recent pilot study randomized patients to a combination of valacyclovir 2000mg orally twice daily for 1 day and clobetasol gel 0.05% twice daily for 3 days or matching oral and topical placebo. Although the study was small, those treated with combination valacyclovir and clobetasol gel saw a mean healing time of 5.8 days compared with 9.3 days in placebo ( $p = 0.002$ ). The efficacy of clobetasol gel alone was not studied.<sup>17</sup>

Systemic famciclovir has been studied in combination with topical fluocinonide gel for use at the onset of prodromal symptoms. Twenty-nine patients were randomized to this combination therapy vs. treatment with famciclovir and topical vehicle control. Famciclovir dosing for both groups was 500mg orally 3 times daily for 5 days after onset of prodromal symptoms. Topical therapy with either fluocinonide or vehicle control was simultaneously initiated 3 times daily for 5 days in the treatment and control groups, respectively. The combination treatment group showed a 70% reduction in lesion size, but measures of ulcer progression and healing time were not statistically significant.<sup>18</sup>

### Other Agents

Lysine is an OTC herpes remedy commonly used by RHL sufferers. One study suggests that topical administration of a mixture of L-lysine, zinc, and herbals may reduce the symptoms of an outbreak.<sup>19</sup> Daily lysine intake (300mg) in 1 small randomized placebo-controlled study was shown to reduce the overall number of recurrences in the treatment group by 2.4 ( $p<0.05$ ).<sup>20</sup>

Other agents may provide symptomatic relief. These include ice, emollients, topical anesthetics, and OTC occlusive preparations. Such treatment measures have not been shown to reduce the number of lesions in a given episode of RHL or to accelerate the healing of established RHL lesions.

### Suppressive Antiviral Therapy

For immunocompetent patients with frequent RHL, daily suppressive therapy may be indicated. Currently, valacyclovir is the only drug approved by the FDA for this indication in immunocompetent patients. Two identical randomized double-blind parallel group studies evaluated the efficacy of oral valacyclovir 500mg daily compared with placebo for the suppression of herpes labialis in subjects with a history of 4 or more recurrences in the previous year. Suppressive treatment was administered daily for 16 weeks. Sixty percent of the subjects in the valacyclovir treatment group remained recurrence free throughout the 4 months compared to 38% of the placebo group.<sup>21</sup> In a study by Gilbert, daily suppressive valacyclovir (1000mg daily) therapy was compared with episodic valacyclovir (2 doses of 2000mg administered 12 hours apart) therapy for RHL. The investigators of this study found fewer recurrences and longer median time to recurrence in those subjects on suppressive valacyclovir.<sup>22</sup> For immunosuppressed patients, the FDA has approved famciclovir for use as a daily suppressive therapy. Although not FDA-approved, daily suppressive therapy with valacyclovir 500mg once daily may be utilized in clinical practice in select immunosuppressed patients.<sup>23</sup>

### Summary

There are numerous treatments for RHL that provide modest improvement to the severity of disease. Suppressive therapy may actually reduce the number of occurrences for those with severe RHL. For those with less frequent occurrences, intermittent episodic therapy is indicated. All of the aforementioned oral antiviral agents have demonstrated the ability to reduce healing time and to decrease the pain of RHL lesions. Valacyclovir and famciclovir offer convenient dosing regimens (1 or 2 doses), which may translate into greater patient adherence to therapy.

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# Flares in Childhood Eczema

S. M. Langan, MRCP, MSc, PhD

Centre of Evidence-based Dermatology, University of Nottingham, Nottingham, UK

## ABSTRACT

*Eczema is a major public health problem affecting children worldwide. Few studies have directly assessed triggers for disease flares. This paper presents evidence from a published systematic review and a prospective cohort study looking at flare factors in eczema. This systematic review suggested that foodstuffs in selected groups, dust exposure, unfamiliar pets, seasonal variation, stress, and irritants may be important in eczema flares. We performed a prospective cohort study that focused on environmental factors and identified associations between exposure to nylon clothing, dust, unfamiliar pets, sweating, shampoo, and eczema flares. Results from this study also demonstrated some new key findings. First, the effect of shampoo was found to increase in cold weather, and second, combinations of environmental factors were associated with disease exacerbation, supporting a multiple component disease model. This information is likely to be useful to families and may lead to the ability to reduce disease flares in the future.*

**Key Words:** eczema; flares; children

Eczema is an important condition that affects 2%-20% of children worldwide, and is associated with significant morbidity for children and their families.<sup>1</sup> Although some progress has been made in understanding factors that are related to the occurrence of eczema, very little is known about factors associated with disease exacerbation. Most textbooks and review articles quote long lists of exacerbating factors, but we have found very little scientific data to support them.

## FLARES OF ECZEMA

### *Defining Flares of Eczema*

In order to address the causes of flares, it is first important to define what is meant by an eczema flare. Langan et al. carried out a systematic review that assessed definitions of flare in the literature and sought parallels with definitions used in other relapsing and remitting diseases.<sup>2</sup> The authors proposed that a flare could be defined as an episode requiring escalation of treatment or additional medical advice. This should be pre-defined by investigators at the onset of a study. For example, in studies of moderate or severe eczema, escalation to the use of topical corticosteroids might constitute a “flare”. The need to use potent or super-potent topical corticosteroids, or to attend a primary care physician or dermatologist for disease exacerbation might be more appropriate. It is not possible to develop an entirely standardized definition for “flare”, as the true meaning is related to the individual patient and his or her perception of disease worsening above baseline.

### *A Review of Evidence for Causes of Flares in Eczema*

A systematic review was also carried out to assess the evidence for causes of eczema flares. This review highlighted the limited evidence for flare factors, but suggested that there may be a role for foodstuffs in selected groups, dust exposure, unfamiliar pets, seasonal variation, stress, and irritants in eczema flares.<sup>3</sup> However, scientific investigation was required to elucidate the relative impact of these factors in studies of longitudinal design over longer study periods. Another aspect requiring study was whether combinations of factors are more important than single factors, suggesting a complex disease model.

## A STUDY OF ENVIRONMENTAL FACTORS

Langan et al. addressed these issues in a prospective cohort study.<sup>4</sup> The objectives were to assess the role of various environmental factors on eczema severity in a cohort of eczematous children with the following identified hypotheses:

*Hypothesis 1:* In hot weather, the combination of heat, sweating, and grass pollen precipitates increased severity in children with eczema in the UK.

*Hypothesis 2:* The combination of cold weather, indoor aeroallergen exposure, and reduced relative humidity from central heating led to increased severity in children with eczema in the UK. These first 2 hypotheses were informed by previous research, which proposed “summer” and “winter” types of eczema.<sup>5</sup>

*Hypothesis 3:* Detergents (i.e., soap or shampoo) increase the propensity to disease flares triggered by other factors at all temperatures, but more so in cold weather due to impaired skin barrier function.

*Hypothesis 4:* Any combination of greater than or equal to 3 exposures at any time is associated with worsening of eczema. The exposures assessed included dust, pets, shampoo, sweating, swimming, nylon clothing next to the skin, and a change in mean temperature of more than 3°C from the previous weekly average.

### *Study Methods*

A prospective cohort study (n=60) of children with moderate-to-severe eczema between 6 and 9 months of age and up to 15 years were enrolled with overlapping start dates to allow for the study of seasonal factors. The exposures studied included temperature, relative humidity, sun exposure, sweating, clothing, cleansing products/washing, outdoor pollen level, the extent and nature of exposure to household pets, dusty environments, and swimming. On a daily basis, children or their parents completed novel electronic diaries programmed for this study recording eczema severity and exposures. Portable dataloggers were used to record temperature and relative humidity. External meteorological data was obtained from a local monitoring center.

The primary outcome was measured as a daily “bother” score; the secondary outcomes were daily “scratch” scores and flares of eczema outcome measures. The daily bother score was determined in response to the question, “How much bother did your (your child’s) eczema cause today?”

Global scores by the patients and their parents were rated on a scale from 0 to 10 (where 0=no bother at all and 10=the most bother you can imagine).

Binary outcomes were recorded with respect to the question, “Have you had to step up your treatment today because your (your child’s) eczema was worse?” Stepping up treatment was defined at the outset and patient-specific for each child.

### **Statistical Methods**

A time series method, autoregressive moving average models (ARMA), was used to model the impact of each exposure on eczema severity for each individual. This method was required to deal with the autocorrelation in the data, i.e., the severity of eczema on 1 day has a relationship with the severity of eczema on the next day and the day before. Standard random effects from meta-analysis techniques were used to pool estimated coefficients across participants. Heterogeneity of responses, as detected using Chi-squared tests, represented inter-individual variation. The body site specificity of reactions was also examined.

### **Findings**

#### **Primary Outcome: “Bother” Scores**

Increased disease severity was associated with direct contact with nylon clothing (pooled regression coefficient 0.23, 95% confidence interval [CI] 0.03-0.43), increasing exposure to dust (pooled regression coefficient 0.53, 0.23-0.83), exposure to unfamiliar pets (pooled regression coefficient 0.22, 0.10-0.34), sweating (pooled regression coefficient 0.24, 0.09-0.39) and shampoo exposure (pooled regression coefficient 0.07, 0.01-0.13). The association between shampoo use and eczema exacerbation was enhanced in cold weather (pooled regression coefficient 0.30, 0.04-0.57). Body site specificity was observed for the reactions to nylon clothing, which was greater on covered sites [trunk (p=0.02), limbs (p=0.03)], and reactions to wool clothing on truncal covered sites (p=0.03), but not limbs (p=0.62), while exacerbation of hand eczema was associated with exposure to pets (p<0.001). Significant heterogeneity of responses between individuals was observed for exposure to grass pollen and outdoor temperature. With regard to the final hypothesis, a combination of any 3 of 7 likely variables was associated with exacerbation of eczema (pooled regression coefficient 0.41, 0.20-0.63).

#### **Secondary Outcome: “Scratch” Scores**

Increased disease severity was seen associated with swimming (pooled regression coefficient 0.14, 95% CI 0.00-0.28), exposure to wool clothing (pooled regression coefficient 0.28, 0.11-0.45), sweating (pooled regression coefficient 0.15, 0.04-0.26), and shampoo (pooled regression coefficient 0.07, 0.01-0.13).

### **Secondary Outcome: Eczema Flares**

Only swimming was clearly associated with eczema exacerbation using this outcome measure (pooled regression coefficient 0.42, 0.05-0.80).

A summary of exposure factors associated with exacerbation of eczema includes:

- Dust
- Nylon
- Shampoo
- Shampoo + cold weather
- Sweating
- Swimming
- Unfamiliar pets
- Wool

Relative to the study hypotheses, the association between shampoo exposure and eczema exacerbation was shown to be increased in cold weather. There was also evidence showing an association between various combinations of exposures and disease worsening. There was insufficient evidence to support the other hypotheses tested in this study, but this may be explained by a low prevalence of these combinations of exposures. The implications of these study findings for clinical practice are that for the first time, it has been shown that shampoo exposure may be associated with eczema exacerbation and this effect is more pronounced in cold weather. This study also strengthens the systematic review findings that support disease worsening with dust, pet, and irritant exposure. Furthermore, this investigation suggests that eczema exacerbation may be more complicated in that multiple exposures acting in concert may be associated with worsening of the disease. The impact of food and stress were not examined in this prospective study.

### **Conclusion**

Future research is required to specifically explore possible gene-environmental interactions with filaggrin mutations and their relevance in relation to disease flares, and to look at shampoo formulations in relation to eczema exacerbation.

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**Update on Drugs**

Name/Company	Approval Dates/Comments
<b>Ustekinumab</b> <i>Stelara</i> <sup>TM</sup> Centocor Ortho Biotech	The US FDA approved this biologic in September 2009 for the treatment of moderate-to-severe plaque psoriasis in adults ≥18 years of age. Ustekinumab is a first-in-class human monoclonal antibody that selectively targets the cytokines interleukin-12 and interleukin-23. Administration is by subcutaneous injection at Weeks 0 and 4, then every 12 weeks thereafter.
<b>Romidepsin</b> <i>ISTODAX</i> <sup>®</sup> Gloucester Pharmaceuticals	The US FDA approved this histone deacetylase inhibitor in November 2009 for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy. Romidepsin is administered intravenously over a 4-hour period on days 1, 8, and 15 of a 28-day cycle. Cycles are repeated every 28 days if the patient continues to benefit from and tolerate the treatment.

**Drug News**

The US FDA issued a warning letter to Galderma Laboratories expressing concern that 2 visual aids (TRI-486 and TRI-487) for Tri-Luma<sup>®</sup> Cream (fluocinolone acetonide 0.01%, hydroquinone 4%, tretinoin 0.05%) have suggested uses that have not been approved by the FDA, thus creating new “intended uses” for the drug. Moreover, these unapproved uses lack adequate directions, broaden the indication for Tri-Luma<sup>®</sup>, and omit and minimize important risk information for this drug. These visual aids also contain unsubstantiated claims that significantly overstate its efficacy, thereby misbranding the drug. Tri-Luma<sup>®</sup> was approved in January 2002 for the short-term treatment of moderate-to-severe melasma of the face in the presence of measures for sun avoidance, including the use of sunscreens. Galderma has been asked to immediately cease the dissemination of these promotional materials and the unapproved product labeling. The FDA has asked Galderma to submit a plan of action to disseminate truthful, non-misleading, and corrective messages.

The US FDA issued a warning letter to Allergan expressing concern about a journal advertisement for Aczone<sup>®</sup> (dapsone) gel 5%. This journal advertisement has been deemed false or misleading because it overstates the efficacy of Aczone<sup>®</sup> and omits material facts and important risk information associated with product usage, thereby misbranding this drug. Allergan has been asked to immediately cease the dissemination of violative promotional material and to submit a plan of action to disseminate truthful, non-misleading, and complete corrective messages. Aczone<sup>®</sup> is indicated for the topical treatment of acne vulgaris.

The US FDA, Health Canada, and Roche/Hoffmann-La Roche have notified healthcare professionals that cases of pure red cell aplasia have been reported in patients treated with mycophenolate mofetil (CellCept<sup>®</sup>). Forty-one cases of this condition have been reported. Some patients were also receiving other immunosuppressive medications (i.e., alemtuzumab, tacrolimus, and azathioprine) that could have contributed to the development of this disease. In 16 of the reported cases, reduction or discontinuation of the mycophenolate mofetil dosage led to resolution of this condition. The Warnings and Adverse Reactions sections of the CellCept<sup>®</sup> Prescribing Information have been revised to reflect this new safety information.