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How to cite

PITTET, Laure, CURTIS, Nigel. Does oral antiviral suppressive therapy prevent recurrent herpes labialis in children? In: Archives of Disease in Childhood, 2019, vol. 104, n° 9, p. 916–919. doi: 10.1136/archdischild-2019-317249

This publication URL: https://archive-ouverte.unige.ch/unige:146587
Publication DOI: 10.1136/archdischild-2019-317249

Does oral antiviral suppressive therapy prevent recurrent herpes labialis in children?

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Word count: 865; 2 tables

Keywords: herpes simplex virus (HSV); cold sore; acyclovir, valacyclovir, famciclovir; prevention, secondary prophylaxis.

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SCENARIO

A 13-year-old girl presents with recurrent herpes labialis (HL) on her face. She gives a history of painful episodes occurring approximately monthly since the age of 9 years. Since becoming a teenager, she has missed a lot of school due to her worry about the cosmetic appearance of recurrences. Her parents ask whether long-term antiviral medication will prevent recurrences.

STRUCTURED CLINICAL QUESTION

In an otherwise healthy child or adolescent with recurrent herpes labialis (patient), is oral antiviral suppressive therapy (intervention) effective in reducing the frequency of recurrences of herpes labialis (outcome).

SEARCH

Medline and EMBASE were searched in January 2019 with no language restriction. PubMed was also searched to retrieve items not indexed in Medline. The search strategy is detailed in the supplementary material.

Of 2032 unique articles, after exclusion of studies investigating immunocompromised patients, pre-emptive treatment, or short-term (<4 weeks) intervention, four were relevant (Table 1). Only one study addressed recurrences in children or adolescent (a retrospective study in 4 patients).[1] The remaining three articles described RCTs in adults,[2-4] also reported in a Cochrane meta-analysis.[5] The references of all relevant publications were reviewed and no further article was identified.

COMMENTARY

HL is caused by herpes simplex virus (HSV), a ubiquitous double-stranded DNA virus that primarily infects through contact or respiratory droplets, subsequently establishing life-long latent infection in regional nerve ganglia. Reactivation can be triggered by physical or emotional stress, fever, menstruation or exposure to sun. Reactivation leads to asymptomatic shedding or lesions around the initial point of entry. Infections can occur anywhere but are more frequent around the oral or genital mucosa.[6] The highest incidence of primary infection occurs in the first four years of life.[7] The worldwide global prevalence of HSV is >70% in those over 15 years of age with geographic and socioeconomic variations in prevalence.[7, 8] Between 14 and 40% of the population have frequent recurrent HL.[9-11] Discomfort and cosmetic appearance can have a significant impact on quality of life, especially in adolescents. In younger children, pain can limit fluid intake. Long-term oral antiviral suppressive therapy is frequently suggested for patients with severe and/or frequent recurrences. However, recommendations for patient selection, choice of antiviral, dosage and duration vary (Table 2).

The retrospective study in children included four teenagers 12 to 14 years of age in Spain with six or more HL episode per year. A 4-month course of oral valacyclovir (500 mg once daily) induced a 3.9-fold reduction in HL episodes and a significant increase in quality of life.[1] Two patients reported adverse events (not detailed) but treatment was not discontinued. The three RCTs included 196 adults in the USA with recurrent HL, defined as between 3 and 6 or more episodes per year.[2-4] All studies had two arms and two had a cross-over design. The studies compared a 4-month course of acyclovir (400 mg twice daily) or valacyclovir (500 mg or 1 g once daily) to placebo or to pre-emptive treatment (valacyclovir 2 g twice daily for one day at first sign of

prodrome). Methodological differences precluded pooling of the data in the Cochrane review.[5] Overall, the results showed that oral antiviral suppressive therapy increased the number of recurrence-free patients (1.6 to 3.3-fold), prolonged the time to first HL recurrence (1.4 to 2.6-fold), decreased the recurrence rate (1.8 to 2.4-fold) and decreased the duration of HL episode (1.8-fold). In one of the studies, the reduction in HL episodes was greater (3.5-fold) when including only culture-positive recurrences, suggesting lower viral shedding in patients receiving long-term acyclovir.[2] Interestingly, another of the studies found that a suppressive approach was superior to a pre-emptive approach.[4] There was no safety concerns, with no difference in adverse events between the groups in all three studies.

Although only four studies have addressed the efficacy of oral long-term suppressive therapy with acyclovir or valacyclovir in patients with RHL, all reported a reduction in frequency, severity and duration of episodes. Suppressive therapy also decreased viral shedding, which reduces the risk of secondary inoculation, a particular risk in children. However, these findings are based primarily on studies in adults.

No study has directly compared the efficacy of different antiviral drugs in preventing recurrent HL, and no study has investigated long-term suppressive therapy with famciclovir. Valacyclovir and famciclovir have superior bioavailability than acyclovir, enabling a once or twice daily administration.[12-14] However, although frequently used in children, valacyclovir and famciclovir are not approved for use in this age group in many countries, and are generally more costly.[12]

Adverse effects of these antivirals include myelosuppression (mostly neutropenia), and rarely renal and liver toxicity. However these adverse effects have mainly been reported in neonates receiving intravenous acyclovir for HSV encephalitis. The low rate of adverse effects is likely explained by the fact that the activity of these drugs depends on phosphorylation by a virally-induced thymidine kinase, and are therefore only active in infected cells, with no effect on uninfected cells.[13] In addition, in immunocompetent patients, selection of antiviral-resistant mutants (which in any case have impaired replicative ability, decreased ability to establish latency and to reactivate) has not been reported in this setting.[15, 16]

Other treatment options for recurrent HL have been studied in individual RCTs, mainly in adults (Table in supplementary material).[5] Amongst them, the greatest benefit was reported for repeated application of sunscreen in patients with sun-induced RHL. In one study, the double application of sunscreen lipstick repeated at least 2-hourly induced a 10-fold decrease in HL recurrence rate, and a 10-fold increase in recurrence-free patients throughout the month of intervention.[17]

CLINICAL BOTTOM LINES

- Oral long-term suppressive therapy with acyclovir or valacyclovir reduces the frequency, severity and duration of episodes in adults with recurrent HL (Grade A) but has not been the subject of a trial in children.
- Oral valacyclovir reduces the frequency of episodes and increases quality of life in teenagers with recurrent HL (Grade C).
- The optimal indication to start, choice of antiviral, and optimal dosage and duration of long-term antiviral therapy is unknown.

114 **Table 1: Long-term antiviral suppressive therapy for reducing the recurrence and severity of herpes labialis.**

Citation Country	Study group	Study type (level of evidence)	Outcome	Key results	Comments
Rooney *et al.* 1993 [2] USA	22 adults aged 18 to 50 years old (mean 38.6) RHL defined as ≥6 lesions per year, and ≥2 HL episode during the pre-randomisation 4-month observation period Group 1: acyclovir 400 mg twice daily for 4 months, then switched to placebo twice daily for 4 months (n=11) Group 2: placebo twice daily for 4 months, then switched to acyclovir 400 mg twice daily for 4 months (n=11)	Randomised double-blind placebo-controlled cross-over trial (Level 1b)	Proportion recurrence-free throughout the 4-month treatment period	Acyclovir: 50% (10 patients) Placebo: 15% (3 patients) P=.04*	2 drops out in Group 1 during acyclovir treatment, excluded from the analysis. No washout period between the 2 phases; HL episodes in first week of each treatment phase excluded from analysis. Results of haematology and blood chemistry testing done on all patients at 4-month intervals not discussed. Study partly commercially-funded.
			Median time (range) to first recurrence clinically determined	Acyclovir: 118 days (22 to >134) Placebo: 46 days (7 to >122) P=.05	
			Median time (range) to first recurrence virologically determined	Acyclovir: >118 days (79 to >125) Placebo: 46 days (7 to >125) P=.002	
			Mean number of recurrences/month clinically determined	Acyclovir: 0.21 episode Placebo: 0.45 episode P=.009	
			Mean number of recurrences/month virologically determined	Acyclovir: 0.10 episode Placebo: 0.35 episode P=.003	
			Mean (SD) duration of HL episode during recurrence	Acyclovir: 4.3 days (4.0) Placebo: 7.9 (7.2) Mean difference -3.6 days (95%CI -7.2, 0) P = 0.11	
Baker *et al.* 2003 [3] USA	98 adults aged 21.0 to 55.4 years old (mean 36.9 in Group 1 and 40.6 in Group 2) RHL defined as ≥4 lesions in previous year Group 1: valacyclovir 500 mg once daily for 4 months (n=49) Group 2: placebo once daily for 4 months (n=49) In case of clinical evidence of HL lesion during follow-up, participants in both groups received oral valacyclovir 500 mg twice daily for 5 days and then resumed their assigned study medication	Randomised double-blind placebo-controlled trial (Level 1b)	Proportion recurrence-free throughout the 4-month treatment period	Valacyclovir: 60% (38 patients) Placebo: 38% (18 patients) P=.041	2 patients in Group 1, 1 patient in Group 2 lost to follow-up. Study partly commercially-funded.
			Mean time to first recurrence	Valacyclovir: 91.7 days Placebo: 67.2 days P=.016	
			Mean number of recurrences/month	Valacyclovir: 0.12 episode Placebo: 0.21 episode P=.042	
			Incidence of adverse events during the 4-month treatment period	Valacyclovir: 22 events in 16 patients (33%) Placebo: 29 events in 19 patients (39%) P=0.7*	

Ruiz-Villaverde *et al.* 2009 [1] Spain	4 adolescents aged 12 to 14 years old (mean 13.3) RHL defined as ≥6 lesions in previous year Valacyclovir 500 mg once daily for 4 months (n=4)	Retrospective study (Level 4)	Number of HL recurrences per year	Before therapy: mean 6.75 episodes (SD 0.96) After therapy: mean 1.75 episodes (SD 0.96) P<.001*	Adverse events not discussed but treatment was continued.
			Quality of life questionnaire (cDLQI)	Before therapy: mean 18.75 episodes (SD 1.71) After therapy: mean 5.50 episodes (SD 0.58) P<.001*	
			Incidence of adverse events	2 patients (50%)	
Gilbert 2007 [4] USA	76 adults (mean age 47.4 years-old, SD 14.9) RHL defined as ≥3 lesions in previous year Suppressive regimen: valacyclovir 1 g once daily for 6 months Pre-emptive regimen: valacyclovir 2 g twice daily for 1 day at first sign of prodrome Patients randomised to prophylactic regimen for 6 months followed by pre-emptive regimen for 6 months. Recurrences of HL during the prophylactic regimen were treated with the pre-emptive regimen	Randomised open-label cross-over trial (Level 1b)	Proportion recurrence-free throughout the 6-month treatment period	Suppressive: 58% Pre-emptive: 42%	21 patients (28%) did not complete the study. Comparison based on the 60 patients with at least one post-baseline assessment. No washout period. Study partly commercially-funded.
			Median time to first recurrence	Suppressive: >180 days Pre-emptive: 81 days P=.02	
			Incidence (recurrence/month)	Suppressive: mean 0.075 episode/month (SD 0.1025) Pre-emptive: mean 0.18 episode/month (SD 0.1975) Mean difference -0.10 (95%CI -0.16, -0.05)	
			Duration of episodes	Suppressive: mean 1.78 (SD 2.92) Pre-emptive: mean 2.86 (SD 3.10) Mean difference -1.08 (95%CI -2.16, 0)	
			Incidence of adverse events	Suppressive: 29 patients (38%) Pre-emptive: 24 patients (32%) RR 1.21 (95%CI 0.78, 1.87)	

95%CI: 95% confidential interval; cDLQI: Children's Dermatology Life Quality Index [18]; HL: herpes labialis; HSV: herpes simplex virus; HR: hazard ratio; MED: minimum erythema dose; n: number of patient; RHL: recurrent herpes labialis; RR: risk ratio; SD: standard deviation; USA: United states of America.

*P-values calculated using Stata 13® (StataCorp, College Station, TX); not provided in original publications.

119 **Table 2: Recommendations for HSV suppressive therapy from major pediatric and infectious disease reference books**

Guideline	Indication	Recommended treatment			Recommended duration
		Acyclovir	Valacyclovir	Famciclovir	
Redbook [19]	"Children with frequent recurrences"	30 mg/kg/day in 3 doses, maximum 1000 mg/day	-	-	"reevaluation after 6 months to 1 year of continuous therapy"
Nelson's Pediatric Antimicrobial Therapy [20]	"Suppressive therapy for frequent recurrence (no pediatric data)"	40-60 mg/kg/day in 2-3 doses, maximum 400 mg/dose	-	-	"for 6–12 months, then reevaluate need"
Harriet Lane [21]	"Suppression of recurrent mucocutaneous outbreaks"	800 mg/day in 2 doses	1000 mg/day in 1 dose, "not approved for <12 years"	500 mg/day in 2 doses, "not approved for <18 years"	"for as long as 12 months continuously"
Mandell [22]	"Consider for patients with frequent (>6 episodes) or severe recurrences, in immunocompromised patients, or as an adjunct to prevent transmission"	800 mg/day in 2 doses	500 mg/day or 1000 mg/day in 1 dose	1000 mg/day in 2 doses	-
Antibiotic and Chemotherapy [23]	"Suppressive therapy"	800 mg/day in 2 doses	500 mg/day in 1 dose	1000 mg/day in 2 doses	-
Australian Anti-Infection Handbook [24]	"Severe recurrences or chronic lesions (suppressive therapy)"	20 mg/kg/day in 2 doses, maximum 400 mg/day	500 mg/day in 1 dose	500 mg/day or 1000 mg/day in 2 doses	"For 6 months. (…) If recurs after 6 months, restart longer term suppression"
Netter's Infectious Diseases [25]	"Frequent recurrences (more than six per year), patients with a history of HSV-associated erythema multiforme, individuals anticipating intense sun exposure, patients undergoing certain surgical procedures, immunocompromised patients, and wrestlers with a history of herpes gladiatorum. (…) May also be considered in patients with less frequent outbreaks whose appearance is very important or those who experience severe anxiety with outbreaks."	800 mg/day in 2 doses	500 mg/day in 1 dose	-	-

Nelson Textbook of Pediatrics [26]	"Long-term daily use of oral acyclovir or valacyclovir has been used to prevent recurrences in individuals with frequent or severe recurrences."	800 mg/day in 2 doses	500 mg/day in 1 dose	-	-
www.uptodate.com [27]	"Chronic suppressive therapy for virologically confirmed recurrent HSV in immunocompetent patients is indicated when: - Recurrences are frequent or bothersome to the patient (eg, associated with significant disfiguring lesions, pain) - Recurrences are associated with serious systemic complications (eg, erythema multiforme, eczema herpeticum or recurrent aseptic meningitis) Patients who do not have a specific prodrome are particularly good candidates for suppressive therapy."	-	-	-	-
Feigin and Cherry's [28]	"Experience with acyclovir prophylaxis for reactivation of HSV in children is limited"	-	-	-	-
Sara Long [29]	"Long-term suppressive therapy with acyclovir reduces reactivation of latent genital and orolabial HSV infections"	-	-	-	-

120 HSV: herpes simplex virus; -: not specified.

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FUNDING

Dr Laure Pittet is supported by the Swiss National Science Foundation (Early Postdoc.Mobility grant number P2GEP3_178155).

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