COLD SORES

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ACKNOWLEDGMENT

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LEARNING OBJECTIVES

- Describe pathophysiology of cold sores
- Identify possible causes and risk factors for cold sores
- Apply the components of the Pharmacist Patient Care Process (PPCP) necessary for a patient consultation on cold sores

SUGGESTED READINGS

1. Sacchierro CP, Bartlett BL, Schlosser BJ. Practical management measures for patients with recurrent herpes labialis. Skin Therapy Lett. 2009 Dec;14(8):1–3.

2. Raborn GW, Grace MG. Recurrent herpes simplex labialis: selected therapeutic options. Journal-Canadian Dental Association. 2003;69(8):498–504.

MEET OUR PATIENT – ALYSSA

Background

- 24 years old
- Retail worker at clothing store
- No medical conditions
- No known allergies

Current medications

- No current medications

Discussion

- She has heard that pharmacists can prescribe medications for cold sores and is looking for a treatment that can help with symptoms.

BACKGROUND

Infection caused by herpes simplex virus (HSV) represents one of the more widespread infections of the orofacial region.[1] HSV type 1 and type 2 (HSV-1 and HSV-2) are two strains of the herpes virus that can infect humans.[1] HSV-1 infections primarily affect areas in the facial region, where HSV-2 is primarily affects the genital area.[1] HSV-1 is the most common cause of herpes labialis (commonly caused "cold sores" or "fever blisters").

It is believed that the majority of Canadians will contract HSV-1 infection during childhood or adolescence, with up to 80% of adults being seropositive for the virus.[2] Approximately one-third of infected patients will develop relapses.[3] Patients with recurrent eruptions, will normally have outbreaks one to six times per year.[4] Although most episodes of recurrent cold sores are self-limiting and mild, frequent recurrences are associated with a significant impact on health-related quality of life (HRQoL).[5]

Step 1: Collect

The first step of the minor ailment process is to find out more information regarding the patient and their symptoms. Let's watch our pharmacist Isabel engage Alyssa through the collection process.

Pharmacist: "Sorry to hear you are getting a cold sore. Before I can make a recommendation, I would need to get a bit more information. Is it ok with you if I ask you a few questions about you and your symptoms?"

Alyssa: "Ok."

Pharmacist: "Let's start with a bit about your symptoms. You mentioned that you are getting a cold sore. Can you tell me a bit more about the symptoms you have?"

Alyssa: "I get these stupid cold sores all the time. Whenever I am stressed, I feel this burning and tingling, and I know that it is going to happen. That is what I feel right now. It started today and I don't want it to pop up."

Pharmacist: "Ok. Do you have any other symptoms?"

Alyssa: "I am a little stressed with work but otherwise I am healthy."

Pharmacist: "Any symptoms like pain or fever?"

Alyssa: "No."

Pharmacist: "You mentioned that you get these often when you are stressed. Can you please tell me when it first started, how often you get them, and what they look like when they flare?"

Alyssa: "Like I mentioned, I get this burning and tingling on my lips and after a few hours I can start to see the blisters on my lips. After a few days they burst and look gross. At about 5-7 days they dry up and within 10 days everything goes back to normal. I would say I get about 4 of these per year. I don't know when they started, but I can remember them flaring up when I started to go to high school."

Pharmacist: "Thank you. What have you used to treat your cold sores?"

Alyssa: "I normally just apply rubbing alcohol to dry them out, but it really doesn't help much."

Pharmacist: "Is there anything that makes them flareup besides stress?"

Alyssa: “Yeah, if I stay out in the sun too long and they tend to come around my period.”

The SCHOLAR questions are designed to help gather the relevant information regarding the patient’s condition. Let us look at the information the pharmacist collected from Alyssa.

Symptoms	• Burning and tingling at lip margin starting today • She normally gets these symptoms prior to a cold sore eruption
Characteristic of symptoms	• Burning and tingling
History of symptoms	• She has had these since high school • Occur approximately 4 times per year
Onset and timing of symptoms	• Symptoms start with burning/tingling, then blisters erupt on lip, after a few days burst, crust and then heal
Location	• Lips
Aggravating factors	• Stress, menstruation, ultraviolet (UV) radiation
Remitting factors	• None reported • Tried rubbing alcohol, but did not help

The HAMS questions are designed to gather more information about the patient. Patient factors are important to determine if the patient is appropriate for a minor ailment assessment.

Health Conditions	• None
Allergies	• None
Medications	• None
Social history	• Non-smoker • Drinks alcohol socially and uses recreational cannabis approximately every two weeks

Step 2: Assess

Clinical Presentation of Primary Cold sores

Primary infection with HSV has two age-related peaks, the first in childhood (6 months to 5 years of age) and the second in the early twenties.[1] When it occurs in children, it tends to have widespread oral ulceration. It is normally completely asymptomatic when it occurs in adolescents and adults.[3]

After primary infection, HSV-1 migrates along the nerve tracks from the oral mucosa to the neuronal cell bodies.[6] Here a restricted replication of the cycle occurs, most often culminating in a latent infection of the neurons.[1] The most common site of latency is in the trigeminal ganglion and the infection remains for the life of the patient.[1]

Clinical Presentation of Recurrent Cold sores

Recurrent infections occur at variable intervals, ranging from months to years.[1] The recurrent lesions occur at or near the site of primary infection and typically occur at a mucocutaneous junction of the face, usually on the lips. The stages of recurrent cold sores are reviewed in the table.[7]

Most episodes of recurrent cold sores are self-limiting and mild.[8] The time from the prodrome phase to healing without scarring occurs over a period of 1-2 weeks.[6]

Prodrome	• 60% of people have this approximately 6 hours before lesion development • Symptoms include: paresthesia, tenderness, pain, tingling, itching • Optimal timing for treatment
Erythema	• The skin is red and raised due to inflammation • Treatment at this stage is still optimal
Papule, vesicle, ulcer and soft crust	• Blisters are filled with viral laden fluid • From blister rupture until crusts are shed will have a reduced treatment effect
Hard crust	• Healing is occurring • Residual erythema/inflammation of area can last a longer period of time

Risk Factors for HSV-1 Infection and Triggers for Recurrent Cold sores

Almost all adults will become infected with HSV-1 infection over the course of their life. It is estimated that between 57% and 80% of adults are seropositive for HSV-1, with a greater prevalence in those from lower socioeconomic status.[2] There are also a number of factors that have been found to trigger a recurrence of cold sores. The table reviews some risk factors for HSV-1 infection and common triggers for a recurrence.

Table 1. HSV-1 infection risk factors and common cold sore triggers[1,9]

Risk factors for HSV-1 infection	Common triggers for cold sore recurrences
• Female gender • Black race • First intercourse occurred prior to or at 15 years of age • Greater total years of sexual activity • History of a partner with oral sores • Personal history of a non-HSV sexually transmitted infection	• Fever • Ultraviolet light exposure • Viral upper respiratory tract infection • Emotional stress • Fatigue • Trauma • Iron deficiency • Oral cancer therapy • Immunosuppression and chemotherapy • Oral and facial surgery • Vaginal infections • Gastrointestinal upset • Menstruation

DIFFERENTIAL DIAGNOSIS AND ALARM FEATURES

The diagnosis of recurrent cold sores is usually straightforward and based on the reported history, classic location and clinical appearance of lesions.[6] Pharmacists should consider referral of patients not presenting with classic cold sore symptoms, those with signs of a bacterial infection (e.g. pus, fever, etc.), immunocompromised patients, those having more than 6 episodes per year and those who have not responded to prescribed therapy.

The table reviews the differential diagnosis of herpes labialis.

Table 2. Differential Diagnosis of HSV-1 Infection[4]

Condition	Features	Diagnosis	Treatment
Aphthous Ulcers	Individual erythematous patches or plaques that may have a central vesicle, erosion or ulcer. These ulcers are painful, but the patient is afebrile and not otherwise ill The cause remains unknown, but is not viral	Clinical appearance: herpes simplex virus culture will be negative	Self-limiting, usually no treatment necessary; topical steroids if needed
Behçet's Syndrome	Produces painful often larger ulcers with disease in the mouth and genitals	Diagnostic criteria: (aphthous) ulcers (any shape, size or number at least 3 times in any 12 month period) PLUS: 2 or more of following: • Genital or anal ulcers • Skin lesions • Eye inflammation • Pathergy reaction (Skin condition in which a minor trauma such as a bump or bruise leads to the development of skin lesions or ulcers that may be resistant to healing)	Tetracycline/minocycline/doxycycline and topical steroids; may need oral prednisone and immunosuppressive agents
Herpangina	Oral infection with small ulcers caused by Coxsackie virus; ulcers characteristically seen	Clinical presentation	Symptomatic management

	on the soft palate. Sudden onset of fever Seen in children ages three to 10 years		

Step 3: Plan

Goals Of Therapy

The goals of therapy of managing cold sores include:[10]

- Reducing any discomfort, including pain, tingling or itchi[illegible]. Treat[illegible]nt manages outbreaks, but is not curative
- Reducing viral shedding
- Reducing the duration of lesions
- Reducing the severity of the episode
- Preventing secondary bacterial infe[illegible]on
- Preventing recurrences

Non-Pharmacological Treatment

Trigger avoidance may help to reduce the risk of cold sore recurrences. As was reviewed earlier, most of these triggers are not easily modifiable. One common trigger the patient can address is UV radiation protection. The use of sunscreens on the face and lips may help reduce the risk of recurrences.

HSV infections are highly contagious.[6] Patients should be educated on the infectious nature of herpetic lesions and asymptomatic viral shedding and should avoid touching the lesions to prevent the spread of HSV to other sites through autoinoculation or transmission to other individuals.[6]

Patients with active lesions should be encouraged to:

- Regularly wash their hands, particularly after application of topical medications; to avoid kissing others; and to avoid sharing utensils
- Keep the lesions clean with gentle washing using a mild soap and water.[10]
    - This can also be accomplished by soaking the area with a cool cloth or gauze compress with tap water.[10]
- Use of ice packaged in a wash cloth and analgesics such as acetaminophen or ibuprofen may help to reduce the pain of herpes labialis.[10]

Pharmacological Treatment

There are two main groups of treatment options for the management of herpes labialis. They can be broadly grouped into:

- Topical treatments (OTC and prescription)
- Oral antivirals

Topical Agents (OTC)

Topical Anesthetics

There are a wide number of topical anesthetics marketed for cold sore relief. These products contain ingredients such as benzocaine, lidocaine, pramoxine).[1] They do not affect the course of the recurrence but can be used to reduce pain and itching.[10] Products containing lidocaine and pramoxine are rare contact sensitizers. Topical benzocaine is a more frequent sensitizer and should be avoided.

Docosanol

Docosanol cream is available over-the-counter (OTC) for the management of herpes labialis. The active component interacts with the stabilized lipids in the target cell membrane, thus making the cell resistant to HSV fusion and entry.[11] It is indicated for the treatment of perioral skin only and its activity does not extend beyond the localized treated region of HSV recurrence.[11] Trials with 10% docosanol cream applied 5 times a day for 10 days, reduced healing time significantly by (1.6 to 4.6 days with early treatment in the prodrome and erythema stage) having the most benefit.[8] The duration of oral symptoms was also reduced (2.2 versus 2.7 days).[4] Evidence suggests that 10% docosanol is effective in reducing the healing time and pain in recurrent herpes labialis.[8]

Additional OTC Agents

Additional over the counter products with limited evidence include the following active ingredients:

- Propolis (honey extract)
- Combination boric acid and benzoyl alcohol
- Combination product combining the cooling effect of menthol, phenol and camphor with sodium/ calcium hydroxide
- Lysine

Topical Agents (prescription)

Although topical acyclovir is indicated for genital herpes simplex infections, it has been used for many years for the treatment of recurrent episodes of herpes labialis. Trials with both a 5% and 10% formulation of acyclovir ointment failed to demonstrate any effect over placebo in terms of lesion duration, pain duration or size of lesions.[8]

Clinical trials with 5% acyclovir cream (in propylene glycol or modified aqueous base) applied 5 times per day for 5 days at the earliest onset of prodrome resulted in a significant reduction in the duration of vesicles, time to crust formation and duration of lesions.[8] It has little effect on reducing pain. Acyclovir penetration in the modified cream was 8 times higher than in the ointment.[8]

Topical acyclovir 5% with 1% hydrocortisone cream applied 5 times per day for 5 days was found to prevent to reduce the number of patients who develop an ulcerative lesion and improve healing time by 1.4 days compared to placebo.[1]

Topical antiviral agents are well tolerated but are generally viewed as less effective than oral agents.

Oral Antivirals

Oral antiviral therapies have been used extensively in the management of recurrent cold sores. The three oral antiviral treatment options available in Canada include acyclovir, valacyclovir and famciclovir. The evidence supporting these agents in cold sores is reviewed in the table below.

Table 3. Evidence supporting oral antivirals for herpes labialis

	Acyclovir	Valacyclovir	Famciclovir
Treatment of cold sores	• 200 mg five times daily for 5 days had no effect on duration of pain or time to recovery.[13] • 800 mg five times daily for 5 days started within 1 hour of the first sign or symptom of recurrence, did NOT reduce the development of the lesion but reduced the mean healing time by 1 to 1.5 days and the mean duration of pain by 1 to 1.5 days.[8,14]	• 1000 mg twice a day for 1 day may abort lesion development if the drug is taken in the prodrome phase.[8] • 2000 mg BID for 1 day shortens the duration of cold sore episodes (0.5 to 1 day reduction) and pain (0.5 to 0.7 day reduction).[15]	• a single dose of 1500 mg or 750 mg twice per day for 1 day within one hour of prodromal symptoms onset was found to reduce healing times (4.4 days for single dose and 4.0 days for 750 mg twice daily versus 6.2 days for placebo) [16]

Prevention of cold sores	• Daily prophylactic therapy is moderately effective at preventing recurrent herpes labialis.[17] • The doses commonly used in the prevention studies was 800 mg/day in 2 or 4 equal doses.[17] • In one clinical trial, this regimen resulted in a 53% reduction in the number of clinical recurrences.[4]	• 500 mg daily for 4 months demonstrated a reduction in the number of cold sore outbreaks.[17]	• No evidence of efficacy in the prevention of recurrent herpes labialis.[17]