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Clinical Evidence. Practical Advice.

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EDITOR-IN-CHIEF

Dr. Stuart Maddin, Chairman of SkinCareGuide, is one of North America's leading dermatologists, and is the author of numerous dermatologic journal articles, monographs and textbooks. In addition to providing consultative input to a number of pharmaceutical and biotech companies, he is the director of the clinical trials unit at the Division of Dermatology, University of British Columbia. Dr. Maddin has also acted in an advisory capacity to a number of drug regulatory agencies, such as the Health Protection Branch (Ottawa), the AAD-FDA Liaison Committee, and WHO (Geneva). He is the founder of the Dermatology Update symposia, now in its 21st year. As well, he is Past President of the Canadian Dermatology Association and served as Secretary-General of the International Committee of Dermatology — International League of Dermatological Societies.

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Topical Therapy of Psoriasis Vulgaris

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Psoriasis Vulgaris

Psoriasis vulgaris is an autoimmune disease with genetic linkages (e.g., HLA-Cw6). Approximately 1/3 of patients have a relative with psoriasis. Activation of T-cells and TH1 cytokines result in epidermal hyperproliferation, reduction of epidermal differentiation, and inflammation.

Impact on the Sufferer

Psoriasis has a significant impact on quality of life.

- In one study in which several diseases were compared, only depression had a greater mental impact, and congestive heart failure a greater physical impact. [Rapp SR, et al. *J Am Acad Dermatol* 41:401-7 (1999).]
- A 2003 survey by the Psoriasis Society of Canada (n=1,108) reported a significant impact on work, school, and leisure pastimes in 81% of respondents.
- A 1998 US National Psoriasis Foundation survey of 17,488 members noted that 40% had trouble receiving service in establishments such as hair salons, pools, and health clubs, and >50% had incorrectly had their disease classified as contagious. [Krueger G, et al. *Arch Dermatol* 137:280-4 (2001).] Of the respondents ages 18-34 years:
 - 81% felt embarrassed
 - 75% felt they were unattractive
 - 54% suffered from depression
 - 10% had contemplated suicide.

Diagnostic Features of Psoriasis Vulgaris

- Red, scaly plaques, which are often very itchy and may bleed when scratched.
- The elbows, knees, lumbo-sacral area, and scalp are commonly involved, although any part of the skin may be affected, including the palms and soles.
- Involvement may be extensive.
- It is chronic with remissions and exacerbations.
- Concomitant nail changes are common (pitting, onycholysis, oil drop changes, subungual hyperkeratosis, and nail plate thickening).
- ~30% may have psoriatic arthritis.

Treatment

Treatment depends on:

- disease extent
- location of plaques
- response to previous treatment
- other medical conditions
- concomitant medications
- proximity to medical resources
- patient preference.

Topical therapy is the most widely used treatment and usually the first step, particularly in patients with <10% total body involvement. In patients with more widespread disease, it is often used as adjunctive therapy for resistant plaques, plaques in visible areas, and pruritic lesions. Phototherapy, traditional systemic treatment (e.g., methotrexate, cyclosporine, acitretin (Soriatane®) and biologic agents (e.g., alefacept (Amevive®), efalizumab (Raptiva®), etanercept (Enbrel®)) are used to treat widespread or resistant disease.

General Skin Care

- Avoid injury to the skin (e.g., scratching) since this may induce psoriasis in the area of injury, i.e., the “Koebner phenomenon”.
- Mild cleansers and tepid water should be used for cleansing.
- Moisturizers minimize scaling, painful fissuring, and itching. They should be applied immediately after bathing. Application of moisturizers in the direction of the patient’s hair minimizes the risk of folliculitis.

Avoid Aggravating Medications

In some patients, **beta-blockers**, **ACE inhibitors**, **antimalarials**, **nonsteroidal anti-inflammatory drugs (NSAIDs)** and **lithium** may aggravate the disease or make it more resistant to treatment. In some patients, it may take up to 1 year of use before the aggravating effects are seen.

Over-the-Counter Treatments

- Salicylic acid is keratolytic and increases the penetration of topical corticosteroids. It decreases scaling which may be particularly thick on the palms, soles, and scalp.
- Urea may also decrease scaling on the palms and soles.
- Tar bath oils, creams, lotions and ointments may relieve itching and reduce plaques.
- Over-the-counter treatments are applied once or twice daily.
- Use is limited by the smell, and potential to stain, irritate, and induce folliculitis.
- Hydrocortisone cream may be helpful for facial and fold psoriasis; however, a stronger topical corticosteroid is usually required elsewhere.
- Relieva®, a *Mahonia aquifolium* extract, is anti-inflammatory and decreases keratinocyte hyperproliferation. Statistically significant improvement in the signs and symptoms of mild-to-moderate psoriasis has been noted in clinical trials.
- Liquid bandaid helps “seal” fissures, thereby decreasing pain and allowing healing to occur.
- Shampoos containing tar, salicylic acid, zinc pyrithione, ketoconazole and many “dandruff” shampoos may decrease scalp scaling.
- Oral antihistamines may improve itching; nonsedating ones are generally used during the day and sedating ones at bedtime.

Prescribed Topical Agents

Compounding should be avoided if possible, since the stability of the resultant product is unknown. In contrast, commercially manufactured fixed combination products have been tested for stability. Some products work better in an acid base (e.g., topical steroids), whereas others (e.g., calcipotriol) are more effective in an alkaline base. Mixing a commercially available steroid such as betamethasone dipropionate (Diprosone®) with calcipotriol (Dovonex®) results in rapid degradation of both active ingredients. In contrast, Dovobet®, a commercially available product containing both ingredients, provides a base in which both products are stable.

Topical Corticosteroids

- Most widely prescribed treatment.
 - Available in low, medium, high, and ultra-high potency.
 - The steroid with the lowest effective potency should be used, particularly on the face and skin folds.
 - On the palms and soles, more potent steroids are usually required.
 - Lotions and gels are commonly used on the scalp.
 - Creams and ointments are used elsewhere.
 - Ointments are often more potent than creams
 - Steroids are safe short-term and intermittently long-term treatments.
 - Once daily application is often as efficacious as twice daily.
 - Use 2-3 times/wk may maintain remission.
- Adverse effects include:
 - atrophy
 - striae (particularly in intertriginous areas)
 - telangiectasia
 - rosacea
 - perioral dermatitis
 - glaucoma
 - cataracts
 - contact sensitization (to the steroid itself as well as to the base and preservatives)
 - tachyphylaxis (lack of effect with continued use)
 - flare upon discontinuation
 - adrenal suppression (don't use >50 mg of ultra high potency steroids/wk).

Topical Calcipotriol (Dovonex®)

- Used twice daily to achieve control and one or twice daily for long-term maintenance.
 - Speed of onset is slower than with topical steroids, but rebound is not associated.
 - Use 100g/wk maximum to minimize the risk of hypercalcemia.
 - Cream and ointment is used for trunk and limbs.
 - Solution is used for the scalp.
 - Commonly used in combination with a mid, high, or superpotent topical steroid (a.m./p.m. regimen).
 - Weekday calcipotriol with weekend superpotent topical corticosteroid (e.g., Ultravate®) may maintain improvement.
- Synergistic with:
 - topical corticosteroids
 - phototherapy [ultraviolet B (UVB), psoralen + ultraviolet A (PUVA)]
 - methotrexate
 - cyclosporine
 - acitretin.
 - Adverse effects:
 - irritation (usually mild and rarely results in discontinuation)
 - facial dermatitis.

Topical Calcipotriol and Betamethasone Dipropionate (Dovobet®)

- Contains calcipotriol and betamethasone dipropionate in the same concentrations as Dovonex® and Diprosone®, respectively.
 - Applied once daily.
 - More efficacious than its individual components with a faster onset.
- After 4 weeks of treatment, ~50% are clear or almost clear.
 - Similar cutaneous adverse events to betamethasone dipropionate and ~ half that of calcipotriol.
 - After control is achieved with Dovobet®, remissions may be maintained with either calcipotriol monotherapy or calcipotriol on weekdays and Dovobet® on weekends.

Topical Tazarotene (Tazorac®)

- Selective retinoid.
- Usually used once daily in combination with a mid or high potency steroid.
- Improvement may be maintained with Mon/Wed/Fri tazarotene and Tues/Thurs clobetasol ointment.
- Synergistic with:
 - topical corticosteroids
 - calcipotriol
 - phototherapy (UVB, PUVA).
- Contraindicated in pregnancy.
- Topical retinoids thin the stratum corneum which may allow more penetration of ultraviolet radiation into the skin and result in a lower threshold for sunburn
- Irritation limits its use.

Topical Calcineurin Inhibitors

- Topical pimecrolimus (Elidel®, 1% cream) and tacrolimus (Protopic®, 0.03% and 0.1% ointment) are efficacious for facial and intertriginous psoriasis.
 - Applied twice daily.
 - Do not cause skin atrophy.
 - May cause burning or stinging, particularly during the first couple of weeks of therapy and when the patient is exposed to heat.
- Sun protection is recommended because of the theoretical risk of skin cancer. However, no studies have shown photosensitivity with calcineurin inhibitors.
 - Health Canada issued a Health Advisory in April 2005 informing healthcare providers and patients about safety information from studies of animals given very high doses of these drugs indicating a potential cancer risk.
 - These drugs are indicated for nonimmunocompromised patients 2 years of age and older.

Herpes Labialis (Cold Sores)

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Introduction

While cold sores may be considered mild and inconsequential compared with many other viral infections, they can be extremely uncomfortable physically, making it painful to eat and talk. Cold sores also cause a huge emotional impact as sufferers change their routines to avoid being seen with an unsightly sore and to prevent spreading the virus to their family and close acquaintances.

Treatment options are available to reduce the discomfort associated with cold sores and to lessen the duration of the outbreak. The newest and most promising clinically demonstrated treatments available are docosanol, a nonprescription viral entry blocking agent, valacyclovir, an antiviral prescription agent, and, soon to be approved antiviral agent, famciclovir. More detailed information on these new treatments can be found in the Continuing Education session Recurrent Herpes Labialis: Assessment and Treatment (at www.skinpharmacies.ca).

Background

Cold sores are most often caused by herpes simplex virus type-1 (HSV-1). Primary infections are usually acquired in early childhood, often from parents or siblings, and more than 70% of children are infected by the age of 14. Once the patient is infected with HSV-1, the virus lies dormant in nerve cells. Reactivation is unpredictable with variable onset and recurrence although it can occur particularly during times of stress or trauma. This recurrent infection can manifest itself as classical cold sores and frequently results in asymptomatic shedding of virus particles. Recurrent HSV-1 lesions occur in approximately 20%-40% of infected individuals.

Diagnostic Features of Cold Sores

Herpes labialis is an infection caused by the herpes simplex virus, characterized by an eruption of small and usually painful blisters on the skin of the lips, mouth, or the skin around the mouth. These blisters are commonly called cold sores or fever blisters.

Cold sores proceed through seven distinct stages from the prodromal stage (pain, burning, itching, or tingling at the site where the blisters will form) that precedes the blisters to the highly infectious blister to the hard scab. It is important to understand the stages and visual appearance of a cold sore, as treatment is most effective when started at the early stages.

A chart fully describing the stages of a cold sore with images can be found at www.coldsores.ca. Patients also often confuse cold sores with canker sores as they share certain physical characteristics. Distinguishing cold sores from canker sores is important because the two conditions have distinct etiologies, presentations, and outcomes. Cold sores are usually on the outside of the lip or on the skin around the mouth. Canker sores are usually on the inside of the lip or mouth on the mucous membranes or buccal mucosa.

Prevention

Prevention of a future outbreak is important to infected individuals. Patients should be counselled to:

- limit sun exposure and apply sun block frequently to the lips and surrounding skin before going out.
- avoid triggers that can reactivate the virus such as windburn, UV light (sun and tanning booths), dry lips, emotional stress, and fatigue.

- be aware of unpreventable triggers such as menstruation, fever, illness, allergic reactions, physical injury, dental injury, and facial trauma.
- exercise caution to avoid transmitting the disease to other body parts or to other individuals.

Self-Help for Prevention

- Use skin protectants, such as moisturizers with a sun protection factor (SPF) of 30 or more, frequently on the lips and surrounding skin especially before sun or wind exposure.
- Avoid triggering situations.

- Get plenty of rest.
- Learn techniques to deal with stress.
- Do not share cutlery, cups, glasses, water bottles, towels, or razors.
- Use proper hygiene, wash hands carefully and frequently.

Medical Treatment

Most cold sores will clear up on their own after 7-10 days. Most treatment options are focused on reducing the discomfort associated with cold sores and lessening the duration of the outbreak. There are some newer options available to prevent the outbreak from progressing beyond the prodromal stage. Things that need to be considered include initiation, duration, magnitude and frequency of the cold sore, as well as accessibility, convenience of treatment to the patient, and cost.

Non-Prescription Treatments

Symptom Support Treatments

- Skin protectants (such as Labello® or Orabase®) provide moisturization as well as a mechanical barrier to guard the skin and lips from irritants.
- Topical analgesics/anesthetics suppress the sensory receptors, preventing the transmission of pain sensation to the brain. They can provide temporary relief of pain and itching. Sensitization and irritation can occur from these products.
- Oral analgesics provide temporary relief from the pain.

Viral Entry Blocking Agent Docosanol (Abreva® Cream)

- Blocks the virus from entering cells and subsequent viral replication.
- Has been clinically proven to reduce both the symptoms (including pain and itching) and the length of the cold sore outbreak.
- Most effective if it is used at the first sign or symptom of a cold sore (prodromal stage).
- Apply 5 times per day from the time of the initial symptoms for up to 10 days.

Possible Anti-viral Activity, Zinc and Heparin (Lipactin® Gel)

- May disrupt viral entry.
- May help shorten the duration of the cold sore if used early during the outbreak.
- Apply 3-6 times daily for up to 14 days.

Prescription Treatments

Anti-virals/nucleoside analogues reduce the number of infectious virions and slow infection between cells.

Topical

Acyclovir Cream/Ointment (Zovirax®)

- Shown to help reduce the severity of cold sores in the immunocompromised.
- Most effective if used at the first sign or symptom of a cold sore (prodromal stage).
- Apply 4-6 times a day for 10 days.

Oral

Acyclovir (Zovirax®)

- Reduces pain and healing time to crust formation, does not appear to affect progression, size or overall healing time.
- Most effective if used at the first sign or symptom of a cold sore (prodromal stage).
- Dosing: 200mg 5 times a day for 5 days.

Famciclovir (Famvir®)

- Reduces duration, healing time, and pain.
- Currently this drug is indicated only for treatment of recurrent episodes of HSV infections in HIV-infected patients (expanded indications are currently being explored).
- Most effective if used at the first sign or symptom of a cold sore (prodromal stage).
- Dosing: 500mg twice daily for 7 days.

Valacyclovir (Valtrex®)

- Reduces duration, healing time, and pain.
- May help suppress cold sore outbreak if taken during prodromal stage.
- Most effective if used at the first sign or symptom of a cold sore (prodromal stage).
- Indicated for suppression of recurrent episodes of Herpes Simplex Labialis.
- Dosing: 2g every 12 hours for two doses.

Counseling Tips

- Review the self-help tips with patients to help reduce their number of cold sore outbreaks and to limit transmission of the virus.
- Counsel patients on the importance of starting treatment at the first sign or symptom of a cold sore.
- Remind patients to wash their hands before and after applying any topical treatment to their cold sore or touching their lips.
- Inform patients that topical treatments may be best applied with a cotton swab or a gloved finger.

For a greater understanding of cold sore stages, treatment options and efficacy, and case studies with counseling scenarios see the cold sore continuing education program, Herpes Labialis: Assessment and Treatment, available at www.skinpharmacies.ca

Hyperhidrosis: Treatment Options

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Hyperhidrosis

Hyperhidrosis refers to the excessive production of sweat. There are many forms of hyperhidrosis, affecting a large proportion of the general population. Until recently, treatment was difficult; however, new advances such as a selective neurotransmitter blockade with botulinum toxin injections have revolutionized the management of many patients suffering from this condition.

Primary focal hyperhidrosis (PFHH) is the most common form of hyperhidrosis and is defined as non-physiological excessive sweating that occurs symmetrically in a localized fashion. Affecting about 5% of the general population, PFHH most frequently affects the axillae, hands, and feet. Other areas, such as the face and the groin, can also be involved. Although it does not endanger the life or physical health of an affected individual, it can cause significant negative impact on the quality of life. Patients most frequently report difficulty with work, school, and social relationships and as a result, they often shy away from situations that require shaking hands or other forms of close physical contact with people.

Treatment Options

Several forms of treatment are available for the management of PFHH. Depending on the locations involved, the options are slightly different.

Axillary Hyperhidrosis

Topical Antiperspirants

- The most commonly used first-line treatment for axillary PFHH. For example, aluminum chloride 20% solutions applied once or twice daily on affected areas (on dry skin to decrease irritation) can be used.
- Rarely offer significant or complete relief of the sweat production.
- Frequent reports of local irritation.
- Preferred by most patients because of relatively low cost.
- Central reagent is aluminum chloride in various concentrations: the higher the concentration is, the more effective it is. However, higher concentrations are also associated with higher risks of local irritation, which can limit compliance.

Subcutaneous Injection of Botulinum Toxin

- Botulinum toxin, when injected by experienced physicians, blocks the release of acetylcholine, a neurotransmitter, by the sympathetic nerves innervating the sweat glands.
- Localized effect to the immediate areas of the administration, with little systemic spread.
- No significant side-effects.
- More than 90% reduction in sweat production for more than 90% of patients.
- Repeated injections necessary, usually one to two injections each year.
- Relatively high in cost. However, since all private health insurance carriers cover the cost of the drug for this indication, it can be offset for anyone who has a private drug plan. In addition, an injection of botulinum toxin eliminates the frequent use of topical antiperspirants and potentially saves costs associated with replacement of clothing. The cost associated with the botulinum toxin injection is only marginally higher than the cost of topical antiperspirants.

Oral Anticholinergics

Oral anticholinergics such as glycopyrolate can offer mild-to-moderate relief for some patients suffering from PFHH. However, because of the systemic side-effects such as dry mouth, blurred vision, and reduced gastrointestinal motility, systemic anticholinergics have not been the accepted therapy for most patients.

Axillary Hyperhidrosis (continued)

Surgical Management of Axillary Hyperhidrosis

Surgical removal of the sweat glands in the axillae, or ablation of the sympathetic chain supplying the sweat glands can also be performed for selected patients. However, there are concerns of surgical complications such as:

- With sweat gland removal
 - necrosis
 - scarring
 - relapsed sweating.
- With sympathectomy
 - risk of intrathoracic injury to the lungs and other nerve structures
 - compensatory hyperhidrosis.

Therefore, these procedures are generally reserved for patients who do not respond to other forms of therapy.

Palmoplantar Hyperhidrosis

Hyperhidrosis affecting the hands and the feet is also very common, alone or in combination with axillary hyperhidrosis. The treatment options are similar to those for axillary hyperhidrosis.

- Topical antiperspirants are often the first therapy tried.
 - Rarely satisfactory.
- Botulinum toxin subdermal injections are highly effective.
 - Cost of therapy significantly higher because palmoplantar hyperhidrosis requires significantly larger doses of the toxin.
- Tap-water-iontophoresis treats the palms and soles of the affected individual with micro-amounts of electric current delivered through the medium of tap water. The mechanism of action is unknown. However, it may involve formation of plugging of the eccrine sweat gland pores.
 - Initially requires frequent treatment sessions to be effective.
 - Once significant control of sweating is attained, infrequent maintenance therapy is all that is necessary for moderate-to-significant long-term control.
 - Relatively low in cost.
 - No significant side-effects.
 - May be tried by patients before sympathectomy.

As for axillary hyperhidrosis, systemic anticholinergics can be used when other nonsurgical options are not effective or suitable.

Facial hyperhidrosis

Excessive production of sweat of the face and scalp can be a significant concern for many individuals.

- This area is not suitable for topical antiperspirants or iontophoresis.
- The most effective therapy is botulinum toxin sub-dermal injections.
- Especially effective and safe for the forehead and scalp, where the side-effect of facial muscle paralysis is not a big concern.
- For the lower face, careful placement of the toxin is required to avoid untoward paralysis of the facial muscles.

Systemic anticholinergics such as glycopyrolate can also be tried for patients when botulinum toxin is not an acceptable choice.

Conclusion

There have been major improvements in the treatment of excessive production of sweat because of the introduction of effective botulinum toxin therapy. For facial and axillary hyperhidrosis, this has become the treatment of choice for most patients. For palmoplantar hyperhidrosis, botulinum toxin is also highly effective and should be offered along with the choice of iontophoresis if topical therapies fail. For both axillary and palmoplantar hyperhidrosis, surgical options are reserved as the last options when all other treatments fail.

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Pharmacist Edition

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