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Clinical Evidence. Practical Advice

Editor-in-Chief: Dr. Stuart Maddin

Dr. Stuart Maddin, MD, FRCPC
EDITOR-IN-CHIEF

Dr. Stuart Maddin is the Chairman of SkinCareGuide. He is one of North America's leading dermatologists and 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 Department of Dermatology and Skin Science, 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 World Health Organization (Geneva). He is the founder of the Dermatology Update symposia, now in its 27th 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.

Dr. Colleen Lawlor, MD, CCFP
FAMILY PRACTICE ADVISOR

Dr. Colleen Lawlor has chosen to build her family practice at Continuum Medical Care located in West Vancouver, BC. Dr. Lawlor has a BA in Psychology, an MSC in Nursing, and her MD, CCFP. She received her medical training at the University of Texas in San Antonio.

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Long-term Management of Psoriasis: Flexible Therapeutic Regimens Providing Safe and Effective Outcomes

Anil Kurian, BScN, MN, MD[1] and Benjamin Barankin, MD, FRCPC[2]

[1]McMaster University, Hamilton, ON, Canada

[2]Toronto Dermatology Centre, Toronto, ON, Canada

Introduction

Psoriasis is a chronic, inflammatory skin condition prone to periods of skin flaring. As with any chronic disease, it requires long-term patient adherence with prescribed management to ensure optimal clinical benefits. There are many safe and effective topical treatment options that provide control of mild-to-moderate psoriatic disease. As our understanding of the etiology of psoriasis becomes clearer, the treatment regimes can be better tailored to control the disease and address psychological fears of patients, thus, resulting in greater clinical outcomes and patient satisfaction.

Etiology of Psoriatic Inflammation

- In the past few decades, much progress has been made in both the understanding and the treatment of psoriasis.
- In general, psoriasis is characterized by four skin abnormalities: redness or erythema, inflammation, hyperproliferation of the keratinocytic layer, and altered epidermal differentiation.[1]
- Psoriasis is no longer regarded as a chronic primary dysregulation of keratinocyte proliferation as was originally thought, but now, is attributed to a combination of genetic (numerous loci have been isolated) and environmental factors (such as streptococcal infections, stress, or drugs including beta-blockers and lithium) that promote a systemic T cell-mediated autoimmune response in the skin with innate immune responses playing an important role.[2]
- The hypothesis for the pathogenesis of psoriasis proposes that a pro-inflammatory stimulus leads to the development of 'immunological synapses' between dendritic and T cells with subsequent antigen-specific T cell activation.[2]
- The subsequent release of cytokines and growth factors initiates the proliferation and altered differentiation of keratinocytes, which further promotes the activation of T cells and antigen-presenting cells (mainly dendritic cells) within the psoriatic plaque.
- The clinical success of anti-TNF therapy in the treatment of psoriasis has further validated the role of these cytokines in psoriasis pathogenesis.[3]

General Treatment Paradigms

- The main goal of treatment in psoriasis is to gain rapid control of the disease and reduce its signs and symptoms.
- This can be achieved by decreasing erythema, scaling, and induration of plaques; reducing the frequency and intensity of psoriatic flare-ups; reducing the extent of body surface area (BSA) disease involvement; and effectively managing side-effects.
- Tailoring treatment to a format that is acceptable to the patient is important.

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- These needs vary depending on body location, characteristics of the psoriasis being treated, including lesion thickness, degree of erythema, and amount of scaling, as well as patient preferences.

Topical Treatment Options

Corticosteroids

- High-potency corticosteroids have been a mainstay in the topical treatment of psoriasis for decades. Their efficacy can be attributed to multiple mechanisms of action, including their anti-inflammatory, immunosuppressive, and antiproliferative effects.[3] Corticosteroids are formulated in a variety of vehicles (e.g., cream, lotion, ointment, gel, shampoo, and spray) to address the possible combinations of treatment conditions. Appropriate selection can promote adherence and improve outcomes.
- The disease severity, location being treated, ease of use, cosmetic acceptability, and patient age and preferences should be taken into consideration when choosing a suitable potency of corticosteroid treatment.[4]

Coal Tar

- Coal tar has been used since ancient times to treat various skin diseases and for approximately 100 years in the treatment of psoriasis.[4]
- Although the mechanism of action of coal tar is not well understood, it is known to suppress DNA synthesis by lessening the mitotic labeling index of keratinocytes.[4]
- Often, coal tar products are not well tolerated by patients due to cosmetic inelegance, including staining of clothes and a potent tar odour that is present in almost all products to some degree.
- Other potential adverse effects include irritant contact dermatitis, folliculitis, and photosensitivity to UVA.

Retinoids

- Retinoids are a unique class within the armamentarium of antipsoriatic treatments, which are largely dominated by immunomodulatory therapies.
- The mechanism of action of retinoids in psoriasis may include direct suppression of inflammation, as well as inhibition of proliferation and normalization of differentiation in the epidermal layer.[3]
- The topical retinoid approved for psoriasis is tazarotene gel and cream and is available in 0.05% and 0.1% formulations. Due to the common side-effect of irritation, they are not frequently used.

Calcineurin Inhibitors

- There are two topical preparations of calcineurin inhibitors: tacrolimus ointment (0.03% and 0.1%) and pimecrolimus cream (1.0%).
- The initial trials indicated treatment efficacy in patients with psoriasis when used under occlusion. Hence, it led to the belief that the penetration of topical calcineurin inhibitors into thick psoriatic plaques was limited.
- Consequently, tacrolimus and pimecrolimus have been used in areas of skin where greater topical penetration is improved, such as on flexural or facial skin.[5]
- Side-effects for calcineurin inhibitors include a burning sensation and pruritus with initial treatments in some patients; however, this discomfort is generally reduced with ongoing use.[5]

Justification for Long-term Treatment Options

Long-term topical treatment options are necessary as psoriasis is a chronic disease requiring ongoing patient adherence to better maintain optimal clinical outcomes. Early intervention can limit flares and minimize progression to more severe disease. As well, over time, psoriasis can become recalcitrant to treatment, requiring more potent medicines that expose the patient to greater risk for adverse side-effects.

Corticosteroids

- Several potencies of corticosteroid treatment are available, ranging from Class 1 (highest potency) to Class 7 (lowest potency).
- Superpotent steroids are suitable for intermittent/pulse therapy or as a component of sequential therapy. Chronic recalcitrant plaques, control of flares, or thickened lesions (i.e., palms and soles) generally require treatment with the higher potency corticosteroids (i.e., Classes 1 and 2). Available data demonstrate safety and efficacy of Class 1 topical steroids when used short-term (2 to 4 weeks); however, the risk of both cutaneous and systemic adverse effects increases if they are used continuously for longer periods of time.[4]
- The ability to vary strength and administration method gives steroids the versatility to mildly treat sensitive and thin-skinned areas, such as the face and body folds, and the option to provide stronger treatment to more resistant areas of the body, such as extensor surfaces and the palmoplantar areas.[6]
- Fear of side-effects is a key reason patients use steroids less often than prescribed, leading to decreased efficacy. Counseling patients on proper usage (e.g., dosing, application, and duration) and the therapeutic objectives can promote treatment adherence.
- Local side-effects to look for include skin atrophy, telangiectasia, striae distensae, folliculitis, acne, and purpura. Systemic side-effects of corticosteroids include hypertension, osteoporosis, Cushing's syndrome, cataracts, glaucoma, diabetes, and avascular necrosis of the hip.[5]

Steroid-sparing Options: Vitamin D3 Derivatives

- Vitamin D analogs are known to play an important role in the treatment of chronic plaque psoriasis, as they have shown to provide good clinical efficacy without the side-effects typically seen with long-term corticosteroid use.
- Vitamin D analogs work through the stimulation of cellular differentiation, inhibition of proliferation, and immunomodulation.[5]
- Their discovery was prompted by the realization that oral vitamin D had a therapeutic effect on psoriatic plaques.
- However, parent vitamin D3 might not be suitable for treating psoriasis owing to the potential for hypercalcemia.[6] Hence, several vitamin D3 analogues have been developed for the treatment of psoriasis.
- Vitamin D analogues, such as calcipotriol and calcitriol, inhibit corneocyte proliferation and stimulate corneocyte differentiation *in vitro*.[5] In addition, these analogues

have only minimal effects on calcium levels and calcium excretion.
- Vitamin D analogs are also valuable and clinically effective in combination therapy, especially with topical corticosteroids, thus allowing for a steroid-sparing effect.[7]
- Newer topical treatments that contain vitamin D analogs and have shown good clinical efficacy and safety profiles include:
  - Calcitriol ointment (Silkis™) - a naturally occurring derivative of vitamin D
  - Calcipotriol + betamethasone dipropionate gel (Xamiol®) - a two-compound scalp formulation containing a synthetic vitamin D3 with a potent topical steroid

Calcitriol Ointment

- Calcitriol 3µg/g ointment is a naturally occurring active form of Vitamin D3 demonstrated to be as effective as other vitamin D analogs, but calcitriol has the advantage of increased tolerability in sensitive areas such as the face, hairline, and postauricular and flexural areas.[8]
- The use of a tolerable vitamin D3 analog in sensitive areas may minimize corticosteroid use in these skin regions, allowing for better individualization of a psoriasis regimen.
- It is indicated to treat mild-to-moderate plaque-type psoriasis in adults ≥18 years of age with up to 35% body surface area involvement and is suitable for long-term therapy.
- Calcitriol ointment has been extensively evaluated for the treatment of chronic plaque-type psoriasis and has been shown to be effective, safe, and well-tolerated in a number of short-term and long-term clinical trials.[9]
- In a 52-week uncontrolled, open label study of 324 patients, efficacy did not appear to diminish over time.[10]
- Recommended dosing is twice-daily (morning and evening) to affected areas. The maximum weekly dose should not exceed 200g and improvement may be seen as early as 2 weeks after initiating therapy.
- Pharmacokinetic studies in patients with psoriasis and healthy control subjects have demonstrated that topical calcitriol ointment produces little systemic absorption of calcitriol and does not result in systemic hypercalcemia even when applied to approximately one-third of the body surface area.[9]

Calcipotriol + Betamethasone Dipropionate Gel

- This once-daily lipophilic gel is specially formulated for the scalp and contains the active ingredients calcipotriol 0.005% and betamethasone dipropionate 0.05%.[11] Studies have shown that the two agents in combination have a more rapid onset of action and greater efficacy than monotherapy with either agent.[12,13]
- A study investigating the combination of betamethasone dipropionate 0.5mg/g plus calcipotriol 50µg/g in a new gel formulation showed that 92% of patients achieved marked improvement to clearance of their scalp psoriasis following once-daily use for up to 8 weeks.[14]
- The gel vehicle improves cosmetic acceptability, minimizes irritation, facilitates ease of use, is odourless, and may encourage patient adherence with a once-daily regimen.
- To avoid the potential effects of calcium metabolism, usage should be limited to 15g daily, or 100g weekly.

Improving Long-term Quality of Life

- Topical corticosteroids are a useful intermittent therapy for managing stable disease affecting relatively small areas of the body, leading to an improved quality of life over a long-term period.
- In general, a gradual reduction in the frequency of corticosteroid use following clinical response is recommended.[4]
- Therapy should be monitored by physicians to limit the risk of cutaneous or systemic side-effects, especially if it is to be used for a prolonged duration.
- Controlling these adverse side-effects will improve patient adherence and outcomes. Hence, the addition of newer vitamin D analogs to the topical armamentarium for psoriasis will no doubt widen therapeutic options and improve adherence.
- Additionally, in quality of life questionnaires administered to psoriatic patients, psychological distress appears to be a self-reported trigger for flare periods in up to 60% of patients.[15]
- Psychological interpersonal difficulties can impinge on all aspects of the patient's daily life. As such, it is important to assess how the patient's life is affected by the psoriasis, what the patient perceives as the most bothersome aspects of their psoriasis, and what their hopes and expectations of treatment are.[16]
- It should also remain a priority to provide treatment that addresses these psychological fears and concerns of patients.
- In order for the treatment to be successful, appropriate therapeutic regimes for patients should take into consideration long-term self-reported assessments for quality of life improvements.

Conclusion

Establishing an effective therapeutic regimen is crucial in managing not only the psoriasis, but also patient adherence to treatment and satisfaction with outcomes. Understanding both patient-specific needs and the available topical therapies are essential in order to successfully treat the majority of psoriatic patients. However, primary care physicians should continually review with patients the therapeutic options and elicit their feedback to optimize long-term management of this chronic condition.

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Optimizing Topical Acne Therapy

Maha Dutil, MD, MEd, FRCPC
Division of Dermatology, University of Toronto, Toronto, ON, Canada
Women's College Hospital, Toronto, ON, Canada

Introduction

Acne vulgaris is a disease of the pilosebaceous follicle characterized by non-inflammatory (open and closed comedones) and inflammatory lesions (papules, pustules, and nodules). Its pathogenesis is multifactorial - the interplay of hormonal, bacterial, and immunological (inflammatory) factors results in the formation of acne lesions. Although acne is not a life-threatening condition, it can have detrimental effects on the quality of life of affected individuals. Fortunately, acne is readily responsive to the wide-range of available medications, with the goals of therapy being to clear the lesions, prevent scarring, and limit any treatment-related side-effects and psychosocial sequelae. Newer fixed-dose combination products target multiple acne pathogenic factors and offer simplified dosing regimens, which may potentially enhance both efficacy and patient adherence when compared with single agent therapy.

Acne Overview

Pathogenesis

- All forms of acne involve one or more of these pathophysiologic factors:
  - hyperkeratinization of the follicular epithelium with comedo formation
  - increased sebum production
  - bacterial proliferation of *Propionibacterium acnes* (*P. acnes*)
  - local immune activity causing inflammation
- Hormones are known to affect sebum production, but may also play a role in follicular hyperkeratinization independent of the effect on the sebaceous gland. During adrenarche, an increase in adrenal androgens leads to:
  - enlargement of sebaceous glands that results in increased sebum production.
  - abnormal desquamation and greater adhesion of the exfoliated keratinocytes in the sebaceous follicle, leading to obstruction in the follicle, and resulting in production of the microcomedo (a plug of keratin and sebum - the precursor of all acne lesions).
- Colonization of the pilosebaceous apparatus by *P. acnes* occurs in this anaerobic environment where sebum provides the nutrition for its survival. This gram-positive bacterium contributes to the inflammation by:
  - releasing enzymes
  - inducing cytokine release from other cells
  - triggering an immune response (e.g., antibody production)

Prevalence and Disease Features

- Acne affects about 85% of individuals between the ages of 12-24 years.[1] Persistent acne (beyond the teenage years) and adult-onset are increasingly common.[2]
- Grading to determine acne severity is inherently subjective, as the process is largely based on clinical observation. Many grading systems have been developed that take into account lesion type and extent of involvement for measuring severity. Depending on the chosen technique, the measurement spectrum can range from Grades 1 to 4 all the way up to Grades 1 to 12. Acne may be classified according to predominance of specific skin lesions and the number of each lesion determines classification from mild to severe:
  - Comedonal (non-inflammatory) - mild, moderate, or severe
  - Papular (inflammatory) - mild, moderate, or severe
  - Pustular (inflammatory) - mild, moderate, or severe
  - Nodular - mild, moderate, or severe
- Acne can be physically and emotionally scarring, causing significant psychosocial morbidity and reduced self-esteem independent of acne severity.

Treatment Overview

- The majority of patients present with mild-to-moderate comedonal or papulopustular acne that can be treated with topical agents (Table 1).
- Severe cases with nodules, cysts, or scarring will require the addition of systemic therapy.
- Available topical anti-acne compounds have a direct or indirect influence on the above mentioned pathogenetic factors.
- Treatment selection is guided by the predominant acne lesion type.

Drug Type	Topical Acne Agents	Comments
Antimicrobials	• Benzoyl peroxide (BP) • Clindamycin • Erythromycin • Sodium sulfacetamide	• Directed against *P. acnes* • Formulated as creams, ointments, lotions, gels, and foams • May induce irritation and dryness • BP has mild comedolytic activity • BP can bleach coloured fabrics
Combination products	• Topical antibiotic + BP • Topical retinoid + antibiotic • Topical retinoid + BP	• Facilitate treatment of multiple pathogenic factors • Combined efficacy is greater than either agent alone • Gel formulations • BP + antibiotic can inhibit bacterial resistance • Simplifies treatment regimen and reduces dosing frequency (i.e., once-daily application) and drug exposure time • Retinoid + antibiotic may increase tolerability • Potentially more cost effective
Retinoids	• Adapalene • Tazarotene • Tretinoin	• May be used for all grades of acne and for maintenance therapy • Non-inflammatory (comedonal) acne is best treated with a topical retinoid; noticeable improvement may take several months • Common side-effects include irritation (e.g., stinging or burning sensation), redness or inflammation, and scaling or dryness • Formulated as gels, creams, and solutions • Advancements in vehicle delivery reduce irritation and enhance efficacy (e.g., emollient cream and microsponge gel)

Table 1: The spectrum of approved topical acne medications[2-4]

Rationale for BP/Antibiotic Combination

Effective treatment considers all pathogenic factors and single-agent therapy does not address all four major pathophysiologic features of acne.

- Topical antibiotics have been used to treat acne for more than 40 years and are still widely used. The efficacy of antibiotics is attributable to their inhibitory effects on both the proliferation of *P. acnes* and inflammatory mediators.
- The emergence of resistant strains has, in some cases, been associated with a failure to respond to antibiotic therapy, which was first reported with the topical antibiotics clindamycin and erythromycin.[3]
- The use of BP reduces the occurrence of resistance and can be effective in the treatment of both nonresistant and resistant *P. acnes* strains.[4]
- BP does not promote antimicrobial resistance and has been shown to prevent such resistance when used concomitantly with topical erythromycin or topical clindamycin.
- A number of clinical studies have demonstrated improved efficacy and safety of combinational BP/antibiotic approach to acne management (Table 2).

Combination Treatment	Study Design/Results
5% BP/3% erythromycin (BP/E) gel vs. erythromycin alone applied for 6 weeks	• Double-blind study of patients with mild-to-moderate acne[5] • The number of erythromycin-resistant strains of *P. acnes* was significantly reduced in the BP/E group compared with the group that received erythromycin alone.
5% BP/3% erythromycin gel vs. erythromycin alone applied for 6 weeks	• Open study of patients with erythromycin-resistant strains of *P. acnes*[5] • Highly significant reductions were also seen in acne grade and lesion counts with the BP/E combination.
BP/clindamycin (BP/C) combination, BP, clindamycin, or vehicle gels applied once nightly for 11 weeks	• Two double-blind, randomized, parallel, vehicle-controlled trials of acne patients[6] • The combination gel was significantly superior to the two individual agents in global improvement and reduction of inflammatory lesions.
5% BP/1% clindamycin, 5% BP/3% erythromycin, or 5% BP applied twice daily for 10 weeks	• Randomized, multicenter, single-blind trial of moderate-to-severe acne patients[7] • Both BP/C and BP/E were comparable and demonstrated significantly greater reductions in inflammatory lesions over BP alone.

Table 2: Clinical trials demonstrating efficacy for combination treatments with BP and erythromycin or clindamycin

Combination Treatment Considerations

- Mild-to-moderate inflammatory acne can usually be managed with two topical drugs. Typically one is applied in the morning and the other at bedtime.
- A retinoid is used to deal with the precursor of all acne lesions (i.e., the microcomedo) and an antibacterial agent for its effects on *P. acnes*. Topical antibacterial options include BP or a BP/antibiotic combination.
- BP is extremely effective against *P. acnes*, but can be irritating. The irritation can be minimized by using the lowest concentration of BP in a water-based vehicle that does not reduce its efficacy. Another way to reduce the irritation induced by BP is to combine it with an antibiotic.
- BP/antibiotic combinations also reduce the irritation that can be induced by a topical retinoid. Only if a patient is allergic to BP (estimates range from 1%-2% of the population[8]) should a topical retinoid be used with a topical antibiotic alone. The topical antibiotic should be discontinued as soon as possible and the retinoid can be used for maintenance alone.

Prescribing Recommendations to Minimize Bacterial Resistance

- Antibiotics should not be used as monotherapy, nor should they be used to treat mild acne.
- Avoid topical antibiotics if non-antibiotic topical preparations will suffice.
- Use alternatives to antibiotics for maintenance.
- Stop antibiotic treatment when the skin clears or if no further improvement is noted.
- If there is a failure to respond to oral antibiotics or a rapid relapse after discontinuation, consider other therapy (e.g., systemic retinoid, anti-androgens in women).
- If the antibiotic is needed again, use the same antibiotic.
- Use full doses of antibiotics and do not taper.
- Avoid concomitant topical and systemic use of different antibiotics to reduce the risk of developing resistance to both agents.
- Do not switch or rotate antibiotics in non-responding patients.
- Use BP during antibiotic therapy.
- BP bleaches clothing and hair, and thus, patients should be warned when prescribed.
- Limit the use of BP on the chest and back to night-time due to its bleaching effect on clothing or recommend that patients wear a white T-shirt under clothing for daytime application.

Non-Adherence

- Patient non-adherence to treatment can influence outcomes, which is of particular concern with topical medications (e.g., proper application and accurate dosing).
- Some clinical strategies to promote treatment adherence include:
  - advocating patient involvement in therapeutic decision-making
  - devoting time to patient education on acne and the selected treatments, instructions for use, potential side-effects, and expected rate of improvement
  - selecting treatments that facilitate ease of use (i.e., once-daily dosing)
  - modifying current treatment if patient dissatisfaction is encountered

Conclusion

Since multiple factors are involved in acne pathogenesis, treatment that targets the majority of these elements can be expected to achieve optimal results. When considering the options for reducing the *P. acnes* population, it is best to choose therapeutic agents that do not encourage resistance patterns. Evidence for improved efficacy, safety, and onset of action, as well as longer remission, has been noted with combination therapies. Advances in dual agent fixed-dose compounds offer simpler dosing regimes that can promote patient adherence. Furthermore, the cumulative benefits of these advances may lead to improved therapeutic outcomes and overall improvements in quality of life for acne patients.

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Update on the Management of Chronic Hand Dermatitis

D. Richard Thomas, MD, FRCPC[1] and Christine E. Malcolm, MD, FRCPC[2]

[1]Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

[2]Division of Dermatology, University of Toronto, Toronto, ON, Canada

Introduction

Hand dermatitis (HD) is a common skin disorder affecting individuals of all ages. HD broadly refers to any type of inflammation involving the skin of the hands that is characterized by a combination of redness, itching, scaling, and fissuring. Both genetic and environmental risk factors are important in its etiology. HD is well known for its recalcitrance, typically following a chronic relapsing course that progresses in severity and may resist conventional treatment. However, recent advances, particularly for chronic severe disease, have broadened the therapeutic landscape. A thorough understanding of pathogenesis, heritability, diagnosis, therapeutic options, and patient-related factors will aid in improving acute and long-term management, as well as treatment outcomes. For this review, the terms eczema and dermatitis are used interchangeably and refer to the same condition.

Prevalence and Prognosis

- Most adult patients with dermatitis have involvement of the hands.
- An estimated 7-12% of the general population is affected by HD.[1]
  - Approximately 5-7% of HD patients have chronic severe disease and 2-4% are refractory to topical treatment.[2]
- Prevalence is considerably higher among certain occupational groups, e.g., domestic workers, hairdressers, health care professionals, and workers in the agricultural, food-related, mechanical, metallurgic, or printing industries.
- HD is also twice as likely to occur in women than in men.[3]
- Strongest negative prognostic factors include extent of involvement, history of childhood dermatitis, and disease onset at <20 years of age.[4]

Common Variants of Hand Dermatitis

An epidemiologic HD study observed irritant contact (35%), allergic contact (19%), and atopic (22%) dermatoses to be the most commonly classified forms; 15% of patients had unclassified eczema.[5]

Irritant Contact Dermatitis (ICD)

- ICD is caused by repeated or prolonged exposure to contactants, which inhibits epidermal barrier repair.
- Substances that can induce reactions: water, soaps, detergents, cleansers, solvents, degreasers, lubricants, oils, coolants, food products, fiberglass dust, metals, plastics, and resins, as well as mechanical trauma.
- Symptoms are usually symmetrical and affect the dorsal fingertips and webspaces.

Allergic Contact Dermatitis (ACD)

- Making a distinct diagnosis between ICD and ACD can be difficult.
- Reactivity occurs when previously sensitized individuals are re-exposed to the antigen.
- Common allergens include nickel, fragrances, and preservatives.
- Occupational allergens include topical antibacterial agents, metallic salts (e.g., chromate and nickel), organic dyes, plants, plastic resins, and rubber additives.
- The dorsal skin is most commonly affected, particularly the fingers.

Atopic Dermatitis (AD)

- AD is a risk factor for HD in adults.
- AD frequently involves the hands and/or eyelids. Other commonly affected areas include the dorsal hands, fingertips, and volar wrists.
- Acute skin lesions appear as erythematous papules with excoriations, vesicles, and oozing. Intense itching is common.
- The chronic phase is characterized by hyperkeratosis (thickened skin), lichenification, and fibrotic papules.

Causes and Risk Factors

- Exogenous and endogenous factors contribute to the etiology of HD. This multiplicity makes identification of all causative elements very difficult.
- HD commonly progresses on a chronic path, even with avoidance of the initially implicated trigger.[2]
- Personal/familial history of atopy (asthma, allergic rhinitis, atopic dermatitis).
- HD can be caused or aggravated by occupational exposure from working in wet conditions, frequent hand washing, or using irritative substances.
  - Severity of occupational HD is associated with prolonged sick leave and increased risk of job loss.[6]

Treatment

Despite its prevalence and considerable disease burden, there are very few well-designed randomized controlled trials (RCTs) evaluating therapies for chronic hand dermatitis (CHD).

- Resultantly, most therapeutic recommendations are based on personal physician experience and the limited number of small studies.
- The EDEN survey by van Coevorden et al. assessed HD studies conducted between 1977 to 2003 and confirmed a lack of RCTs, with most exhibiting poor methodology and quality of reporting.[7]
- Consequently, this dearth of evidence-based data fails to sufficiently guide therapeutic decision-making.
- The absence of clarity is even more evident for severe CHD, as therapeutic options are further restricted.[8]

Topical Agents

Topical treatments may be used in combination or with systemic or light therapies.

Emollients

- The regimented use of emollients contributes to repair of the skin barrier.
- Adequate moisturization can support pharmacologic treatment by reducing the need for topical corticosteroids or immunomodulators, and mitigating side-effects from drug therapy.

Corticosteroids

- Topical steroids are used to reduce inflammation and are a mainstay of therapy.
- Ointments are generally more effective and contain fewer preservatives and additives than creams.
- The thick stratum corneum (e.g., palms, palmar aspects of fingers, and around nails) often requires higher potency preparations, such as clobetasol propionate 0.05% ointment 1-2 times daily for a few weeks and then 2-3 times a week thereafter, as needed.
- Topical steroids should be used on affected areas twice-daily until improvement is seen, then the dosage may be tapered to intermittent use for maintenance therapy.
- A poor response may indicate a corticosteroid allergy.
- Cross-reactions between groups of corticosteroids and flares with systemic steroids may complicate therapy.
- Limitations can include tachyphylaxis, skin atrophy, and systemic side-effects, especially if used long-term.

Topical Calcineurin Inhibitors

- Topical calcineurin inhibitors (TCIs) are nonsteroidal immunomodulators that exert anti-inflammatory effects.
- Pimecrolimus and tacrolimus are useful when conventional agents fail or are unsuitable.
- Pharmacokinetic activities of TCIs include skin absorption, but they do not enter the bloodstream.
- Onset of effect is slower than corticosteroids.
- Common side-effects of TCIs include mild and transient itching and burning upon application.

Salicylic Acid and Coal Tar

- These agents are sometimes prescribed for hyperkeratotic areas to help soften skin, reduce thickness, and improve penetration of medications.
- Salicylic acid can cause irritation.
- Tars can have an unpleasant odour and cause irritation and staining. Potential carcinogenicity is also a concern.

Systemic Agents

Antihistamines

- Sedating antihistamines (e.g., hydroxyzine or diphenhydramine) may be useful adjuncts when taken at bedtime for intractable itch, especially during flares.

Antibiotics

- Oral/topical antibiotics are used to treat infected lesions.
- Most infections are caused by *Staphylococcus aureus* colonization. Cephalexin is commonly prescribed at the dose of 500mg 4 times daily for 7 days.

Oral Corticosteroids

- Oral corticosteroids are effective in a short course for treating acute or widespread outbreaks.
- Prednisone may be initially prescribed at 0.5-1mg/kg or 20-40mg, then tapered over several weeks. Patients must be given information on side-effects (e.g., avascular necrosis of the hip) and precautions.
- Long-term use is rarely advisable due to undesirable and potentially harmful side-effects.

Oral Immunosuppressive Agents for Severe HD

- Azathioprine may be used in AD, pompholyx, and psoriasis.
  - Side-effects include elevated liver enzymes, leucopenia, infections, and sun sensitivity.
  - Rare side-effects from long-term use include squamous cell cancers and non-hodgkins lymphoma.
- Cyclosporine suppresses inflammatory responses.
  - Long-term use can lead to severe side-effects, including organ damage.
- Methotrexate (MTX) has an immunomodulatory effect and is usually taken at a dose of 7.5-20mg weekly.
  - Side-effects of MTX include nausea, vomiting, diarrhea, liver fibrosis and cirrhosis, pulmonary fibrosis, and pancytopenia, as well as other severe adverse effects from long-term use.
  - Folic acid is generally co-prescribed, as this may reduce MTX associated side-effects.
  - During MTX treatment, patients should undergo regular tests to monitor for hepatic abnormalities; alcohol avoidance is essential to prevent liver damage.
- Mycophenolate mofetil (MMF) may be used for patients who are non-responsive or inadequate responders to other HD therapies.
  - There are concerns over MMF's teratogenicity and long-term carcinogenicity.

Phototherapy (Light Therapy)

For severe or treatment resistant HD, narrowband UVB light or oral/bath psoralen + long-wave UVA (PUVA) light therapy are helpful due to their local immunosuppressive effect.

- Long-term use of UV light therapies can cause skin damage and increase cancer risk.
- Patients may consider the required time commitment to be inconvenient.
- Access to clinic-based phototherapy may be limited.

Therapeutic Advance for CHD

One of the few adequately controlled studies, which represents the largest HD trial to date, explored the oral use of alitretinoin in severe CHD refractory to standard care.[1] The investigation provides much-needed evidenced-based data and demonstrates the therapeutic potential for this non-immunosuppressive agent.

- Alitretinoin (9-cis retinoic acid) is a new oral retinoid that received regulatory approval in Canada in November 2009 and has been commercially available since November 2010. It is the only systemic agent that is indicated for the treatment of adults with severe CHD that is refractory to high-potency topical steroids.
- Two randomized, double-blind, placebo-controlled, multicenter trials involving over 1300 patients treated with alitretinoin demonstrated significant clinical improvements in moderate-to-severe CHD.[1,9]
- One study assessing once-daily use for 12 weeks showed a dose-dependent improvement in 53% of HD patients, who exhibited up to 70% mean reduction in disease signs and symptoms.[9]
- A second study looking at once-daily use for up to 24 weeks reported 48% of alitretinoin-treated patients achieved clear or almost clear hands, with up to 75% median reduction in disease signs and symptoms, compared with 17% of placebo. After cessation of therapy, the median time to relapse was 5.5-6.2 months.[1]
- Alitretinoin was well-tolerated. Side-effects were dose-dependent and included headache, flushing, mucocutaneous events (e.g., dryness of the skin, lips, and eyes), hyperlipidemia, and decreased levels of free thyroxine and thyroid stimulating hormone.
- For most patients, the recommended starting dose is 30mg once-daily for up to 24 weeks, depending on response.[10] A starting lower dose of 10mg daily may be tried in patients exhibiting unacceptable adverse reactions to the higher dose.[11]
- Intermittent treatment with alitretinoin can be effective for long-term CHD management.
  - The efficacy of alitretinoin following relapse was demonstrated in a double-blind study of 117 CHE patients who had responded previously to therapy and subsequently relapsed.[12] Response rates were 79.6% in patients retreated with 30mg alitretinoin vs. 8.3% for placebo. Retreatment with 10mg alitretinoin produced response rates of 47.6% vs. 10.0% in the placebo group. Retreatment was well tolerated and typical retinoid class effects were observed.
- Alitretinoin is an endogenous retinoid, with concentrations returning to normal range within 1-3 days after treatment cessation. It is rapidly eliminated and does not accumulate in the body.[11]
- As with all systemic retinoids, alitretinoin is teratogenic and requires strict monitoring when used in women of childbearing potential. Pregnancy testing and the use of acceptable methods of contraception are required just prior to, during, and 1 month after therapy.

Self-Care Tips for Patients

An essential part of HD management is to restore the normal skin barrier function by regularly moisturizing with emollients, both during and in between flares. Lifestyle modifications and patient self-care are critical components for successful ongoing management and minimizing adverse effects on quality of life (QoL).

- Use mild cleansers instead of harsh or perfumed soaps.
- Maintain the regimented use of bland moisturizers (e.g., petrolatum).
- Avoid products containing fragrances and preservatives.
- Bathe with warm water and limit the duration.
- If triggers are known, avoidance is a central HD management strategy.
- Reduce exposing hands to water, cleaning products, and aeroallergens by wearing gloves (wear cotton gloves under latex/rubber to absorb perspiration).
- Use barrier creams and practice glove hygiene to reduce antigen exposure and severity of skin reactions.
- Scratching can cause cracks to form, allowing bacteria to enter the damaged epidermis and resulting in infection.
- Antipruritic strategies include applying a cold compress to the affected area, keeping fingernails short, and using over-the-counter (OTC) products containing hydrocortisone.
- Avoid skin contact with fruits, vegetables, and raw meats.
- If possible, wear vinyl gloves to shampoo hair.
- Remove rings before wet-work or hand washing, as they can trap moisture and irritants.
- Efforts aimed at reducing stress are beneficial for controlling HD. Psychological stress may cause immunological changes that can aggravate HD.
- For education and social support, patients may benefit from interactions with national organizations or web-based social networks.

Conclusion

Formulation of an effective treatment strategy will depend on many factors, including findings from diagnostic investigations, extent and severity of HD, treatment history, age, and patient preferences. Aside from achieving tangible improvements, the adopted therapeutic approach must also minimize QoL impairment from sleep interference, discomfort, disability, and heighten self-consciousness, which can lead to social avoidance behaviours. Consequently, early diagnosis and ongoing medical and adjunctive care are crucial for controlling chronicity and disease severity.

There is a significant unmet need for pharmacologic agents that are effective in the long-term management of severe CHD. Present treatment options are plagued with side-effects and unable to induce sustained periods of remission. However, the recent introduction of alitretinoin has broadened the therapeutic options and improved the outlook for patients who are unresponsive to conventional therapies. Within the framework of patient care, family physicians play an integral role by counseling on adjunctive OTC medications, drug side-effects, proper usage, and tips for daily management. Such efforts directed at patient education convey practical advice and reinforce both the rationale and aims of prescribed therapies, which can help to optimize treatment outcomes.

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