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Clinical Evidence. Practical Advice.

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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 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 WHO (Geneva). He is the founder of the Dermatology Update symposia, now in its 26th 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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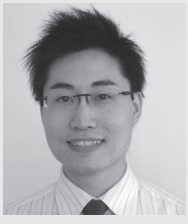

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New and Existing Therapies for Chronic Hand Dermatitis

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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]

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.[5]

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.[6]

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.

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 (TCIs)

- TCIs are nonsteroidal immunomodulators that exert anti-inflammatory effects.
- Pimecrolimus and tacrolimus are beneficial 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 during dispensing.
- 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, alcohol avoidance is essential to prevent liver damage.
- Mycophenolate mofetil (MMF) may be used for patients who are nonresponsive 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 light therapy (PUVA) 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. 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 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]
- 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 result in infection.
- Antipruritic strategies include applying a cold compress to the affected area, keeping fingernails short, and using 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 behaviors. 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, pharmacists 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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Update on the Management of Actinic Keratoses

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Introduction

Actinic keratoses (AKs), or solar keratoses, are pre-malignant cutaneous lesions that predominantly manifest in sun-exposed areas. They are one of the most common skin conditions seen by dermatologists, preceded only by acne vulgaris and dermatitis.[1] AKs are clinically relevant lesions due to their potential to evolve into invasive squamous cell carcinoma (SCC).[2] Additionally, they are considered a risk factor for the subsequent development of melanoma and non-melanoma skin cancer. There are numerous treatments available for managing AKs including those broadly categorized as destructive, topical field, and procedural field therapies. The recent introduction of imiquimod 3.75%, approved for the treatment AKs on the face and scalp, widens the therapeutic arsenal.

Prevalence and Risk Factors

- In the northern hemisphere, it is estimated that between 11-25% of adults have at least one AK.[3]
- These lesions are most commonly seen in the older fair-skinned population or in individuals classified under Fitzpatrick skin phototypes I-III.
- Cumulative ultraviolet (UV) radiation exposure and older age are the most important contributing risk factors.
- Immunocompromised individuals or those with certain genetic syndromes (e.g., xeroderma pigmentosum and albinism) are at greater risk.

Pathogenesis

- UV radiation is involved in the pathogenesis of AKs through inducing cellular DNA mutations in the skin, which may affect cell proliferation genes (e.g., p53 and ras) or prompt evasion of apoptosis.[2]
- Disruption of one of these genes may lead to formation of atypical keratinocytes in the basal layer and development of an AK; all of these histopathologic changes are limited to the epidermis.
- The absence of further UV light exposure may result in resolution through inherent repair mechanisms. However, additional UV light exposure may induce further DNA mutations resulting in the development of invasive SCC.

Diagnostic Features

- AKs typically manifest as small (1-3mm), erythematous, scaly papules with a hyperkeratotic texture.
- They are best identified with touch rather than visual inspection alone.
- AKs are characteristically distributed in sun-exposed areas, including the face, bald scalp, ears, neck, anterior chest, dorsal forearms, and dorsal hands. Surrounding areas may show evidence of solar elastosis (e.g., telangiectasia, blotchy hyperpigmentation, and yellow discolouration of the skin).[4]
- The clinical variants of AKs include the cutaneous horn, lichen planus-like keratosis, pigmented actinic keratosis, and actinic cheilitis.[4,5]
- The natural history of AKs is variable and unpredictable; a lesion can follow one of three paths: it can persist, regress, or transform into an invasive SCC.
  - It is impossible to predict which path any given AK may take.
  - The risk of a single lesion progressing from an AK to a SCC ranges from 0.025-16% per year.[6]
- Over several years, these lesions can progress, becoming thicker and developing into a hypertrophic AK, Bowen's disease (SCC *in situ*), or an invasive SCC.
  - The stages of this biologic continuum are clinically indistinguishable, therefore, a biopsy should be performed if a SCC is suspected.
  - A presentation that includes pain, pruritus, induration, larger size, rapid growth, ulceration, bleeding, or resistance to treatment may point towards a more sinister pathology (i.e., SCC).[4,5]

Treatment Overview

It is recommended that all AKs be treated, as there are no reliable clinical predictors to discern an AK from a SCC. If a SCC is missed, it may become locally invasive and destructive; these lesions are capable of metastases, resulting in death. Therapeutic choices are guided by efficacy, adverse effects, cosmetic results, and patient adherence.

Destructive Therapy

The most common therapies for individual AKs work destructively by physically removing the lesion. These modalities should be considered first-line for isolated lesions or early presentations of AKs. Destructive therapies include liquid nitrogen cryotherapy, curettage with or without electrodessication, and shave excision. The main advantages of these procedures are that they are quick, procedurally simple, and provide adequate clearance of abnormal tissue.

Cryotherapy

Cryotherapy is the most frequently utilized technique, with liquid nitrogen being the most commonly applied cryogen. Applying cryotherapy to the affected area lowers the skin to temperatures that destroy atypical AK cells.[7]

- This technique is ideal if lesions are scattered, limited in number, or for patients who are nonadherent to topical regimes.[7]
- Reported cure rates range from 39-83%.[8]
- Treatments are generally well-tolerated and do not require local anesthetic, but the procedure can be painful and result in permanent hypopigmentation.
- Potential side-effects include blisters, scarring, textural skin changes, infection, and hyperpigmentation.

Curettage and Shave Excision

Curettage consists of using a curette to mechanically remove atypical cells. A shave excision using a surgical blade is another technique. These may be followed by electrocautery, which will destroy additional atypical cell layers, as well as provide hemostasis.

- These techniques are most appropriate for treating individual AKs, cases where a biopsy is required to rule out frank carcinoma, or for hypertrophic AKs that are refractory to other treatments.
- Potential side-effects include infection, scarring, and dyspigmentation, as well as anesthetic related side-effects.

Topical Field Therapy

Commonly, physicians are faced with patients who are covered in actinic damage, a clinical scenario now described as field cancerization, which includes both clinical and subclinical lesions within a given anatomical region.[9] For these patients, a different therapeutic approach, known as field therapy, is needed for the clearance of both clinically visible and subclinical AKs within the treatment area.

Topical 5-fluorouracil (5-FU)

The antimetabolite 5-FU was the first approved agent for topical field therapy. Discovered serendipitously when AKs were noted to become inflamed and subsequently resolved in patients receiving systemic 5-FU as a chemotherapeutic agent; it was eventually designed into an effective topical formulation. It acts as a thymidylate synthase inhibitor by blocking a methylation reaction, which in turn disrupts DNA and RNA synthesis and effectively stops the growth of the rapidly proliferating or cancerous cells.[10] As such, 5-FU preferentially targets the atypical cells over normal skin tissue.

- The average cure rate is 62.5%,[11] but for optimal results full patient adherence is necessary. Recommended dosing is twice-daily for 3 weeks.
- There is evidence showing concurrent treatment with topical tretinoin enhances the effectiveness of 5-FU.[12]
- It is common for all patients undergoing successful treatment with 5-FU to experience inflammation, erythema, and erosions.
- Common side-effects include pain, pruritus, photosensitivity, and burning at the site of application.
- 5-FU can worsen preexisting cutaneous conditions (e.g., melasma or acne rosacea), as such, use should be avoided in these patients.[7]

Diclofenac

Diclofenac 3% gel is a nonsteroidal anti-inflammatory drug, which is believed to exert its effects through the inhibition of cyclooxygenase (COX), especially COX-2. The production of prostaglandins is thought to suppress the immune system, thereby allowing tumours to form.[13] Without COX, prostaglandin production is reduced and the cascade is disrupted.[13]

- Despite the more rigorous treatment regimen (twice daily for 90 days), only mild to moderate local skin reactions are noted.
- Though rare, drug-induced hepatotoxicity reports have surfaced, consequently transaminases should be measured periodically in patients on long-term therapy.

Imiquimod

Topical 5% imiquimod cream was originally indicated as a treatment for genital and perianal warts; additional approved indications for treating AKs and superficial basal cell carcinomas followed. It is used off-label for Bowen's disease, invasive SCC, lentigo maligna, molluscum contagiosum, keloid scars, and others.[14] Imiquimod acts as a toll-like receptor-7 agonist, which results in modification of the immune response and stimulation of apoptosis, thereby disrupting tumour proliferation.[15] Stockfleth et al.[16] demonstrated that 84% of treated AKs showed clinical clearance with one cycle of 5% imiquimod therapy.

- Common localized irritation coupled with its long duration of treatment (twice-weekly for 16 weeks) can discourage patient adherence.
- Treatment should be applied to both the lesion and surrounding tissue to target subclinical AKs.
- Rare systemic effects include fatigue, flu-like symptoms, headaches, myalgias, and angioedema.

Topical Field Therapy (continued)

In December 2009, Health Canada approved the use of imiquimod 3.75% for the treatment of AKs on the face or balding scalp. Two identical placebo-controlled trials have evaluated the safety and efficacy of imiquimod 3.75%.[17,18]

- In the trial by Swanson et al.,[17] creams were applied daily to the entire face or balding scalp for two 2-week treatment cycles, separated by a 2-week interval without treatment.
  - Patients applying imiquimod 3.75% achieved a median lesion reduction of 82%, while just over one-third experienced complete clearance.
  - These efficacy data rival those achieved using imiquimod 5% twice-weekly for 16 weeks, but with the advantage of significantly improved patient tolerance.
  - Therapy was found to be safe and did not result in any serious adverse events.
  - Erythema was observed in most patients, with about 25% developing severe erythema. However, no patients withdrew from the study as a result of this.
  - Compliance rates were noted to be >90%.[17,18]
- Overall, the newly approved formulation of imiquimod 3.75% is a reasonable alternative to imiquimod 5%, as it demonstrated comparable efficacy, but with a much more simplified, shorter dosing regimen, and seemingly produced less severe adverse effects.
- Additionally, imiquimod 3.75% is approved for the treatment of a larger surface area of up to 200cm^2, compared with 25cm^2, and thus, is able to target more AKs.

Procedural Field Therapy

Procedural field therapies may be an appropriate option for patients who require minimal down time, are unlikely to adhere to a topical approach, have AKs resistant to topical therapy, or favour an improved cosmetic result.

- Treatment options for procedural field therapy include photodynamic therapy, manual dermabrasion, laser resurfacing, cryopeeling, and chemical peels.
- Each of these techniques treats AKs by destroying the superficial layers of the skin through physical or chemical means.

Photodynamic Therapy (PDT)

PDT is a procedural field therapy that utilizes topical 5-aminolevulinic acid (ALA) or methyl aminolevulinate to target AKs. These molecules preferentially find their way into the hyperproliferating cells, which lack normal cell to cell adhesion junctions, and are converted intracellularly to protoporphyrin IX (PpIX).[19] This photosensitizer is then exposed to blue or red light, which corresponds to the peaks in the absorption spectrum of PpIX, resulting in a phototoxic reaction that destroys the abnormal cell.[19]

- PDT is effective for the treatment of multiple and diffuse AKs, and the cosmetic results are generally excellent.
- PDT is not suited for treating thicker or deeper AKs[19] and is generally reserved for patients who exhibit an inadqueate response to topical field therapy or cryosurgery.
- Patients may experience erythema, edema, and a burning sensation during therapy.

Conclusion

There is no widely accepted algorithm for the treatment of AKs. Often several different treatment regiments must be employed to manage AKs, especially with widespread or resistant cases. As always, the best way to manage AKs is prevention by avoiding exposure to significant or unnecessary UV radiation. Pharmacists can play an important role in encouraging patients to wear broad-based sunscreens, wide-brimmed hat, protective eyewear, and avoiding the sun during peak hours, which may prevent recurrence or limit the progression of AKs. Furthermore, patients are well-served by pharmacists offering education on the potential side-effects and expected onset of action of topical field therapies.

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