

Dyshidrosis: Epidemiology, Clinical Characteristics, and Therapy

Sabra M. Lofgren and Erin M. Warshaw

Dyshidrosis is a common chronic dermatitis of the hands and feet that may cause significant physical discomfort, psychological distress, and occupational impairment. Topics reviewed in this article include epidemiology, clinical findings, quality of life, and therapeutic considerations. Dyshidrosis is often difficult to manage; therefore, extra attention is given in this review article to current treatment options.

DYSHIDROSIS, sometimes called pompholyx or dyshidrotic eczema, is a common chronic dermatitis of the palms and soles that may lead to significant impairment of occupation and quality of life. This review discusses the epidemiology and clinical characteristics of dyshidrosis and the quality of life of patients with dyshidrosis. Particular emphasis is placed on the therapeutic options for this often clinically frustrating disorder.

Definition

Tilbury Fox first described dyshidrosis in 1873.^{1,2} He chose the term “dyshidrosis” (which means “difficult sweating”) because of his belief that this condition was the result of poral occlusion leading to sweat retention.^{1,2} Hutchinson described the same condition 3 years later but named it “cheiropompholyx,” meaning “vesicular eruption of the hands.”³ This author did not implicate dysfunctional sweating as a pathogenic factor. It is now accepted that sweat glands do not play a role in dyshidrosis; however, debate regarding the proper name for this condition persists. Consequently, many authors have used the terms “dyshidrosis,” “dyshidrotic eczema,” and “pompholyx” interchangeably.

It is our belief that the terms “dyshidrotic eczema” and “pompholyx” describe discrete entities. Dyshidrotic eczema or dyshidrosis is a common, chronic, and recurrent eruption of small (1–2 mm) vesicles on the palms, soles, and/or lateral aspects of the fingers.

Pompholyx, in contrast, is a rare condition characterized by an explosive onset of large bullae on the hands.⁴ Because many investigators have used these terms interchangeably without clearly describing their clinical criteria, it is not always possible to know which condition was studied. Therefore, this review will use the term “dyshidrotic eczema” or the term “dyshidrosis” when discussing studies in which it is clear from the authors’ description that the study population’s condition fits the above-mentioned definition of dyshidrosis.

Epidemiology and Risk Factors

Dyshidrosis is a relatively common dermatitis. Agrup conducted a survey and examination of 107,206 Swedes; in this general population, 51 persons (0.05%) were reported to have dyshidrosis.⁵ Further, dyshidrosis accounted for 3% of hand dermatoses in this population. Magina and colleagues retrospectively evaluated the records of 714 subjects with hand dermatitis over a 6-year period in Porto, Portugal. They found that 20% of these patients had dyshidrotic eczema.⁶

Although hand dermatitis in general is more common in young women, dyshidrosis does not appear to correlate with age or sex.^{5–8} Lodi and colleagues found that of 104 Italian dyshidrosis patients, more than half (56%) were male, ages ranged from 4 to 76 years, and the mean age was 38 years.⁷

A commonly considered risk factor for dyshidrosis is atopy. In the case-control study by Lodi and colleagues, in which subjects were matched for age and sex, it was reported that of 104 patients with dyshidrosis, 50% had familial or personal atopic diathesis, versus 11.5% of controls ($p < .001$).⁷ Lehucher-Michel, comparing 59 workers with dyshidrotic eczema with 160 workers who

From the University of Minnesota Medical School, Minneapolis, MN, and the Veterans Affairs Medical Center, Minneapolis, MN.

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had other types of hand dermatitis, found no significant difference in the rates of atopy between the two groups.⁸ This finding likely reflects the fact that atopy is a recognized risk factor for hand dermatitis in general as well as for dyshidrosis.

Other researchers have not found an increased rate of atopy in patients with dyshidrosis.^{9–12} De Boer and colleagues reported that of 21 workers with dyshidrosis, only one (5%) was atopic.⁹ Edman found no association between atopy and dyshidrosis in 425 consecutively patch-tested individuals, 141 of whom had dyshidrosis.¹⁰ Thelin and Agrup reported that of 68 Swedish patients with dyshidrosis, 18 reported a history of atopic dermatitis, asthma, and/or allergic rhinitis; this was the same rate of atopy as was expected in a Scandinavian population.¹¹ In a study of 398 subjects, 283 of whom had hand eczema, Bryld and colleagues found that dyshidrosis and atopy were not significantly associated (relative risk [RR], 0.54; 95% confidence interval [CI], 0.20–1.46).¹²

In the occupational setting, dyshidrosis may account for a higher percentage of hand dermatitis. De Boer and colleagues, in an epidemiologic study of 286 metalworkers, reported that 14% had dermatitis (of any type); of these, 21 (51%) had dyshidrotic eczema.⁹ However, in the previously cited study by Lehucher-Michel, dyshidrosis was found to be less likely related to work than were other forms of hand dermatitis ($p = .0013$).⁸

Clinical Characteristics

The diagnosis of dyshidrosis is made by careful history and clinical examination. The clinical picture of this condition was well described by Shelley in 1953.¹³ Dyshidrosis is characterized by transient (but recurrent) and often symmetrical vesicular eruptions on the palms, soles, and/or lateral aspects of the fingers. These eruptions do not occur elsewhere on the body. The vesicles are 1 to 2 mm in size and are deep-seated on non-erythematous bases. After persisting for 2 to 3 weeks, the vesicles resolve via involution, and desquamation is observed in the terminal phase. Attacks recur at variable intervals. Intense pruritus is associated with eruptions, and an itching prodrome may precede vesicular development. The course is frequently chronic. Dyshidrosis can develop into a debilitating disorder.

Pompholyx is distinguished from dyshidrosis by a more acute and severe eruption of large bullae on the palms. It is likely to occur much more infrequently and be far less prevalent than simple dyshidrosis.⁴

To quantitatively assess the severity of dyshidrotic eczema, Vocks and colleagues developed the Dyshidrotic Eczema Area and Severity Index (DASI),¹⁴ which is based on a score derived from measures of the following single items: erythema, desquamation, itching, number of vesicles per square centimeter, and extension of the affected area.¹⁴ Thus, unlike other hand dermatitis scoring systems, this grading system is specific to the distinctive features of dyshidrotic eczema.^{15–17} The maximum DASI score is 60. Dyshidrotic eczema may be graded on this scale as mild (0–15), moderate (16–30), or severe (31–60).¹⁴

Histopathology

Histologic examination of dyshidrotic eruptions by conventional and electron microscopy has consistently revealed intraepidermal spongiotic lesions in which the intraepidermal portion of the eccrine sweat duct (acrosyringium) is unaltered by the spongiosis.¹⁸ Dyshidrosis, therefore, is a misnomer^{13,18,19} for spongiotic dermatitis phenotypically altered by the unique adaptive features of palmar and plantar skin.¹⁸ Most important, this skin has a greatly thickened stratum corneum. The thick cornified layer impedes vesicular rupture, creating the classic “tapioca,” “frog spawn,” or “sago grain” clinical appearance of dyshidrosis.¹⁸

Pathophysiology

Dyshidrosis is of unknown origin. Indeed, only modest progress in the knowledge of its origin has been made since Shelley’s review of this topic in 1953.¹³ Dyshidrosis likely has a multifactorial etiology. Commonly cited factors include allergy to metals (particularly nickel), genetic determinants, and dermatophyte infection.^{20–26}

Allergic Contact Dermatitis from Metals

Several investigators have evaluated the association between dyshidrosis and metal allergy. Lehucher-Michel reported that of 59 workers with dyshidrotic eczema, 72.8% had at least one positive patch-test reaction to any allergen.⁸ Of these workers with positive patch-test reactions, 34.8% exhibited a reaction to nickel, 16.3% reacted to chromium, and 13.9% reacted to cobalt.⁸ In a prospective observational study, Thelin and Agrup reported that 18 of 64 (28%) subjects with dyshidrosis had positive patch-test reactions to one or more antigens and that nickel allergy was the most common allergy.¹¹ On patch-testing 25 patients with dyshidrosis, Yokozeki and

colleagues found sensitivity to the following metals: chromate (20% of patients), cobalt (16%), and nickel (28%).²⁷ Lodi and colleagues, in the previously cited case-control study, reported that 20% of the patients with dyshidrosis had positive reactions to nickel, as opposed to 6% of controls matched for age and sex ($p < .001$).⁷

Other researchers, however, have not found a correlation between nickel contact sensitivity and dyshidrosis.^{12,28} Bryld and colleagues found no association between dyshidrosis and nickel allergy (RR, 0.45; 95% CI, 0.06–3.36).¹² Li and Wang reported that of 7 patients with dyshidrosis, only one had a positive patch-test reaction to nickel.²⁸ Further complicating this issue is the observation that individuals may vary in their patch-test reactivity to nickel with time.²⁹ Other contact allergens that are reported to have significant association with dyshidrosis are carba mix, diaminodiphenylmethane, potassium dichromate, para-phenylenediamine, nitrofurazone, and fragrance mix.^{22,30,31}

It is thought that sweating of the palms and soles may increase nickel sensitization. The high density of eccrine sweat glands on the palms and soles leads to an increased perspiration rate in these areas, which may cause a higher concentration of salts of metals such as nickel.³⁰ Although patients with dyshidrosis do not have sweat gland dysfunction, hyperhidrosis may be an exacerbating factor and could be the mechanism of exacerbation in nickel-sensitive patients with dyshidrosis.³⁰

Systemic Allergens

The oral administration of agents including chromium, nickel, neomycin, and quinolones have been reported to elicit a dyshidrotic eruption in some individuals.^{11,25,32–35} Prystupa and Rudzki studied 20 nickel-sensitive dyshidrosis patients and 54 nickel-sensitive patients with other types of hand eczema. They found that 35% of patients with dyshidrosis reacted positively to oral challenge with 2.24 mg or less of nickel and that 31% of patients with other types of hand dermatitis reacted to the same dose ($p > .05$). Their study suggests that patients with dyshidrotic eczema are not more sensitive to oral nickel challenge than are individuals with other varieties of hand dermatitis.³⁶

Oral nickel administration has also been reported to elicit an exacerbation of vesicular hand dermatitis in patients who have had negative patch-test results. Veien and colleagues reported that of 202 patients with symmetric vesicular hand eczema and negative patch-test results, 26 flared with oral administration of 2.5 mg of

nickel sulfate, 20 flared with oral cobalt chloride, and 21 flared with oral potassium dichromate.³³

Fungal Infection

Tinea pedis has long been implicated in the pathogenesis of dyshidrosis.³⁷ Bryld and colleagues, in a population study of 398 individuals (283 with a history of hand eczema), found a statistically significant relationship between dyshidrosis ($n = 16$) and tinea pedis infection ($n = 3$) (RR, 3.58; 95% CI, 1.19–10.82; $p < .05$).¹² Yet, Crosti and Lodi found that although some dyshidrosis patients with concomitant tinea infection experience resolution with antifungal therapy, many others exhibit no change in clinical course.³⁰ Some authors have suggested the term “pompholyx-like tinea pedis” to describe the condition of individuals who have dermatophytes in the vesicular fluid.³⁰ However, it is our opinion that this condition should be considered vesicular tinea pedis until proven otherwise.

Photoinduction

One recent study described photoinduced dyshidrotic eruptions. Man and colleagues, in a case series of 5 patients whose histories were suggestive of photoinduced flares, described the development of biopsy-proven dyshidrosis after provocative exposure to ultraviolet A (UVA) radiation.³⁸

Intravenous Immunoglobulin Therapy

There have been recent reports of intravenous immunoglobulin (IVIg) therapy-related eruptions of dyshidrosis.^{39,40} Iannaccone and colleagues reported a case series of 23 patients treated with IVIg therapy for a variety of neurologic conditions; 3 patients (13%) developed dyshidrotic hand eczema 5 to 7 days after treatment.³⁹ The IVIg was given at a dose of 0.4 g/kg/d over a period of 12 hours for 5 consecutive days. The authors speculated that this was a hypersensitivity reaction to the drug or vehicle; however, neither patch nor scratch tests were performed.^{39,41}

Hyperhidrosis

Hyperhidrosis and seasonal variation are the most commonly noted aggravating factors in dyshidrosis. Lodi and colleagues found that 43 (41%) of 104 patients with dyshidrosis reported seasonal variation and that 38 (37%)

reported sweating to be an exacerbating factor.⁷ Thelin and Agrup, in a prospective study, reported that 13 (72%) of 18 subjects with dyshidrosis had hyperhidrosis of the palms and soles but that none described exacerbation with sweating.¹¹ This study also reported seasonal variation in 18% of subjects; exacerbations occurred in spring and autumn.¹¹ Yokozeki and colleagues found that the perspiration volume of 25 patients with dyshidrosis was 2.5 times higher than that of age-matched controls ($p < .01$).²⁷ Investigators also reported resolution of both hyperhidrosis and dyshidrosis following cervical sympathectomy.⁴² However, this result could simply reflect the importance of intact innervation in supporting an eczematous response.⁴³

Irritants

Exposure to common irritants (such as detergents and solvents) or excessive exposure to water may exacerbate symptoms in some patients.⁴⁴ De Boer and colleagues found a positive correlation between exposure to soluble oils and dyshidrosis in an epidemiologic study of 286 metalworkers.⁹ Of the 21 individuals with dyshidrosis in this study, 11 (52%) reported frequent contact with soluble oil. Of the 181 workers who were exposed to soluble oil, 87 (48%) exhibited skin changes (dry rough skin, mild erythema, chapping, induration, and damage to the cuticles) considered to be caused by irritants. These results may suggest an irritant character to dyshidrosis in this population.⁹

Other Causes

Less commonly cited potential etiologic factors of dyshidrosis include smoking and the use of oral contraceptives and acetylsalicylic acid. Edman, in a cross-sectional study of 425 patients, examined the relationship between vesicular palmar eczema (92% of which was considered dyshidrosis) and a variety of clinical factors. He reported a statistically significant association with acetylsalicylic acid use ($p = .006$), use of oral contraceptives ($p = .028$), and smoking in males ($p = .029$).¹⁰

Smoking may also predispose individuals with dyshidrosis to have worse therapeutic outcomes because of its overall ill effects on skin and wound healing.⁴⁵⁻⁴⁷ It has been reported that smoking negatively influences the outcome of bath psoralen-plus-UVA (PUVA) therapy in patients with dyshidrotic eczema.⁴⁸ Douwes and colleagues, in a retrospective study, compared the response to bath PUVA therapy in 62 patients (39 nonsmokers and 23

smokers) with chronic palmar or plantar dermatoses.⁴⁸ Bath PUVA therapy was administered to all patients in concordance with the European standard regimen, and the total number of treatments and total UVA doses were similar between the groups.⁴⁸ Of the nonsmokers with dyshidrosis, 48% (vs 0% of the smokers) experienced complete remission ($p < .05$); 33% of nonsmokers with dyshidrosis (vs 29% of smokers) showed partial remission. The remainder exhibited no change.⁴⁸ Van der Vleuten and van der Valk described four young patients with dyshidrosis who developed painful ulcerations of the feet.⁴⁹ Smoking was the only common ulcer risk factor among these patients. These findings could be attributed to smoking-induced delayed wound healing,⁵⁰ reduced tissue oxygenation,⁵¹ and inhibition of epithelialization.^{48,52}

In an interesting case report, Matin and colleagues reported resolution of dyshidrosis in a patient with obstructive sleep apnea after the commencement of treatment with continuous positive airway pressure (CPAP).⁵³ The authors hypothesized that increased tissue oxygenation during sleep as a result of CPAP treatment led to a reduction in proinflammatory cytokines.⁵³

Quality of Life

Dyshidrosis is a disorder that does not affect mortality, but it can significantly affect quality of life.⁵⁴ Chronic disease may lead to the formation of fissures and to skin tightening, causing pain and decreased dexterity.⁵⁵ Also, dyshidrosis may lead to a greater susceptibility to secondary infections, lymphedema, and ulceration.^{49,56}

In a prospective observational 1-year study by Thelin and Agrup, 56 (82%) of 68 Swedish dyshidrosis patients took sick leave because of their skin disease.¹¹ Of these, 48 (86%) took a sick leave lasting longer than 1 month.¹¹ No change in occupation was required for any of the subjects, and no disability pensions were granted on account of their dyshidrosis.¹¹

Additionally, dyshidrosis may affect the psychosocial aspects of patients' lives. Because the hands are nearly always visible, hand dermatitis in general may lead to greater psychological distress than do skin lesions located on body parts that are typically covered.^{57,58} Picardi and colleagues conducted a questionnaire study of 389 Italian dermatologic outpatients. They found that the rate of psychiatric morbidity in this population was 21%, about twice the point prevalence in Western populations. Further, they found that in women, psychiatric morbidity was more prevalent when lesions occurred on the hands or

face.⁵⁸ Most morbidity consisted of mild depression or anxiety or both.⁵⁸ This study did not establish causality but does suggest that the psychosocial aspects of hand dermatoses (including dyshidrosis) are important.

Differential Diagnosis

The differential diagnosis of dyshidrosis includes pustular psoriasis of the palms and soles, chronic vesicular hand dermatitis contact allergy, vesicular tinea pedis and tinea manus, scabies, vesicular id reactions, herpes simplex, and bullous disorders such as pemphigoid, pemphigus, and epidermolysis bullosa. Psoriasis can usually be differentiated by histopathologic analysis. Chronic vesicular hand dermatitis is an inflammatory process characterized by vesicles with erythematous bases. In contrast, dyshidrotic vesicles have non-erythematous bases. The course of chronic vesicular hand dermatitis also tends to be more intractable. Patch testing will confirm contact allergy. A potassium hydroxide preparation and microscopic examination will detect fungal infection. Finding a mite with a scabies preparation will confirm a diagnosis of scabies. In contrast to other bullous diseases, dyshidrosis is distributed exclusively on the palms and/or soles and lacks the immunologic markers specific to those other diseases.

Management

Conservative Measures

The first step in managing dyshidrosis is identifying potential causative or aggravating factors via a detailed history and possible patch testing, then advising patients to avoid these factors accordingly. It is also important to maintain an effective skin barrier mechanism with the regular use of emollients.⁵⁹ Petrolatum-based products are efficacious, inexpensive, and readily available for this purpose. Further, standard precautions for avoiding irritants and irritation, such as infrequent hand washing with careful drying and immediate moisturization, avoiding direct contact with cleansers, and wearing dry cotton socks and protective vinyl gloves with white cotton gloves underneath, should be recommended.⁴⁴

To manage the pruritus that often occurs in dyshidrosis, antihistamines such as hydroxyzine, cetirizine, and loratadine are occasionally prescribed.⁴⁴ Soaks or cold compresses of weak solutions of potassium permanganate, aluminum acetate, or vinegar, applied for 15 minutes four

times daily, may relieve pruritus for some patients.^{44,60} However, no published studies have evaluated the efficacy of these agents for the treatment of dyshidrosis.⁴⁴

There are very few randomized controlled trials that have evaluated treatments of hand dermatitis in general.⁶¹ A review of published trials that involved the treatment of dyshidrosis follows.

Topical Corticosteroids

Topical corticosteroids are often used as a first-line treatment of dyshidrosis.^{59,62} A superpotent topical corticosteroid may initially be required for up to 2 weeks, but it should then be tapered to a preparation of lower potency. Generally, ointments are considered superior because of their greater efficacy and lower preservative and additive content.⁵⁹

Veien and colleagues conducted a prospective open randomized trial of 120 patients with chronic hand eczema (including 38 patients with dermatitis of the palms, fingers, or both, consistent with our definition of dyshidrosis).⁶³ All patients with palmar dermatitis were cleared after 9 weeks of daily applications of mometasone furoate cream. Next, the subjects were randomized into three groups for the 30-week maintenance phase. Each group adhered to one of the following treatment plans: (1) treatment with mometasone furoate three times weekly, (2) treatment with mometasone furoate twice weekly, and (3) treatment with an emollient, as needed. Of the 38 patients with palmar dermatitis, 86% of those who were treated three times weekly remained relapse free. Of palmar dermatitis patients who were treated twice weekly during the maintenance period, 64% remained relapse free. Only 44% of untreated patients did not experience recurrence during this period.⁶³

Adding occlusion to steroid treatment enhances efficacy and may also reduce the amount of required corticosteroid. In a clinical trial of 141 patients with chronic skin disease unresponsive to therapy, including 11 patients with pompholyx (no clinical description reported), Volden reported that treatment with clobetasol propionate under occlusion with a hydrocolloid dressing (DuoDERM, ConvaTec, Princeton, NJ) led to clearing in all 11 patients after a mean duration of 8 days (range, 1–2 weeks).⁶⁴ However, in the follow-up period of 1 to 2 months, 9 (82%) of these patients experienced relapse.⁶⁴

Long-term use of topical corticosteroids is limited by their side effects, which include skin atrophy, striae, and telangiectasia.^{65,66} Impaired collagen synthesis may persist for up to 2 weeks after discontinuation of topical very-

high-potency corticosteroids.⁶⁷ It is also important to bear in mind that the use of topical corticosteroids may mask signs of infection.⁶⁰

Topical Immunomodulators

Another topical therapeutic option is the nonsteroidal immunomodulating agent tacrolimus. Tacrolimus inhibits the release of inflammatory cytokines by T lymphocytes and mast cells.^{68,69} The most commonly encountered side effect is a sensation of skin burning or warmth. Unlike in the case of corticosteroid use, skin atrophy and telangiectasia are not side effects.^{62,70}

In a randomized observer-blinded trial, Schnopp and colleagues compared the treatment of 16 dyshidrosis patients with tacrolimus 0.1% to treatment with mometasone furoate.⁶² Tacrolimus was found to be as effective as mometasone furoate in the treatment of chronic palmar dyshidrotic eczema.⁶² Both agents reduced the DASI by approximately 50% after 2 weeks of treatment. However, tacrolimus had no effect on plantar dyshidrotic eczema. This finding may be explained by the lack of penetration of tacrolimus in the setting of hyperkeratosis, as has been shown in plaque psoriasis studies of this agent.^{71–73} Schnopp and colleagues speculated that this problem could be ameliorated by the development of different ointment preparations and/or by treatment under occlusion.⁶²

Pimecrolimus, another nonsteroidal topical immunomodulating agent, has shown promise in the treatment of other chronic eczematous diseases, and one published study indicates that it may be helpful in the treatment of dyshidrosis.^{59,74–77} Belsito and colleagues, in a double-blind, randomized, and vehicle-controlled 3-week study of 294 patients with chronic hand dermatitis including dyshidrosis, reported that while the benefit in the vehicle group plateaued after 15 days, the group that was treated with pimecrolimus 1% continued to improve over the course of the trial.⁷⁴ On the last day of the trial (day 22), the pimecrolimus group showed a trend toward improvement ($p = .068$). However, patients with palmar involvement did not respond as well as those without palmar involvement (in the group with palmar involvement, 27 of 116 patients were improved as compared with 15 of 35 patients in the group without palmar involvement).⁷⁴ Pimecrolimus was well tolerated in this study; there was no difference between the two groups in the rates of common adverse effects such as burning at the application site.⁷⁴

Systemic Glucocorticoids

Systemic glucocorticoids often lead to a dramatic improvement of severe dyshidrosis, but their use is limited by significant side effects, including osteoporosis, glaucoma, cataract formation, hypertension, hyperglycemia, immunosuppression, and hormonal suppression. Starting doses are 40 to 100 mg per day, depending on the severity and the size of the area affected.⁴⁴ Prednisone at a dose of 60 mg per day for 3 to 4 days may be especially helpful during acute flares of pompholyx (explosive bullae).⁴

Methotrexate

Methotrexate is another option for the treatment of dyshidrosis. It inhibits the dihydrofolate reductase enzyme, which is required for cell division. Methotrexate also has antiinflammatory effects. Its metabolites cause increased adenosine release from cells.^{78,79} Adenosine inhibits lymphocytic proliferation and the production of inflammatory cytokines while it increases levels of monocytic interleukin-1 receptor antagonists.⁸⁰ Relevant side effects include gastrointestinal intolerance and hepatotoxicity.

Egan and colleagues described five patients who had dyshidrotic eczema unresponsive to conventional therapy or who were intolerant of glucocorticoids. The patients experienced clearing or significant improvement after 1 to 2 months of treatment with 12.5 to 20.0 mg of methotrexate weekly.⁸¹

Azathioprine

Azathioprine is a synthetic purine analogue with immunosuppressive and antiinflammatory properties. It may be used in the treatment of dyshidrosis either as a steroid-sparing agent or as monotherapy.⁸² In a retrospective chart review study reported by Scerri, 6 patients with pompholyx (no clinical description reported) severe enough to warrant second-line treatment were given azathioprine at a starting dose of 100 to 150 mg per day and were maintained on 50 to 100 mg per day for a mean duration of 33.5 months.⁸² Three patients had excellent responses (sustained remission), 1 had a good response (almost complete remission), and 2 had fair responses (reasonable symptomatic control).⁸²

The most significant drawbacks to the use of azathioprine are a long latency period before the onset of action (6–8 weeks) and, rarely, profound bone marrow toxicity. Other potential side effects are nausea, vomiting, diarrhea, leukopenia, macrocytosis, thrombocytopenia,

and elevated liver enzymes.⁸² Hepatotoxicity occurs in less than 1% of dermatologic patients.⁸² Azathioprine-induced bone marrow toxicity occurs in 1 of 300 persons and is due to a genetically determined metabolic defect.⁸² These patients should be identified by screening with a thiopurine methyltransferase enzyme assay prior to the initiation of therapy.⁸³

Cyclosporine

Cyclosporine, another immunosuppressive agent, is sometimes used in the treatment of chronic hand eczema.^{84,85} The most commonly reported side effects of cyclosporine are gastrointestinal symptoms, paresthesias, and headache. The important side effects of this drug include hypertension and renal dysfunction. These effects are most often seen when the dose is greater than 3 mg/kg/d.⁸⁶ However, renal function should be monitored by observing creatinine levels or glomerular filtration rates. Cyclosporine is not typically administered for longer than a year in the treatment of benign processes.

In a randomized double-blind study of 41 patients with a variety of chronic hand eczemas unresponsive to conventional treatments, Granlund and colleagues found that treatment with cyclosporine was as effective as treatment with topical betamethasone 17,21-dipropionate.⁸⁶ Subjects were treated with oral cyclosporine (3 mg/kg/d) or with topical betamethasone 17,21-dipropionate 0.05% cream. Disease activity was decreased in both groups by approximately 50% ($p > .05$).⁸⁶ There were no cases of hypertension or abnormally elevated creatinine levels in the cyclosporine group.⁸⁶ Although the types of hand dermatitis were not specified in this study, cyclosporine could be considered for the treatment of severe recalcitrant dyshidrosis or pompholyx.

Mycophenolate Mofetil

Mycophenolate mofetil is an immunomodulating agent that inhibits de novo purine nucleotide synthesis.⁸⁷ Pickenacker and colleagues described a 39-year-old man with severe recalcitrant dyshidrotic eczema who was treated with 1.5 g of mycophenolate mofetil twice daily.⁸⁸ His dermatitis cleared after 4 weeks; at this point, he was able to return to work after having been on leave for more than a year owing to his dyshidrotic eczema. His dose was then decreased to 1 g twice daily and was gradually tapered during the next year.⁸⁸ However, in a case reported by Semhoun-Ducloux, mycophenolate mofetil induced a dyshidrotic eruption of the hands and feet.⁸⁹ This resolved

on discontinuation of the drug and later re-appeared with oral challenge. The biopsy specimen was consistent with dyshidrosis.⁸⁹

Mycophenolate mofetil is well tolerated at doses of less than 3 g per day; potential side effects include nausea and diarrhea.⁸⁸ Hepatotoxicity is not seen, even with long-term use.⁸⁸

Other Oral Agents

Other oral agents that may be used for the treatment of dyshidrosis include dapsone and thalidomide. Both of these agents cause significant side effects, and their usefulness is therefore limited.

Dapsone may be used alone or in combination with corticosteroids.⁴⁵ Patients must be screened for glucose-6-phosphate dehydrogenase deficiency prior to the initiation of therapy.⁴⁵ The typical starting dosage is 100 to 150 mg per day.⁹⁰ Dapsone has been well studied for the treatment of dermatitis herpetiformis, but examinations of its effects on dyshidrosis have not been reported in the literature.

Thalidomide blocks tumor necrosis factor- α and has severe teratogenic effects when used during pregnancy. It is sometimes listed as a treatment option for dyshidrosis⁹¹; however, a literature search revealed no published reports of its efficacy in the treatment of dyshidrosis.

Radiotherapy

Radiotherapy is an important modality in the treatment of dyshidrosis. Major categories of radiotherapy include ionizing and non-ionizing (UVA and ultraviolet B [UVB]) radiation.⁵⁹ The mechanism of action is thought to involve immunomodulation via the inhibition of radiosensitive immune effector cells, T cells, and antigen-presenting Langerhans' cells.⁹²⁻⁹⁴

Ionizing Radiation

Ionizing radiation techniques include the use of superficial x-rays, grenz rays, and megavoltage therapy. King and Chalmers conducted a double-blind study of superficial radiotherapy involving seven patients with pompholyx (no clinical description offered). In each patient, one hand was treated and the other hand served as a control.⁹⁵ Superficial radiotherapy was administered at a focal distance of 30 cm and in three fractionated doses of 100 rads (100 cGy) at 50 kV, given at 1-week intervals. A significantly better response to active treatment was seen at 1 month ($p < .01$), but there was no difference after 3 and

6 months of therapy.⁹⁵ Fairris and colleagues conducted a double-blind trial of 24 patients with dyshidrosis, in which a topical steroid ointment was used on both hands and in which one hand also received superficial x-ray therapy.⁹⁶ The radiotherapy-treated hands were irradiated with three doses of 100 rads at 50 kV at 21-day intervals. The authors reported a significant improvement on the irradiated hands, most evident at 6 and 9 weeks after the commencement of therapy ($p < .01$ and $p < .05$, respectively) but still present after 18 weeks. It is believed that this dose of radiation does not increase the risk of cancer.^{97,98}

Sheehan-Dare and colleagues, in a double-blind study of 21 patients with chronic bilateral constitutional hand eczema (possibly consistent with dyshidrosis but difficult to determine from the reported clinical description), compared topical PUVA therapy with superficial radiotherapy.⁹⁹ In this study, significantly greater clinical improvement was observed in the superficial radiotherapy group as compared with the topical PUVA group after 6 weeks of therapy ($p = .014$). The clinical responses of the two groups at 9 and 18 weeks, however, were not significantly different. Superficial radiotherapy in this study was administered at 0.9 Gy at 50 kV in 3 doses with a focal distance of 30 cm, at 21-day intervals. The topical PUVA therapy consisted of the application of a 1% solution of 8-methoxypsoralen to the affected area, followed 5 minutes afterward by UVA exposure. Doses of UVA were started at 2 J/cm² and were gradually increased to 15 J/cm². This therapy was administered three times weekly for 6 weeks. The authors concluded that superficial radiotherapy leads to faster response and is less time consuming.⁹⁹

Therapy with grenz rays is another treatment option that has been studied. This mode of therapy is considered safe and effective for the treatment of a variety of benign dermatoses.¹⁰⁰ Grenz rays incur small (if any) cancer risk when used as recommended.¹⁰¹

Because the following studies used a variety of different protocols, they are difficult to compare. Fairris and colleagues, in a double-blind trial of 25 patients with dyshidrosis, compared therapy using superficial x-rays with therapy using grenz rays and found that therapy with superficial x-rays was superior.¹⁰² In their study, the superficial x-rays had a much greater depth of penetration (half-value layer: 13 mm in tissue) than did the grenz rays (half-value layer: 0.4 mm in tissue).¹⁰² Superficial x-rays were administered to one hand and grenz rays (3 cGy) were administered to the other hand in 3 doses at 21-day intervals, at a focal skin distance of 30 cm.¹⁰² The skin

condition of hands treated with superficial x-rays was significantly better than that of the grenz ray-treated hands at 3, 6, 12, and 18 weeks after the initiation of treatment ($p < .005$, $p < .05$, $p < .01$, and $p < .05$, respectively).¹⁰²

In a double-blind trial of 30 patients with dyshidrosis, Cartwright and Rowell found no differences between grenz ray therapy given in 3 doses of 300 rads at 21-day intervals and placebo.¹⁰³ However, Lindelof and colleagues, in a double-blind study of 24 patients with chronic symmetrical hand eczema (including one patient with pompholyx [no clinical description provided]), reported that when 3 Gy of grenz rays were administered to one hand of patients 6 times at 1-week intervals, significant improvement was recorded 5 and 10 weeks after the start of treatment as compared with the untreated control hands ($p < .01$ and $p < .001$, respectively).¹⁰⁴

Stambaugh and colleagues reported success in the treatment of refractory dyshidrosis with megavoltage low-dose external beam radiotherapy.¹⁰⁵ In this case, numerous therapies, including PUVA therapy, had been attempted with little positive effect. The patient was treated with twice-weekly 150 cGy doses from a Clinac 4MV linear accelerator (Varian Medical Systems, Salt Lake City, UT) through anterior and posterior parallel opposed fields, for a total of 900 cGy during 18 days.¹⁰⁵ Complete resolution of dyshidrotic eczema was reported 1 month after therapy. The patient was withdrawn from steroids after 6 weeks, without flare of disease, and remained in remission without medications 6 months post therapy.¹⁰⁵ Superficial radiation penetrates deeper than non-ionizing radiation and may allow increased intensity and better dose distribution.¹⁰⁵

Non-ionizing Radiation: Oral and Topical PUVA

Non-ionizing UVA and UVB radiation (broadband and narrowband) has been used in a variety of ways in the treatment of chronic hand dermatitis. Recently, UVA-1 has shown promise in the treatment of many dermatologic conditions.⁹²

Photochemotherapy (ie, PUVA) is a commonly used treatment in dermatology, consisting of the administration of a psoralen followed by UVA irradiation (320–400 nm). Oral 8-methoxypsoralen (8-MOP) has been shown to be effective in the treatment of dyshidrosis.^{106–109}

LeVine and colleagues, in a clinical study of 7 patients with severe dyshidrotic eczema, treated each patient three times weekly with oral 8-MOP (0.6 mg per kilogram of body weight) 2 hours prior to UVA irradiation.¹¹⁰ The initial UVA dose was 2.5 J/cm²; this was increased by

increments of 0.5 J/cm^2 for six treatments, then increased by 1.0 J/cm^2 per treatment until remission, and finally tapered in frequency to once every 2 weeks. All patients remained in remission on the maintenance schedule for 2 to 6 months.¹¹⁰

Rosen and colleagues performed a randomized controlled study involving 35 patients with chronic hand dermatitis (including one patient with dyshidrosis) to compare the efficacy of PUVA and UVB treatment.¹¹¹ Patients received either oral psoralen and UVA irradiation to one hand or UVB irradiation to one hand. The PUVA treatment consisted of the ingestion of 0.6 mg of 8-MOP per kilogram of body weight 1.5 hours prior to irradiation. The initial UVA dose was 2 J/cm^2 , which was titrated up to a maximum of 15 J/cm^2 as tolerated. UVB irradiation was about 1 mW/cm^2 at a distance of 25 cm. Irradiation treatment times were increased from 30 seconds to 14 minutes as tolerated. All PUVA-treated hands (14 of 14) were cleared of disease, as compared to the hands in this group that were not irradiated (1 of 14) ($p < .001$). However, 9 of the 14 hands (64%) showed relapse within 3 months. No patients in the UVB group experienced remission, and there was no statistically significant difference in improvement between the irradiated and untreated hands.¹¹¹ Similarly, in patients with a variety of chronic hand dermatoses, narrowband UVB irradiation has not proven to be very efficacious.¹¹¹

The side effects of oral PUVA therapy include nausea and vomiting, an increased rate of cataracts, and whole-body persistent photosensitivity.^{107,108,112,113} Important, treatment with PUVA has been shown to increase the risk of malignant melanoma and squamous cell carcinoma in a dose-dependent manner.^{114–117}

Topical PUVA therapy minimizes the systemic absorption of psoralens and body exposure. Additionally, less cumulative UVA exposure is required for a similar clinical response.^{118,119} PUVA bath or soak therapy consists of soaking the affected area in a basin of 8-MOP solution. In PUVA paint therapy, a highly concentrated solution of 8-MOP is applied directly to the affected skin or is applied as a cream, gel, or ointment.^{108,120} Both methods avoid the systemic side effects of oral psoralens.^{118,119,121} PUVA bath therapy allows a more uniform distribution of the solution, resulting in fewer phototoxic reactions from uneven application,^{108,121–123} and requires less 8-MOP¹¹⁸ whereas PUVA paint therapy may be more practical because no basin or other set-up is required.¹²¹ Side effects may include erythema, blistering, photosensitivity, and hyperpigmentation. Systemic effects are rare. It seems reasonable that topical PUVA would have less carcinogenic

potential than would oral PUVA, but this has not yet been definitively determined.

Davis and colleagues conducted a retrospective review of 35 patients with palmar and plantar dermatoses (including 5 patients with dyshidrotic eczema) who were treated with topical PUVA therapy.¹²⁴ The affected areas were soaked in a solution of 10 mg of methoxsalen in 2 L of warm water for 30 minutes, then treated with stepwise increasing doses of UVA three times per week until the dermatosis cleared or subsided. Of the patients with dyshidrosis, 2 (40%) were cleared of disease, 1 (20%) was improved, 1 (20%) exhibited no response, and 1 dropped out of the study, citing inconvenience. For all 35 patients, the mean time to clearing was 2.8 months (range, 2 weeks to 7 months), and the mean cumulative UVA dose was 140 J/cm^2 (range, 9–530 J/cm^2). These parameters were not reported separately for the patients with dyshidrosis.¹²⁴

In a case series, Behrens and colleagues described the effect of PUVA bath therapy on 30 patients with dermatoses of the hands and feet, 12 of whom had dyshidrosis.¹¹⁹ Patients soaked their hands and/or feet for 20 minutes in a dilute water solution of methoxsalen (1.0 mg/L) at 37°C . The initial dose of UVA for all patients was 0.3 J/cm^2 , which was gradually increased to a maximum dose of 3.0 J/cm^2 . Treatments were given three to four times weekly for 8 weeks. Of the 12 patients with dyshidrosis, 6 (50%) showed complete remission, 3 (25%) had significant improvement, and 3 (25%) had slight improvement after 8 weeks.¹¹⁹ In the follow-up period of 8 weeks after completion of treatment, only 2 (17%) of these 12 patients experienced flares.¹¹⁹

Schempp and colleagues conducted a clinical trial involving 28 patients with palmar and plantar eczema (14 of whom had dyshidrotic eczema) to study the effects of PUVA bath therapy.¹¹⁸ The affected area on each patient was soaked for 15 minutes in a warm water solution of 8-MOP (1 mg/L), followed by UVA treatment at a starting dose of 0.5 J/cm^2 . Treatments were performed four times weekly, to a total of 25 treatments. Excellent or good results were reported for 13 (93%) of the 14 patients with dyshidrotic eczema.¹¹⁸ No phototoxic reactions were observed.¹¹⁸

UVA therapy alone is another option that may be useful in the treatment of dyshidrosis.¹²⁵ It is well tolerated and does not require the use of psoralens, which have been found to increase the risk of carcinogenesis. UVA-1 has been shown to cause less photodamage in murine skin than is caused by a solar simulator light¹²⁶ and induces less of the tumor suppressor gene *TP53* than broadband UVA radiation induces.¹²⁷

Polderman and colleagues conducted a double-blind controlled study in which 28 patients with dyshidrotic eczema were randomized to receive UVA-1 irradiation (40 J/cm²) or sham irradiation, five times weekly for 3 weeks.¹²⁸ Patients treated with UVA-1 had significant improvement compared to the placebo group after 2 and 3 weeks ($p = .006$ and $p < .005$, respectively). The DSAI of the treated group decreased an average of 6.5 points after the second week and 8.7 points after the third week whereas the score of the placebo group respectively increased by an average of 1.1 and 0.4 points. No side effects were reported.¹²⁸ In a blinded randomized clinical trial, Petering and colleagues evaluated 27 patients with dyshidrotic eczema who received UVA-1 therapy on one hand and topical cream PUVA on the other for 3 weeks. There was no statistically significant difference detected between the two therapies.¹²⁹ Schmidt and colleagues, in an uncontrolled clinical trial, exposed the hands of 12 patients with dyshidrotic eczema to 15 sessions of UVA-1 irradiation.¹³⁰ Doses of 40 J/cm² per day were administered over 3 weeks. Ten (83%) of these 12 patients experienced gradual relapse-free improvement during the 3 months following treatment.¹³⁰

UVA-1 appears to confer less risk than PUVA, with similar efficacy, but longer studies are needed to evaluate long-term risks.⁴⁴ Suberythematous doses of UVA-1 have been shown to increase expression of *TP53* and *BCL2*.¹³¹

Nickel-Directed Therapies

Many authors have favored a systemic role for nickel aggravation of dyshidrosis, citing implausible patterns for contact allergy and positive reactions in nickel oral challenge tests resulting in flares of dermatitis in numerous patients.^{21,25,132–135} Nickel-sensitive patients may be identified via patch testing or oral challenge. It is important to first rule out simple contact allergy as the cause of vesicular hand dermatitis. Patients may be taught how to use a dimethylglyoxime kit to test frequently encountered objects at home and work for nickel content.¹³⁶ Potential therapies directed at decreasing systemic nickel levels include low-nickel diets, oral therapies, and hyposensitization.

Low-Nickel Diet

The theory behind low-nickel diets is controversial.^{137–140} Whereas oral challenge with nickel sulfate doses of 1 to 5 mg often results in a flare of dermatitis in nickel-sensitive patients, doses closer to actual daily dietary levels (0.1–0.8 mg) produce flares less reliably.³⁴ Cronin and colleagues

found that of 5 women with dyshidrosis and nickel sensitivity, all experienced a flare with 2.2 mg of orally administered nickel whereas only 3 women had a flare with 1.25 mg of oral nickel and 2 women flared with a 0.6 mg dose of oral nickel.¹⁴¹ Nonetheless, low-nickel diets appear to produce clinical improvement for some patients with chronic dyshidrosis.^{132–134} In addition to nickel in food, nickel levels in drinking water may also be important for some nickel-sensitive dyshidrosis patients.¹⁴²

Veien and colleagues evaluated a low-nickel diet in 204 dermatitis patients (including 104 with hand and/or foot eczema [clinical findings were not described]) who had positive patch-test reactions to nickel or positive results on oral challenge to nickel. Of these patients, 121 (59%) were cleared or markedly improved after 2 months.¹³⁴ This diet involved the avoidance of nuts; canned fish, vegetables, and fruit; asparagus; beans; chocolate and cocoa; whole grain flour; soy flour; and wine, as well as a variety of other items. After 1 to 5 years, 150 patients responded to a questionnaire; 88 (59%) of these patients stated that they had experienced long-term improvement as a result of the diet. Among the 117 patients who believed specific foods caused flares, the most frequently cited items were wine (44 patients), beer (31), chocolate (28), various vegetables (23), and herring (19).¹³⁴ Veien and colleagues noted that many of these foods also contain or induce the release of vasoactive amines, despite having relatively low nickel levels, and therefore advised the avoidance of foods with a high nickel content, vasoactive amines, or both.¹³⁴

Kaaber and colleagues found that 9 (53%) of 17 patients with chronic nickel dermatitis improved during 6 weeks on a low-nickel diet. Of the 9 patients who improved, 7 (78%) flared on resumption of a regular diet.¹³² In a clinical trial, Veien and colleagues reported that of 32 metal-sensitive patients with hand dermatitis, 21 (66%) experienced long-term improvement after dietary restriction.¹³³

A low-nickel diet may be helpful even for patients who are not allergic to nickel. Veien and colleagues reported that of 56 patients who had vesicular hand dermatitis that flared with the oral administration of metal salts but who had negative patch-test results, 36 improved after 1 month of adhering to a diet low in the metal that caused the individual to flare. After 1 year, 28 of these patients reported improvement with a low-metal diet and flares upon the resumption of a normal diet.³³

In sum, dietary restriction is likely effective for a subset of nickel-sensitive patients with dyshidrosis. It requires a highly motivated individual because nickel is found in many common foods (Table 1).^{132,134,143}

Table 1. Low-Nickel Diet: Nickel-Containing Foods to Avoid

All canned foods
Foods prepared with or in nickel-containing utensils, pots, pans
Fruits and vegetables
Asparagus
Beans
Broccoli
Carrots
Corn
Lettuce
Mushrooms
Kale
Alfalfa sprouts
Leeks
Lentils
Pineapple
Raspberries
Prunes
Dates
Figs
Seafood
Herring
Oysters
Mussels
Shrimp
Crawfish
Grains and cereals
Whole wheat flour
Bran
Buckwheat
Millet
Muesli
Multigrain bread
Oatmeal
Rice, unpolished
Rye bran
Other foods
Tea
Soy protein powder
Chocolate and cocoa
Baking powder
Marzipan
Nuts
Sunflower and sesame seeds
Licorice
Vitamins with nickel

Adapted from Kaaber K et al¹³²; Veien NK et al¹³⁴; Veien N et al.¹⁴³

Oral Agents

As compliance with a low-nickel diet is difficult, several oral agents have been investigated for their ability to neutralize the immunostimulatory effects of nickel.

Chelating agents have been examined for their theoretical ability to bind nickel in vitro. Menne and Kaaber evaluated the use of tetraethylthiuram disulfide (TETD; also called disulfiram) and its metabolite diethyl dithiocarbamate (DDC) in a woman with dyshidrosis and nickel sensitivity.¹⁴⁴ Treatment with regimens of both DDC (100 mg four times daily for 20 days) and TETD (100 mg three times daily for two months) led to improved skin findings.¹⁴⁴

Kaaber and colleagues, in a double-blind controlled trial of 24 nickel-allergic patients with pompholyx (clinical description not reported), found positive results from treatment with disulfiram (Antabuse, Odyssey Pharmaceuticals, East Hanover, NJ).¹⁴⁵ The patients were started on 50 mg daily, and the dosage was slowly increased to 200 mg daily, which was continued for 6 weeks. Over the course of treatment, 5 (45%) of 11 patients treated with disulfiram healed as compared with 2 (15%) of 13 patients in the placebo group. Two patients in the disulfiram treatment group developed signs of hepatic toxicity, and one of these two patients was diagnosed with toxic hepatitis. The authors recommended regularly monitoring liver enzyme levels in patients treated with disulfiram.¹⁴⁵ It should be noted that the use of disulfiram also may initially cause a flare of dermatitis.¹⁴⁶ DDC chelates divalent metals ions, including nickel. Shortly after the initiation of therapy, there is a marked increase in serum and urinary concentrations of nickel because DDC probably mobilizes nickel from body stores.¹⁴⁷ Therefore, it may be helpful to start patients on smaller doses.¹⁴⁷

Another oral agent that has been studied for dyshidrosis is disodium cromoglycate (DSCG).¹⁴⁸ DSCG has been used to treat immunoglobulin E (IgE)–mediated diseases such as asthma. It is believed to work by inhibiting mast-cell degranulation in the gastrointestinal tract.^{149,150} Pigatto and colleagues conducted a 3-month randomized controlled single-blind clinical trial in which 24 nickel-sensitive patients with dyshidrosis were divided into three groups: 8 patients were treated with a low-nickel diet, 9 were treated with DSCG (1,500–2,000 mg three times daily, before meals) without dietary restrictions, and 7 were simply observed. The patients who were on the low-nickel diet did not show significant improvement over the patients in the control group. The group treated with DSCG, however, was noted to have significant improvement over the entire course of treatment as evaluated by a blinded observer ($p < .05$).¹⁴⁸

Hyposensitization

Nickel hyposensitization is another modality that has been investigated. Santucci and colleagues, in an uncontrolled

clinical trial of 25 nickel-sensitive females with dermatitis (including 3 patients with dyshidrotic eczema), reported success with hyposensitization.¹⁵¹ The patients were initially given 10 mg of nickel sulfate (NiSO_4) in water, and 18 (72%) of the patients developed a flare of dermatitis. Fifteen days later, the subjects were started on daily incrementally increasing doses of NiSO_4 for 3 months. By the end of the trial, the dermatitis of 14 (56%) of the patients was controlled. Data were not reported separately for the patients with dyshidrosis. Three patients (12%) dropped out of the study owing to severe dermatitis exacerbation.¹⁵¹

In a randomized controlled clinical trial conducted by Troost and colleagues, 21 nickel-allergic patients with hand and/or face dermatitis were assigned either to UVB therapy alone or to subcutaneous NiSO_4 administration (hyposensitization) plus UVB therapy.¹⁵² However, during the 2 years of this study, no significant difference was seen between the two groups, either clinically or in terms of immunologic findings (lymphocyte proliferation and cytokine expression).¹⁵²

Iontophoresis

Iontophoresis has also been studied as a treatment option for dyshidrosis. Iontophoresis causes ion transfer through the skin and is believed to effect a functional disturbance in eccrine sweat duct secretion.¹⁵³ As previously discussed, although sweat glands are not involved in the pathogenesis of dyshidrosis, hyperhidrosis may exacerbate the condition in some patients. Iontophoresis decreases sweat production and may also enhance the absorption of therapeutic agents.¹⁵³ Oda and colleagues, in a randomized single-blind right hand–left hand study, treated 20 patients with tap water iontophoresis on one hand and with a topical tar solution and zinc oxide paste with bismuth on both hands.¹⁵³ Patients included in the study had stable-phase mild to moderate dyshidrotic eczema that was poorly controlled with nonsteroidal topical therapy. Iontophoresis was applied in 15-minute sessions, for a total of 20 sessions for one hand for 3 weeks. Seventeen patients (85%) showed significant improvement on the hand treated with iontophoresis. The average DASI score decreased from 16 to 8 during the course of the study on the hands treated with iontophoresis whereas the DASI score for the hands not treated with iontophoresis decreased from 16 to 15 ($p = .001$).¹⁵³

Botulinum Toxin A

The use of botulinum toxin type A (BTXA) is a relatively new therapeutic option in the treatment of dyshidrosis.

BTXA inhibits acetylcholine release, which in turn decreases eccrine sweat production. BTXA may be particularly useful for the subset of patients for whom sweating is an exacerbating factor. BTXA has also recently been reported to decrease the release of substance P and, therefore, may also exert an antipruritic effect.^{154–157}

In a prospective right hand–left hand clinical study by Wollina and Karamfilov, 8 patients with dyshidrotic eczema were intracutaneously injected with 100 units of BTXA on the hand with the worse DASI score on the first day of the study.¹⁵⁴ Patients continued topical corticosteroid therapy on both hands throughout the study. For the 6 patients who completed the study, the mean DSAI score dropped from 28 to 17 during 8 weeks on the side given topical treatment alone whereas the score for the side treated with BTXA decreased from 36 to 3 over the same period.¹⁵⁴

Swartling and colleagues, in another prospective right hand–left hand controlled clinical trial, studied 10 patients with dyshidrotic eczema who were injected in one hand with 162 units of BTXA and were untreated on the other hand.¹⁵⁸ Seven (70%) of the 10 patients reported a good to very good effect on the treated side after 5 to 6 weeks. Interestingly, 6 (86%) of these patients had reported at baseline that their dyshidrosis was worse with sweating and during the summer, which again suggests that BTXA may be an important therapy for this subset of dyshidrotic patients.¹⁵⁸

Relaxation Techniques

Cognitive relaxation techniques have been reported to be effective for some patients with dyshidrosis.^{159,160} Niemeier and colleagues, in a cross-sectional study of 101 patients with hand dermatitis (including 33 patients with various types of vesicular hand dermatitis), reported that approximately half of the patients believed that stress aggravated their dermatitis.¹⁶⁰ Koldys and Meyer reported success with the use of biofeedback training on five individuals with dyshidrosis unresponsive to conventional therapies.¹⁶¹ The patients were taught techniques of hand relaxation and warming via biofeedback training. All five patients experienced improvement; the greatest improvement was seen in patients who had previously noted a correlation of stress with flares of dyshidrosis.¹⁶¹

Psychological Considerations

Niemeier and colleagues, in the previously cited cross-sectional study of 101 patients with hand dermatitis,

reported that patients who are identified as high-stress responders and who have also had a negative patch-test result require more psychological support.¹⁶⁰ They speculated that coping may be more difficult for patients who are without a defined etiology for their disease, possibly leading to a greater need for adjuvant psychological treatment.^{160,162,163}

Discussion

Dyshidrosis is a relatively common variant of hand dermatitis. It may lead to considerable disability in terms of occupational difficulty, physical discomfort, and psychological distress. After a thorough history, physical examination, and diagnostic work-up as indicated, patients with dyshidrosis should first be counseled about conservative measures to optimize skin-barrier function and to avoid exacerbating and irritant factors. If further therapy is required, it is reasonable to start with a topical corticosteroid or immunomodulating agent. Chronic or severe cases may benefit from systemic immunosuppressants and/or radiotherapy. Of the radiotherapeutic options, topical PUVA currently has the most supporting data. For cases of classic pompholyx (explosive bullae), a limited course of systemic glucocorticoids may be especially helpful.

More randomized controlled trials are warranted, to direct therapy for dyshidrosis. Also, more basic science studies are needed to elucidate the pathophysiology of this condition.

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