

Treatment of Eczema

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Abstract Eczema is a chronic inflammatory skin disease that has reached nearly epidemic proportions in childhood. Moreover, it is a difficult disease to control and, with its onset in childhood, is often the first manifestation of atopy. The clinical features of eczema include itchy red skin accompanied by dryness and lichenification. In the past, treatment options consisted primarily of avoidance of soap and water. These options have considerably improved with both nonpharmacologic and pharmacologic approaches. However, eczema is still a treatment challenge. Part of the problem in developing new treatment options has been the relative failure in translating basic science information into clinical application. It is hoped that the newer biologics will help bridge this gap and lead to greater success rates.

Keywords Atopic dermatitis · Immunoglobulin E · Food allergy · Soap · Immunotherapy

Introduction

Eczema is a chronic condition of varying severity and may be a difficult disease to control. Eczema typically begins in childhood, and may be the first manifestation of atopy with red, itchy skin, dryness, erythema, and lichenification.

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The general principles for the treatment of eczema are well-known, and include the use of moisturizing soaps and lotions, topical corticosteroids, and immunomodulatory agents.

In the late nineteenth century, treatment was limited to the use of dusting powders, cold water compresses, rest, and scant bodily coverings such as a sheet. Other protective ointments including zinc, tar, and lanolin were used, as described by Dr. Moriz Kaposi in his book, “Pathology and Treatment of Diseases of the Skin”, published in 1895 [1]. Today, however, there are significant variations in the recommendations amongst health care providers, even among specialists. Treatment of eczema is typically done by primary care physicians and midlevel caregivers. In severe or difficult to treat cases, referral to a specialist, either an allergist or dermatologist, is recommended [2].

The Different Forms of Eczema

Whereas the clinical features of eczema are fairly consistent, there is some evidence that eczema can exist in more than one form, including atopic and nonatopic forms. The atopic form is generally IgE-mediated, and the nonatopic form is non-IgE mediated. Both forms can manifest eosinophilia. Other variants of eczema include nummular eczema, seborrheic dermatitis, and hand eczema. Eczema may also occur as a dermatologic manifestation of other systemic illnesses, such as Wiskott–Aldrich syndrome, human immunodeficiency virus (HIV) infection or allergy to foods.

Making the Right Diagnosis

Eczema or atopic dermatitis has been classically described as “a chronically relapsing inflammatory skin disease commonly associated with respiratory allergy”. There is no pathognomonic skin lesion associated with eczema and, in

fact, the diagnosis is based upon a set of clinical features that can be divided into major or minor groups. Various “algorithms” have been developed to diagnose eczema, but even in clinical drug trials, the disease has not been well-defined. Major features of atopic dermatitis include pruritus, facial and extensor involvement in infants and children, flexural lichenification in adults, chronic or relapsing dermatitis, and a personal or family history of atopic disease. The successful treatment of eczema depends first on the correct diagnosis. The differential diagnosis is extremely

broad, ranging from infectious diseases such as scabies to metabolic diseases such as zinc or pyridoxine deficiency. A complete list of differential diagnoses is shown in Table 1.

Risk Factors for Atopic Dermatitis

During the first 2 years of life, risk factors for atopic dermatitis and wheezing may be different, suggesting varying mechanisms for these two phenotypical manifestations of atopy. Risk factors associated with an increase in the

Table 1 Differential diagnosis of atopic dermatitis

Condition or disease	Dermatologic manifestation	Pruritis	Affects	Treatment
Zinc deficiency	Can produce a bullous pustular dermatitis	Variable	Any age	Zinc replacement
Niacin deficiency	Rash can be variable, but usually dry, scaly, thickened, red and sometimes bullous	Minimal	Any age	Oral or parenteral niacin replacement, balanced diet
Psoriasis	Raised red patches with silvery scales, discrete border	Minimal	10–40 years	Topical corticosteroids and UV phototherapy
Pyridoxine deficiency	Seborrheic dermatitis	Yes	Any age	Pyridoxine replacement
Netherton's syndrome	Pruritic dry skin, bamboo hair		Infants	
Scabies	Burrows in linear pattern, frequently between fingers, very pruritic	Extreme	Any age	Scabicides such as permethrin cream
Mycosis fungoides	Chronic pruritic rash progressing to plaque like lesions that can become nodular or ulcerated	Yes	>50 years	Electron beam radiotherapy, topical corticosteroids and sunlight for dermatological lesions
Generalized exfoliative dermatitis	Red, scaly, thickened, crusted skin affecting entire body, can be secondary to other illnesses	Variable	Any age	Oral corticosteroids, vascular support in severe cases
Stasis dermatitis	Affects ankles, edema, erythema, mild scaling and discoloration	Variable	Elderly	Compression stockings, corticosteroids and/or antibiotics if needed
Wiskott–Aldrich syndrome	Eczema is primary dermatologic manifestation, affects boys only	Yes	Early age	Stem cell transplantation
HIV infection	Variable from rashes to Kaposi's sarcoma	Variable	Any age	Treat underlying disorder
Seborrheic dermatitis	Greasy, diffuse scaling of the scalp	Variable	Infancy	In children, baby shampoo and 1% hydrocortisone cream
Nummular eczema	Discoïd lesions, pruritic patches of vesicles and papules	Yes	Middle age	None uniformly effective, can try corticosteroids and/or antibiotics
Contact dermatitis	Varies from redness to severe swelling with bullae and vesiculation	Yes	Any age	Topical corticosteroids, antihistamines and parenteral corticosteroids in severe cases
Lichen simplex chronicus	Dry scaling, well-demarcated hyperpigmented lichenified plaques of oval, irregular or angular shape	Extreme	Ages 20–50	Topical corticosteroids to break cycle of scratch and itch
Hyper IgE syndrome	Associated with eczema and asthma	Yes	Any age	Treat eczema
Letterer–Siwe disease	Scaly, itchy rash on abdomen, arms, and other sites leading to raw skin, form of Langerhan cell histiocytosis	Yes	Starts in infancy	Chemotherapy/radiation
Phenylketonuria	Lighter skin and hair, but often have eczema also	Mild	Infancy	Special diet

incidence of atopic dermatitis include a shortening of the duration of exclusive breast-feeding, male gender, a parental history of atopic dermatitis, asthma or hay fever, increased maternal age, greater than 37 weeks gestation, increased head circumference, and increasing birth weight [3].

Diagnostic Tests

A study in Denmark demonstrated the value of cord blood IgE. The authors found that there was a significantly higher incidence of atopy at age 18 months in those infants with elevated cord blood IgE. Family history was also predictive of atopy. The results were similar at 5 years of age [4–7].

Skin testing to evaluate allergic sensitivity is not recommended in the young child because of the length of time required to complete the test and the difficulty of restraining the child for prolonged periods, not to mention the psychological impact. Other laboratory tests can provide information regarding specific triggers. An alternative method of identifying sensitivities is by radioallergosorbent test (RAST), which utilizes an immunoassay to measure specific IgE to foods and environmental allergens in the serum of atopic patients. Atopic dermatitis is heterogeneous and thus only a portion of these patients will be RAST positive. In childhood eczema, about 50% of patients will have elevated levels of food or environmental allergen-specific IgE on RAST. The total IgE may be elevated in these children as well.

Skin biopsy may reveal intercellular edema of the dermis (spongiosis) and intracellular edema. Mast cells can be detected in normal numbers and in varying stages of degranulation. A T cell infiltrate occurs in the epidermis, but particularly perivascularly, and rare eosinophils, basophils, and neutrophils can be seen in the dermis. In chronic lesions, activated eosinophils are increased in number. Hyperkeratosis can be detected in chronic lichenified lesions, and in these specimens, mast cells can be increased. Immunofluorescence studies can reflect extracellular major basic protein staining.

Recording Disease Severity

Because of the varied nature of the presentation of the disease, the validity of clinical studies is highly dependent on the ability to access severity. Studies in which the effect is monitored solely by subjective reporting by patients carry a bias, which may be insurmountable in establishing efficacy or tolerability. A number of scoring systems have been designed for the evaluation of eczema. One is the scoring atopic dermatitis (SCORAD) system, developed by the European Task Force on Atopic Dermatitis in 1993 [8]. Other examples of scoring systems include the eczema area and severity index (EASI); a basic clinical scoring system

(BCSS); a three-item severity score (TIS) [9], where the three clinical signs of excoriation, erythema, and edema papulation are assessed; and a six-area, six-sign atopic dermatitis score (SASSAD) [10]. Another scoring system is the W-AZS score [11], combining both subjective and objective signs in a rapid and efficient way. The objective severity assessment of atopic dermatitis (OSAAD) is derived from measurements of stratum corneum barrier function and hydration [12], normalized for extent of disease. The SCORAD system is used most often in clinical trials of atopic dermatitis [13]. However, it may be pertinent to note that in comparative studies of scoring systems, there seems to be little agreement in terms of severity amongst the different systems [14].

Non-Pharmacologic Approaches to Treatment

Handwashing

Most physicians recommend that bathing should be restricted in children with atopic dermatitis. Frequent bathing, especially with hot water, tends to remove protective oils from the skin surface, leading to the disruption of a natural barrier to desiccation. On the other hand, good hygiene must be observed, as infection can lead to exacerbations of atopic dermatitis. The dry skin noted in atopic dermatitis shows increased transepidermal water loss and decreased water-binding capacity. Using a wet washcloth or soaking the affected area can help soothe the skin, and then applying an occlusive agent can help retain the absorbed water. Occlusive agents should be applied immediately because evaporation of water on the skin surface can cause drying and irritation.

Early Intervention in Exposure to Foods

A Canadian study evaluated the effects of both breast-feeding and maternal avoidance of common food allergens in Western culture, namely, eggs, soybean, milk, fish, and peanuts. The study included 97 mothers who wished to breast-feed, and 128 mothers who did not. All families had a history of atopy. Compared to cow's and soy milk, they found that the incidence of eczema was lower in breast-fed infants (48%) and especially in breast-fed infants where mothers avoided ingestion of the above foods (22%). The remaining infants were fed either casein hydrolysates, soy milk or cow's milk. The incidence of eczema was 21%, 63%, and 70%, respectively. Infants were followed-up for 18 months. The study was not blinded nor controlled for other variables [15]. A second study of 72 infants in 1991 comparing breast-feeding, a whey hydrolysate formula, and conventional cow's milk and soy milk formulas showed

that the incidence of eczema was lower in those infants fed either breast milk or the whey hydrolysate [16]. However, we should note that both of these studies [15, 16] are controversial and remain to be replicated. There also appears to be an inverse relationship between the content of *n*-3 long chain polyunsaturated fatty acids in breast milk and the development of allergic symptoms, although no such effect was found on sensitization rate [17].

Weaning

It is now well-established that breast-feeding decreases the incidence of eczema. There have been studies which show an increased risk of eczema with breast-feeding, but there may be a “cause or consequence” issue with these studies. In other words, do parents with atopic children breast-feed longer? But when should a parent wean a child who is at risk for atopic dermatitis off breast milk? In a large cohort study of over 4,000 infants, breast-feeding was found to lower the incidence of atopic dermatitis, if the duration of breast-feeding was at least 4 months. If parents were able to exclusively breast-feed for the first 4 months, a beneficial effect was noted up to 4 years of age [18]. Once a child is weaned off breast milk, what is the best formula or milk to give? In a small study comparing the effects of weaning off breast milk at the median age of 6 months to either a whey hydrolysate or a cow’s milk formula, results were not significantly different, although the three infants who developed skin symptoms all fell in the cow’s milk formula group [19].

Avoidance of Environmental Allergens in Atopic Dermatitis

Aside from foods, infants and children are exposed to a variety of environmental allergens, both indoor and outdoor. Outdoor allergens include weed and grass pollens. Indoor exposures include dust mite, cat, dog, mouse, rat, cockroach, and mold allergens. The role of environmental allergens in the clinical presentation of atopic dermatitis has been studied, and individuals with atopic eczema have a high incidence of dust mite sensitivity based on skin testing or RAST testing. A study of 48 subjects (24 children and 24 adults) with a history of atopic dermatitis were randomized into an active treatment group, which consisted of Goretex bedcovers, benzyltannate spray, and HEPA vacuum cleaners [20]. In contrast, those randomized into the control group received cotton covers, placebo spray, and a conventional domestic vacuum cleaner. The dust collected from the homes of the active treatment group showed a significantly larger reduction in weight of dust. Der p 1 concentrations were reduced in both groups. The severity of eczema was reduced to a greater degree in the active treatment group, leading the authors to conclude that

effective avoidance measures to dust mite leads to improvement in the clinical status of eczema patients. In a two-phase study of 41 children with atopic dermatitis where one group was instructed on mite avoidance measures (including encasing mattresses and pillows, frequent vacuum cleaning of living room and bedrooms, regularly cleaning of soft toys, weekly hot washes of bedding, and no pets being allowed), and the other group received no recommendations, clinical scores for atopic dermatitis were significantly improved in the former group after 2 months compared with the latter. After 2 months, both groups were given environmental avoidance measures, and the symptom scores for atopic dermatitis assessed again after a year at which time all of the patients showed improvement, again demonstrating the effectiveness of environmental avoidance of allergens in the treatment of eczema [21]. Exposure to mold was irrelevant in these studies.

Food Diaries, Food Challenges, and Elimination Diets

It is difficult to effectively implement food diaries and elimination diets in adults; children are even more affected. Foods are complex mixtures of numerous ingredients with spices, sauces, and other additives to generate flavor. Conducting an elimination diet is time-consuming and requires compulsive attention for a lengthy period of time. Even the most accurate of food diaries generally does not have sufficient detail to yield meaningful information. Dietary advice alone may be sufficient to reduce symptoms and severity of eczema, as evidenced by a study of 55 children randomized to a 4-week regimen in which one group received specific advice regarding egg exclusion, whereas the control group received only general advice [22].

The gold standard for diagnosis of a food allergy is a double-blind placebo-controlled study. But in the case of atopic dermatitis when the reaction is not immediate, it is difficult to assess the contribution of a specific food tested. A study of 91 eczematous patients showed improvement in eczema scores after stopping common allergenic foods, such as cow’s milk and eggs. Improvement was seen in erythema, excoriation, lichenification, and surface area. Once the elimination of these foods with improvement was achieved, the subjects were challenged with cow’s milk, tomato, and eggs. There was significant worsening after cow’s milk and tomato exposure. This was not seen with egg but the study was limited by incomplete challenges secondary to patient refusal and reactions [23]. Moreover, food challenges can be risky and can provoke life-threatening reactions. The risk of having a systemic reaction is unpredictable with most common allergenic foods, but with egg allergy, it is dependent upon the patient’s specific IgE level [24].

Soaps and Detergents

The number and variety of soaps on the market makes it difficult to recommend a specific brand of soaps. Clearly, however, there are some soaps which have historically been extraordinarily irritating to children with eczema, i.e., Ivory. This is particularly ironic considering that Ivory has often been advertised as the “mild soap” for children. In atopic dermatitis patients, soaps contain ingredients that can have an irritant effect on affected skin. The best soaps should have a neutral pH and be void of fragrances and preservatives. They should have minimal defatting activity. Laundry detergents that are not rinsed off of clothes can be irritating. Again, some laundry detergents are stronger than others. As powdered detergents must first be solubilized, they tend to leave more residue.

Coal Tar

A study of the use of Clinitar, a form of coal tar, to treat eczema demonstrated little difference in effectiveness between Clinitar and 1% hydrocortisone cream after treatment for 4 weeks. Parameters evaluated included skin erythema, lichenification, dryness, and excoriations [25]. Tar shampoos are also available for scalp eczema. Tar products can be used in conjunction with a moisturizer. Sometimes, application of tar to inflamed skin can increase irritation.

Salt Baths

Balneotherapy, or water therapy, can be in the form of spa therapy or bathing in water with a high salt content. These types of therapy have been found to be effective in treating atopic dermatitis. The mechanism of action is unknown, and may possibly be solely a psychological or placebo effect as a result of the soothing nature of the baths.

Hot spring bathing has also been suggested to be of benefit in atopic dermatitis, possibly for the same reasons. Skin symptoms were improved in 76% of 70 patients who took twice daily 42°C acidic hot spring baths for 10 min. Colonization of skin with *Staphylococcus aureus* disappeared in 30 of 42 of the responders who were tested [26].

Special Clothing

It is usually recommended to avoid occlusive clothing. A study of silk fabric use in 46 children with atopic dermatitis showed that atopic dermatitis severity and local atopic dermatitis scores in children who wore silk clothing for 1 week were more favorable than those areas covered with cotton clothing. The only other therapy used was topical moisturizing creams or emulsions. Thirty-one children were assigned to the silk clothing group, whereas 15 served as

controls [27]. Other newer synthetic materials are being developed, usually made of a light-weight breathable 100% microfiber polyester, and some contain silver, which is used as a natural antimicrobial. Manufacturers of such garments claim that they are designed to provide relief for patients with itchy, dry, and sensitive skin, although no double-blind studies exist to confirm efficacy in treating atopic dermatitis.

UV Phototherapy

Ultraviolet light has been used successfully as an adjunct therapy for atopic dermatitis. A study of narrow band UVB therapy (311 nm wavelength) was found effective in reducing atopic dermatitis in five patients [28]. A trial of daily topical psoralen chemotherapy and ultraviolet light (PUVA) was conducted in 114 patients with complete clearing in 50% of patients. Histologically, responders showed reduced epidermal thickness and decreased numbers of epidermal Langerhans cells and dermal mast and mononuclear cell infiltrates. The authors also looked at skin permeability and found that patients with atopic dermatitis had increased permeability in lesional skin only, suggesting that barrier dysfunction also plays a role in the pathogenesis of atopic dermatitis [29]. Ultraviolet light has also been shown to have a suppressive effect on superantigen production by *S. aureus*. These superantigens can activate T cells and potentially enhance the inflammatory reaction in patients with atopic dermatitis. This may be one mechanism by which ultraviolet light exerts its therapeutic effect in atopic dermatitis.

Pharmacological Agents to Treat Eczema

Moisturizers and Wet Dressings

The goal of using moisturizers is to maintain skin hydration. For this reason, moisturizers, also known as emollients, consist of a mixture of water and oils, which when applied in generous amounts, form a nonporous barrier to keep water on the skin. Moisturizers can be used in conjunction with other topical treatments, including coal tar and topical corticosteroids. Wet dressings can be used in combination with moisturizers as well. Wet wraps provide prolonged hydration and occlusion and can also prevent scratching. Wet dressings can also help increase the absorption of topical medications. Care must be taken to use wet dressings appropriately. Overuse can cause secondary infection, chills, and can weaken the barrier function of the skin. A metaanalysis of 24 clinical studies on wet wrap dressings emphasized that large prospective studies on the efficacy and safety of wet wrap dressings are lacking, but that some conclusions could be made: wet wrap dressings in conjunction with a moisturizing cream or ointment, with diluted

topical corticosteroid can provide short-term relief in severe or refractory atopic dermatitis, and that treatment for up to 14 days with topical corticosteroids is safe [30]. However, a randomized trial of 50 children between the ages of 4 and 27 months conducted to compare the efficacy and safety of wet wraps versus conventional application of topical medications showed no difference in efficacy, but a higher rate of skin infections in the wet wrap group [31].

The Difference Between Lotions, Creams, and Ointments

The most common vehicles used for the application of nonmedicated and medicated agents on skin include lotions, creams, and ointments. Other less commonly used vehicles are gels, sprays, shampoos, solutions, tapes, and more recently, foams [32]. The difference between lotions, creams, and ointments is in the oil/water ratio. The lipid content is highest in ointments and lowest in lotions. Because of this, ointments tend to feel heavier, greasier, and stickier. Ointments cause more shine on the skin when applied. Creams may be the more favorable choice in humid climates because the excessive occlusiveness of ointments may lead to folliculitis or itching. All three types of vehicles can carry moisturizers only or can be engineered to carry a pharmaceutical agent. Fragrances and preservatives are frequently added to moisturizers, and this can cause drying or irritation.

Moisturizers have no active pharmaceutical ingredient, and other than those with a high concentration of fragrances, can be used as frequently as needed. Moisturizers should be applied after showering or swimming. Pat dry rather than rub dry before immediately applying moisturizer. Ointments tend to last longer, but are messy. Lotions generally need to be applied more often because of their higher water content. In general, lotions and creams are used for mild cases, whereas ointments are used for severe cases. For best results, moisturizers should be used regularly in patients with atopic dermatitis, even when symptoms have abated.

Antihistamine and Other Antipruritic Creams

1% Pramoxine hydrochloride

Pramoxine is a topical anesthetic that has been used in wound care. An open-labeled study of a lactic acid and pramoxine hydrochloride cream showed improvement in skin dryness and itchiness by day 3 of application compared with no treatment. The improvements continued through day 7 [33]. The study was conducted in 24 women with a history of dry itchy skin. Whether or not pramoxine has an indication for use in atopic dermatitis has not been determined.

Topical Diphenhydramine

Topical antihistamines are recommended as over-the-counter (OTC) preparations for the relief of itching. There have been no double-blind placebo-controlled trials evaluating the effectiveness of these preparations in the treatment of atopic dermatitis. It is also important to remember that these medications can be associated with toxicity, as in the example of an 8-year-old boy given topical Caladryl and Benadryl spray who developed mental confusion and hallucinations [34]. Furthermore, delayed hypersensitivity reactions have been reported.

Corticosteroid Creams

Topical corticosteroids are the treatment of choice for eczema and remains the gold standard by which all other therapeutic modalities are judged. Multiple studies have been conducted comparing the efficacy of topical corticosteroids with placebo and comparative studies between various corticosteroids of varying potency. A study comparing the efficacy of 0.05% desonide ointment and 1.0% hydrocortisone ointment in 113 children over a period of 5 weeks with extension of the treatment to 6 months in 36 of these children was conducted. The children were evaluated for efficacy, as determined by erythema, excoriations, oozing or crusting, pruritus, induration, lichenification, and global improvement and safety, as determined by skin atrophy. Results showed the desonide ointment to be significantly more effective, but that a similar safety profile existed between the two groups [35]. Two separate studies evaluated the efficacy of fluticasone 0.05% cream in children between 2 and 14 years of age. The comparative treatment was hydrocortisone 1% cream in one study and hydrocortisone butyrate 0.1% cream in the other. In both studies, total atopic dermatitis scores were lower in the fluticasone-treated group. There were no signs of skin atrophy in either group of either study.

A study of 194 adults with clinically proven atopic dermatitis showed a significant improvement in those who were given hydrocortisone butyrate 0.1% cream over placebo. Only local side effects were noted in both groups, and these were infrequent and mild, the most common being burning, which occurred in 4% of placebo patients and 2% of hydrocortisone butyrate patients [36]. Fluticasone propionate and clobetasone butyrate have also been shown to be effective in treating atopic dermatitis, but studies showed that with cessation of therapy, lesions return, demonstrating the need for ongoing intermittent therapy [37, 38].

There is a paucity of data regarding the side effects of topical corticosteroids. Information regarding this sensitive issue is mostly extrapolated from inhaled corticosteroid data. The most widely known side effect of topical

corticosteroid use is atrophy of skin. As in the case of inhaled corticosteroids, systemic absorption can potentially lead to HPA-axis suppression and growth retardation in children. A study examining the effects of desonide 0.05% ointment and hydrocortisone 2.5% ointment on the HPA-axis in children demonstrated no suppression of early morning cortisol levels in either treatment group. Moreover, ACTH-stimulated mean cortisol levels after 4 weeks of treatment did not change from baseline values for either group [39]. An open-labeled study examining a 3-week use of alclometasone dipropionate 0.05% cream in 39 children with atopic dermatitis was conducted. Improvement in clinical signs and symptoms of induration, erythema, and pruritus was observed. Plasma cortisol levels remained within the normal range of 7–25 µg/100 ml throughout the course of the study. At the end of the study, complete clearing was noted in 72% of the children, whereas moderate to marked improvement occurred in 18% [40]. Exaggerated concern regarding the side effects of topical steroids can produce unfounded anxiety in parents of children with atopic dermatitis, leading to a reluctance to medicate and resulting in suboptimal treatment. It is therefore imperative that risk benefit ratios of topical corticosteroid treatment be explained in great detail to patients and parents of children with the disease [41, 42].

There are numerous other studies comparing topical corticosteroids. Whereas some studies indicate that certain topical corticosteroids are more effective than others, there are no studies that demonstrate any significant side effects if the medications are used according to recommended doses. With that in mind, the indications for choosing one corticosteroid preparation over another often depends on the variation in disease severity. More potent preparations may be needed for severe cases, whereas one can use a low potency preparation in mild cases. To confuse the issue even further, a side-to-side comparison of topical corticosteroids in atopic dermatitis did not demonstrate a clear and consistent difference in efficacy between high potency and low potency topical corticosteroid [43]. Available topical corticosteroid preparations and their potency are shown in Table 2.

Leukotriene Antagonists

Antileukotriene pathway drugs that have been used successfully in the treatment of allergic rhinitis and asthma includes agents that block leukotriene synthesis via the 5-lipoxygenase pathway and leukotriene receptor antagonists. Historically, leukotriene synthase inhibitors have not been widely used because of their associated liver toxicity. Zileuton is a leukotriene synthesis inhibitor that has been used in the treatment of asthma. It must be given four times daily. A pilot study of six patients showed encouraging results of Zileuton in the treatment of eczema [44]. A similar study of 15

patients with moderate to severe atopic dermatitis using the leukotriene receptor antagonist, montelukast, also showed improvement based on subjective scoring and single observer evaluation [45]. Subsequent studies have studied other parameters, such as effects on eosinophil cationic protein (ECP), and whereas these studies have persisted in using small numbers of patients, results continue to suggest that leukotriene pathway modifiers may have a role in the treatment of eczema [46, 47]. However, large-scale studies are necessary to confirm this.

Oral Antihistamines

Antihistamines are utilized in atopic dermatitis primarily to decrease pruritus. Eczema tends to worsen significantly with additional insults to the skin. Thus the idiom, “scratching begets itching begets scratching”. First generation antihistamines include OTC sedating antihistamines including diphenhydramine and chlorpheniramine. Second generation antihistamines were previously only available by prescription, but several years ago loratadine became available both in generic form and OTC. Fexofenidine will also be available in generic form in the near future. A recent double-blind multicrossover study demonstrated that loratadine was only slightly better than placebo in reducing pruritus symptoms in atopic dermatitis who were concurrently on a topical corticosteroid [48]. A randomized double-blind study of the long-term use of cetirizine in 817 infants with atopic dermatitis showed that the duration of topical steroid use in treating atopic dermatitis can be shortened from a mean of 25.2 to 18.8 days with concurrent treatment with cetirizine compared to placebo [49]. Treatment for 1 week with fexofenidine 60 mg twice daily, when added to a topical corticosteroid regimen in a study of 400 patients with atopic dermatitis, was able to decrease the severity of pruritus in a double-blind randomized placebo-controlled study. Side effects were low and similar to the placebo group [50].

Other medications with antihistaminic activity that are frequently used in the treatment of atopic dermatitis include hydroxyzine, doxepin, and periactin. Hydroxyzine is metabolized to cetirizine after ingestion. Doxepin is a tricyclic antidepressant with both H1- and H2-binding affinity. Each of the above medications carries sedative properties and is available only by prescription. A summary of available non-sedating antihistamines is shown in Table 3. Symptomatically, pruritus is the most bothersome and intolerable feature of atopic dermatitis [51]. Even partial resolution of pruritus can result in a much-improved quality of life for patients [52].

Antibiotics and Antiseptics

An increased incidence of skin infections occurs in patients with atopic dermatitis caused by a variety of microorgan-

Table 2 Potency of topical corticosteroids

Scientific name	Brand name	Available forms	Potency category	Potency
Clobetasol propionate	Temovate	0.05% ointment	1	High
Clobetasol propionate	Temovate	0.05% cream	1	High
Betamethasone dipropionate	Diprolene	0.05% cream	1	High
Betamethasone dipropionate	Diprolene	0.05% ointment	1	High
Mometasone furoate	Elocon	0.1% ointment	2	High
Mometasone furoate	Elocon	0.1% cream	4	Medium
Triamcinolone acetonide	Kenalog	0.1% ointment	4	Medium
Triamcinolone acetonide	Kenalog	0.1% cream	4	Medium
Halcinonide	Halog	0.1% ointment	3	Medium
Desonide	DesOwen	0.05% ointment	6	Low
Desonide	DesOwen	0.05% cream	6	Low
Desonide	DesOwen	0.05% lotion	6	Low
Alclometasone dipropionate	Aclovate	0.05% ointment	6	Low
Hydrocortisone base	Cortisporin	0.5% cream	7	Low
Hydrocortisone	Hytone	2.5% ointment	7	Low
Hydrocortisone	Hytone	1% ointment	7	Low
Hydrocortisone	Hytone	2.5% cream	7	Low
Hydrocortisone	Hytone	1% cream	7	Low
Halcinonide	Halog	0.1% cream	2	High
Flucinonide	Lidex	0.05% ointment	2	High
Flucinonide	Lidex	0.05% cream	2	High
Betamethasone valerate	Valisone	0.1 % ointment	3	Medium
Hydrocortisone valerate	Westcort	0.2% ointment	5	Medium
Fluocinolone acetonide	Synalar	0.025% ointment	5	Medium
Desoximetasone	Topicort	0.25% ointment	2	High
Desoximetasone	Topicort	0.25% cream	2	High
Fluticasone propionate	Cutivate	0.005% ointment	3	Medium
Halobetasol propionate	Ultravate	0.05% ointment	1	High
Halobetasol propionate	Ultravate	0.05% cream	1	High
Flurandrenolide	Cordran	4µg/cm ² tape	1	High
Fluticasone propionate		Lotion		

isms, including viruses, bacteria, and fungi. In addition to the disruption of the protective barrier function normally provided by the skin as a result of the inflammation associated with atopic dermatitis, other immunological changes contribute to the higher incidence of infection. For example, T cell associated cytokines including interferon-gamma, IL-4, and immunoglobulins play a role in susceptibility to infection. Normal skin colonizers such as *S. aureus* are found in a greater proportion of atopic dermatitis than in nonatopic patients. Herpes simplex virus

[53], molluscum contagiosum [54], and human papilloma-virus are also found to colonize the skin of patients with atopic dermatitis. Fungal infections of the skin can cause exacerbations of atopic dermatitis [55]. Because of this prevalent association between infectious agents and atopic dermatitis, antibiotics and antiseptics have become a part of the treatment of atopic dermatitis.

In addition to oral antibiotics, topical antiseptics or antibiotics have been found to be of benefit in the treatment of atopic dermatitis. A study comparing the effects of a

Table 3 Comparison of second generation antihistamines

Name	Trade name	Pregnancy category	Sedating	Typical adult dose	Typical child dose	Approved age indications
Fexofenidine	Allegra	C	No	180 mg qd	30 mg bid	6 years and up
Loratadine	Claritin	C	No	10 mg qd	5 mg qd	2 years and up
Desloratadine	Clarinx	C	No	5 mg qd	1–2.5 mg qd	6 months and up
Cetirizine	Zyrtec	B	No ^a	10 mg qd	2.5–5 mg qd	6 months and up

^a May be sedating in some patients.

corticosteroid preparation, a tar preparation, and gentian violet showed that all treatments led to a decrease in severity score with the corticosteroid preparation being the most effective. However, only in the gentian violet group did the bacterial density decrease [56]. Mupirocin and fusidic acid have also been used as topical antibiotics in the treatment of *S. aureus* in atopic dermatitis [57]. In a short-term study of 46 patients with atopic eczema, 28 patients were treated with topical 2% fusidic acid and 18 patients were treated with topical 2% mupirocin. Both groups were also given betamethasone 0.1% cream. *S. aureus* was detected in 76% of patients, whereas fusidic acid resistant *S. aureus* was present in 26%. Neither treatment group experienced a change in the resistance pattern to antibiotics, and both groups showed similar significant clinical improvement [58].

Prednisone

Whereas topical corticosteroids are the mainstay for the treatment of atopic dermatitis, occasionally, in severe cases, one must resort to systemic steroids. Unlike asthma where exacerbations are usually time-limited and, therefore, only short bursts of systemic steroids are needed, eczema presents a more difficult problem. Those patients with severe enough eczema to warrant the use of prednisone, frequently require chronic use to control symptoms. Because of the numerous side effects of chronic corticosteroid use, ongoing research has focused on other modes of therapy as steroid sparing agents.

The Dangers of Chronic Corticosteroid Usage

It is important to address the risk benefit ratio of using corticosteroids in treating atopic dermatitis. Fortunately, the percentage of atopic dermatitis patients that would be severe enough to be on systemic steroids is low. The risks of systemic (oral or parental) steroids are well-known and are shown in Table 4. Osteonecrosis of the hip is a common side effect, which is not always recognized in a timely fashion. Any pain in the hip should alert the physician when treating a patient with chronic systemic steroids. Bone densitometry should also be done periodically to monitor for osteoporosis. The patient should also have regular blood pressure checks and ocular examinations.

Immunosuppressive/Immunomodulatory Agents

Pimecrolimus and Tacrolimus

Tacrolimus is the topical form of FK506, which is an immunosuppressive agent with activity similar to cyclosporin A. FK506 also interacts with FK506-binding protein,

Table 4 Examples of the numerous adverse effects and side effects of corticosteroids (this list is not all inclusive)

Adverse effects and side effects of corticosteroids
Hypertension
Glaucoma or cataracts
Diabetes
Cushing's syndrome
Immunosuppression
Osteoporosis
Kidney disease
Peptic ulcers
Depressions
Skin rashes
Photosensitivity
Nausea and vomiting
Hirsutism
Menstrual problems
Easy bruising
Mood swings
Changes in appetite
Weight gain
Additional effects in children
Growth retardation
HPA-axis suppression

a cyclophilin-like cytoplasmic protein. The resulting complex inhibits the calcium binding phosphatase, calcineurin, and interferes with gene transcription. A multicenter double-blind study of 317 children between the ages of 2 and 15 with mild to moderate atopic dermatitis was conducted to compare the safety and efficacy of 0.03% tacrolimus ointment with vehicle ointment. Evaluation of eczema was accomplished using the Investigator's Global Atopic Dermatitis Assessment and the Eczema Area and Severity Index. In addition, the total affected body surface area and patient assessment of itch were assessed. The ointment was applied twice daily over 6 weeks. The tacrolimus treated group had a significantly greater percent improvement from baseline in the EASI score (54.8% vs 20.8%). Improvement in the total body surface area affected also improved. There was no difference in burning or stinging between the two groups. The authors concluded that tacrolimus provides a safe and efficacious alternative to topical corticosteroids in the treatment of atopic dermatitis in children [59]. Pimecrolimus similarly inhibits calcineurin and binds to macrophilin-12 (FKBP-12). Long-term control of atopic dermatitis was demonstrated in an open labeled study of 99 infants with atopic dermatitis with a 1-year double-blind extension. The EASI and tolerability were assessed. The mean decrease in EASI score from baseline in the pimecrolimus treated group was 67.8% at 3 months and 70.8% at 24 months. A 4-week double-blind efficacy study of pimecrolimus in 196 infants showed improvement in the

mean percentage change from baseline in eczema area and severity index of 71.5% compared with only 19.4% in the control group treated with vehicle only. Secondary parameters related to parents quality of life were also significantly improved [60]. A large-scale study of 1,133 infants between 3 and 23 months of age with varying degrees of severity of atopic dermatitis demonstrated that 1% pimecrolimus cream was well-tolerated. There was no associated increase in the overall incidence of skin or systemic viral, bacterial, fungal or parasitic skin infections [61]. Pimecrolimus had low systemic bioavailability when evaluated in 22 infants below 2 years of age. On skin biopsy, pimecrolimus demonstrated a decrease in the extent and severity of lymphocytic and eosinophilic infiltrates. Pimecrolimus reduced expression of the Th2 cytokines, IL-5, IL-10, and IL-13 in both CD4+ and CD8+ cells. Expression of the Th1 cytokine, interferon-gamma, was also reduced [62].

A metaanalysis of 25 randomized trials comparing topical corticosteroids with topical tacrolimus and pimecrolimus revealed that the two therapies were similar in efficacy, and there was no clear conclusion favoring the use of one mode of therapy over the other. As of 2005, over 7 million patients have been treated with either pimecrolimus or tacrolimus, and no systemic immune suppression-related malignancies have been observed [63].

Cyclosporin A

Cyclosporin A is an immunosuppressive agent, which primarily acts on T cells modulating cytokine transcription [64], that is used in the treatment of organ transplantation, rheumatologic [65, 66], and oncologic disorders [67]. As increased IL-5 gene expression has been associated with chronic inflammation in atopic dermatitis [68] and as cyclosporin A has been shown to suppress IL-5 production in mononuclear cells from atopic patients [69], there existed optimism that cyclosporin A would provide an additional therapeutic option in the treatment of severe cases of atopic dermatitis. A study of 15 patients (9 male and 6 female) with severe atopic dermatitis showed significant improvement in clinical disease state after 2 weeks of treatment with cyclosporin A, which was sustained after 10 weeks of treatment. The mean initial dose of cyclosporin was 2.8 mg/kg/day and the maximum dose was 3.3 mg/kg/day; the patients were treated for a mean of 6 months. A comparative trial of oral cyclosporin A and topical tacrolimus in 30 patients who were randomized to one of the two groups reflected effectiveness in SCORAD scores after 42 days of treatment in both groups. However, those treated with tacrolimus had a greater reduction in scores, and safety of the treatments, as assessed by vital signs and hematologic, biochemical, and urinary testing, was similar. Because of the greater potential for side effects in the cyclosporin group and the greater reduction in

SCORAD scores in the tacrolimus group, the authors concluded that tacrolimus is the treatment of choice. A study comparing the cost-effectiveness of cyclosporin A in comparison with UVAB phototherapy demonstrated that cyclosporin A is at least as effective as UVAB phototherapy and is similarly cost-effective. More side effects were noted in the UVAB group. The study was a 1-year open prospective clinical trial conducted in Finland [70]. In view of the current data, cyclosporin A use in atopic dermatitis should be reserved for severe cases that are refractory to more conventional modes of therapy.

Methotrexate

Methotrexate has been widely used in the treatment of psoriasis. Twenty adult patients with atopic dermatitis who were refractory to conventional treatments were given a weekly dose of methotrexate between 7.5 and 25 mg [71]. Endpoint evaluation was the physician's global assessment during 3 months of methotrexate use. Improvement in eczema was observed in 75% of the patients after 3 months of use with responses beginning at 4–8 weeks. However, there were significant side effects, including nausea and elevated liver enzymes.

Azathioprine

A study of 10 adults with severe atopic dermatitis with 0.7 to 2.5 mg/kg/day of azathioprine for 12 months or longer demonstrated marked improvement or complete clearance in 8 patients. One patient developed lymphoma 8 months after cessation of treatment, but otherwise, the drug was well-tolerated, and there were few side effects [72]. A larger double-blind placebo-controlled, crossover trial of 37 patients with severe atopic dermatitis showed that disease scores improved in the azathioprine group compared with the placebo group. Parameters that were improved included pruritus, sleep disturbance, and disruption of work/daytime activity. Unfortunately, 16/37 subjects withdrew, including 12 during azathioprine treatment. In addition, 14 patients developed gastrointestinal disturbance. Leukopenia occurred in two patients and abnormal liver enzymes in eight, indicating that there may be serious safety concerns with the use of azathioprine [73]. Another study of 38 patients showed that atopic dermatitis was controlled in 80% of patients when treated with 25–200 mg of azathioprine [74]. However, safety concerns again dampened enthusiasm. In a study of children with severe atopic dermatitis, pretreatment thiopurine methyltransferase levels helped identify those patients who are at risk for myelosuppression. Ninety-one children had erythrocyte thiopurine methyltransferase assays done, and of these, 48 were selected for treatment with azathioprine [75]. Of these, 38 had an excellent

Table 5 Immunological, cellular, and clinical effects of immunomodulatory agents

Drug	Immunological effects	Clinical effects	Safety	Effectiveness in atopic dermatitis
Infliximab	IgG1 monoclonal antibody against the tumor necrosis factor alpha	Pilot study shows initial, nonsustainable improvement in 9 patients	Not known	Needs further studies
Meclophenolate mofetil	Blocks proliferative responses of T and B lymphocytes, shift in Th1/Th2 balance toward Th1	Improvement in disease severity	Good	Significantly effect in patients treated with meclophenolate mofetil
Cyclosporin A	T cell immunosuppressive agent, suppresses IL-5 gene expression in mononuclear cells from atopic patients	Clinical improvement in SCORAD scores in several studies	Potential for side effects	Significant effect on clinical outcome
Azathioprine	A prodrug metabolized to 6-mercaptopurine which inhibits DNA synthesis, and has is cytotoxic	Clinical improvement in pruritis, sleep disturbance and quality of life	Myelosuppression, liver toxicity	Improved compared to placebo
Methotrexate	Antimetabolite, blocks dihydrofolate reductase, and kills fast growing cells	Improvement in symptom scores in 75% of patients after 3 months	Nausea and elevated liver enzymes	Effective in atopic dermatitis
Phosphodiesterase inhibitors	Suppresses IL4 and IL-5 secretion from Th2 cell lines, inhibits proliferation of peripheral blood mononuclear cells	Cipamfylline was significantly better than placebo, theophylline was not	Not known	Variable
Topical corticosteroids	Inhibition of cytokine gene transcription, breakdown of cytokine mRNA, and inhibition of cytokine receptor synthesis	Multiple studies showing improvement in symptom scores	Topical corticosteroids have low side effects, even in children	Effective
Leflunomide	Inhibitor of de novo pyrimidine synthesis, inhibits T-cell proliferation and B-cell antibody production	Partial remission after 20 months of use	Not known	Needs further studies
Interferon gamma	Affects eosinophil activation	Clinical improvement in a placebo controlled study of 83 patients	Mild	Effective
Pimecrolimus and tacrolimus	Inhibits calcineurin, and interferes with gene transcription	Large double blind placebo controlled studies show significantly greater percent improvement from baseline compared to placebo	Well-tolerated	Provides effective alternative to topical corticosteroids
Intravenous gamma globulin	Increases serum-soluble CD5 levels	Metaanalysis shows overall improvement rate of 61%	Good	Variable findings from multiple studies

response, 13 had a good response, and 7 had a poor response. None of the children developed neutropenia, and it was concluded that patients at low risk for adverse effects of azathioprine can be identified satisfactorily before initiating azathioprine. Whereas these and other studies consistently demonstrate that azathioprine is an effective medication in severe atopic dermatitis, the long-term and short-term side effects have not been completely resolved and further studies are needed [76, 77]. Clinical, cellular and immunological effects of various immunomodulatory agents is shown in Table 5.

Variations of Eczema and their Treatment

Infantile Eczema

When eczema occurs in the young infant, this presents a special problem. It is quite common to see severe eczema occur in infants under 6 months. None of the topical corticosteroid preparations available have been approved by the Food and Drug Administration (FDA) for this age group of patients. The antihistamines desloratadine and cetirizine are approved down to 6 months of life.

Hand Eczema

Hand eczema refers to hand dermatitis with an atopic component. There is no reliable way to clinically distinguish hand eczema from other forms of hand dermatitis, including allergic contact dermatitis, irritant contact dermatitis or dyshydrotic eczema [78]. Topical PUVA (0.1% 8-methoxypsoralen and UVA) was used to treat hand eczema in 17 patients. The duration of treatment was 8 weeks. Over 80% of patients had at least a moderate improvement in symptoms. The results were independent of duration of hand eczema, positive patch test reaction or atopic status [79]. Topical corticosteroids have also been effective in the treatment of hand eczema. A prospective, open, randomized trial examined the use of mometasone furoate fatty cream for a maximum of 9 weeks in 120 patients with chronic hand eczema. Initially, treatment was daily, but after resolution of eczema, the responders were randomized to three groups, receiving either thrice weekly mometasone furoate, twice weekly application or no corticosteroid treatment. Mometasone furoate given daily was found to be initially effective in 50 of 106 randomized patients. All of the subjects were successfully maintained on subsequent intermittent therapy. There were no side effects, leading to the conclusion that intermittent use of topical corticosteroids is effective and safe in patients with hand eczema [80].

Nummular Eczema

The etiology of nummular eczema is unknown. Clinically, it may be indistinguishable from atopic dermatitis, but nummular eczema is not atopic in nature. Treatment of nummular eczema includes antipruritic medications and topical corticosteroids. Coal tar may be useful. As in atopic dermatitis, keeping the skin lubricated helps control symptoms.

Novel Therapeutic Modalities for Eczema

Immunotherapy

Immunotherapy to dust mite has been attempted as a therapeutic modality to treating eczema. In 1992, a study of 24 children who underwent either immunotherapy or placebo treatment over a course of 8 months failed to demonstrate a significant difference between the two groups. However, the numbers were too small to conclusively prove that immunotherapy does not work [81]. At about the same time, Leroy et al. studied the use of *Dermatophagoides pteronyssinus* allergens and autologous specific antibody complexes in treating atopic eczema. They were able to demonstrate between 70% and 83% improvement in symptoms in the treated group only. They

concluded that this is a potentially effective means of treatment of atopic eczema and that exposure to house dust mite is indeed a factor in eczema exacerbations [82, 83]. They subsequently showed that the same effect can be achieved by preparing complexes of *D. pteronyssinus* antibodies and the F(ab)₂ fragment of specific antibodies instead of whole antibody molecules [84]. A more recent study of 89 adults with chronic atopic dermatitis, a SCORAD score greater than or equal to 40, and a positive skin prick sensitivity to dust mite was conducted in which the subjects were randomized to either a placebo group or one of three groups receiving immunotherapy with maintenance doses of house dust mite extract of 20, 2,000, and 20,000 per week for 1 year. After a year, there was a dose-dependent increase in reduction in SCORAD scores in the groups receiving immunotherapy. The use of topical corticosteroids was also reduced in the groups receiving immunotherapy, leading the authors to speculate that specific immunotherapy can be an effective adjunct therapy in selected patients with atopic dermatitis [85].

Sublingual Immunotherapy

A total of 35 patients with atopic dermatitis were recruited to receive sublingual immunotherapy for 36 months. All subjects had initial eczema scores between 1 and 3 (on a scale of 0–4). Effectiveness was gauged by complete resolution (a symptom score of 0). The subjects were divided into two groups, one with no respiratory allergic symptoms and one with mild asthma and/or rhinitis. Overall effectiveness of sublingual immunotherapy was 68.8% after 24 months in the first group and 73.7 % in the second group. There were no life-threatening reactions to the immunotherapy [86].

Monoclonal Anti-IgE Therapy

Omalizumab is a humanized murine monoclonal antibody that binds to IgE. It has been suggested that omalizumab may present a potentially valuable therapy in patients with atopic eczema who have elevated IgE levels. Only pilot studies on small numbers of patients have been conducted with mixed results [87, 88].

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) has been used in a number of immune disorders, including autoimmune thrombocytopenia (ITP), primary immunodeficiencies, and Kawasaki disease. The use of IVIG in atopic dermatitis has been extensively studied, but the results have been inconsistent. A metaanalysis of studies done between 1966 and 2001 identified 32 reports of IVIG being used

to treat atopic dermatitis. The overall improvement rate was 61%. Children were more likely to respond than adults and the duration of response was also longer [89]. In 2001, a study of 40 patients with atopic dermatitis showed that IVIG therapy increased serum-soluble CD5 levels. Clinical severity scores improved as well by day 21 of therapy [90]. A small study of 10 patients were randomized to receive IVIG at 2 g/kg either immediately or delayed by 1 month [91]. Atopic dermatitis was evaluated by SCORAD index at day 30. There was no significant difference in SCORAD scores in either of the two groups at 30 and 60 days. Another study evaluated the effects of IVIG administered over a period of 3 months in five children (age 7–12 months) with atopic dermatitis [92]. Parameters studied included serum interleukin-2 levels, intercellular adhesion molecule-1 (ICAM-1), endothelial leukocyte adhesion molecule (ELAM-1), and eosinophil cationic protein (ECP). Clinical severity of atopic dermatitis was also monitored. Results showed a reduction in all inflammatory markers and SCORAD indices. In comparison, a control group of seven patients who only received topical corticosteroid therapy had no changes in these markers. IVIG therapy did not change the Th1/Th2 ratio in either group, although the atopic dermatitis children had elevated Th1/Th2 ratios and decreased Th2 cells to begin with.

A study of 41 steroid-resistant atopic dermatitis patients treated with 500 mg/kg of IVIG (maximum 15 g) showed a variable response [93]. About a third of the patients showed a significant response, another third showed a mild response, whereas the remainder showed no response at all. Eosinophil counts and serum IgE levels were reduced only in the significant responder group. A study of ten patients, one with hyper-IgE syndrome and nine with atopic dermatitis were given IVIG as a 10% solution at a dose of 2 g/kg per 30 days for seven infusions. Average prednisone dose dropped from 6.8 to 5.1 mg/kg and skin disease improved slightly in 6 patients. This study did not show a significant benefit of IVIG in atopic dermatitis. Further studies need to be done to characterize the response of patients with atopic dermatitis to IVIG therapy.

Doxepin

The use of topical doxepin as an antipruritic in atopic eczema was studied in 270 patients randomly selected to receive either medication or the vehicle cream only. Whereas there was a significant placebo effect, relief of pruritus was achieved in over 80% of the doxepin-treated group. Physician evaluated relief and severity of eczema was also significantly better in the doxepin-treated group. Side effects were minor and local, and included burning or stinging [94]. Doxepin hydrochloride 5% cream was also useful in treating pruritus in patients with other forms of

eczematous dermatitis, such as lichen simplex chronicus, nummular eczema or contact dermatitis [95].

Mecophenolate Mofetil

Mycophenolate mofetil blocks the proliferative responses of T and B lymphocytes. It has been successfully used as an immunosuppressive agent in renal transplantation [96]. A small study of 10 patients with severe atopic eczema were treated successfully with 1 g daily during the first week and 2 g daily for 11 subsequent weeks with oral mycophenolate mofetil. Median scores for disease severity improved by 68% in patients treated with mycophenolate mofetil over baseline levels. Serum IgE levels also decreased, from an average of 10,300 to 7,830 kU/l. There was also a significant increase in interferon-gamma (a Th-1 related cytokine) and a significant decrease in IL-10 (a Th-2 related cytokine) [97]. A further pilot study showed that mycophenolate mofetil was effective in treating severe atopic dermatitis and was generally well-tolerated. In this study, severity of atopic dermatitis as measured by subjective SCORAD index improved by 74% in those patients treated with mycophenolate mofetil [98].

Leflunomide

Leflunomide is an immunosuppressive agent, which acts as an inhibitor of de novo pyrimidine synthesis. Lymphocytes are primarily affected because of their need for both salvage and de novo pathways. Leflunomide inhibits T cell proliferation and B cell antibody production. Using an in vivo murine model, leflunomide downregulates the production of total and allergen-specific IgE [99]. Leflunomide was clinically able to inhibit the production of immediate cutaneous hypersensitivity responses to allergen challenge in mice. Downregulation of IgG1 and IgG2a in serum was also observed. A clinical study of two patients with recalcitrant severe atopic dermatitis with leflunomide over a 20-month period showed partial remission which persisted after cessation of drug dosing. Whereas no conclusions can be made from this anecdotal report, it suggests that further studies are indicated to evaluate the safety and efficacy of leflunomide in the treatment of atopic dermatitis [100].

Phosphodiesterase Inhibitors

Atopic dermatitis is characterized by high cyclic-AMP phosphodiesterase activity. A potent type 4-phosphodiesterase inhibitor, CP80,633 was studied for clinical and in vitro antiinflammatory effects in atopic dermatitis. Leukocyte enzyme activity was evaluated by radioenzyme activity, and IL-10, IL-4, and prostaglandin E-2 activities were measured

in 24-h culture supernatants of mononuclear leukocytes using immunoassay. Clinical effects were measured after the topical application of phosphodiesterase inhibitor and compared with placebo in a double-blind study. Improvement in multiple clinical parameters of atopic dermatitis were noted in the active drug group. Phosphodiesterase inhibitors showed immunomodulatory and antiinflammatory effects *in vitro* [101]. A randomized double-blind study of cipamfylline, a new and potent inhibitor of phosphodiesterase-4, compared its effectiveness in the treatment of atopic dermatitis with that of vehicle and hydrocortisone 17-butyrate 0.1% cream. The length of treatment was 14 days and response was gauged using a total severity score. The results showed that whereas cipamfylline was significantly more effective than vehicle alone, it was significantly less effective than the topical corticosteroid [102].

Papaverine and Theophylline

Papaverine is a phosphodiesterase inhibitor, which has been reported anecdotally to have beneficial effects in the treatment of eczema. However, a double-blind placebo-controlled trial showed no significant differences between the use of papaverine or placebo in terms of both physician-evaluation and patient-reported parameters [103]. Other studies have also not shown papaverine to have significant clinical benefits in eczema [104, 105]. Theophylline is another phosphodiesterase inhibitor, which suppresses the secretion of IL-4 and IL-5 from human Th-2 cell lines and also inhibits the proliferation of peripheral blood mononuclear cells [106]. Theophylline-sensitive suppressor cell numbers were reduced in atopic eczema patients. Preincubation of normal lymphocytes with aminophylline enhanced proliferative responses to pokeweed mitogen, whereas incubation with lymphocytes from atopic dermatitis patients produced an opposite effect [107]. In spite of the theoretical advantages of theophylline, there is a paucity of studies showing the clinical effectiveness of theophylline in the treatment of atopic eczema.

IFN-Gamma

The distortion of the balance of Th1 and Th2 helper type immunity may play a significant role in the development of atopic disease, including atopic dermatitis. Neopterin is released by human monocytes and macrophages upon stimulation by the Th1-cytokine interferon-gamma. Urinary and cord blood neopterin can potentially be a marker for Th1 activity. A study of 505 infants born between 1997 and 1999 were enrolled and their cord blood neopterin concentration was obtained. The children were followed-up until 6 years of age, and at that point, the prevalence of atopic disease was 31%. The authors found no correlation

between cord blood and urinary concentration of neopterin. However, urinary neopterin concentrations were significantly lower in the children with a family history of atopic disease [108]. Children with atopic dermatitis were found to have lower spontaneous production of the regulatory cytokines IL-10, interferon-gamma, and tumor necrosis factor-alpha. The children with atopic dermatitis also had attenuated IL-10 responses to stimuli by a variety of infectious agents and allergenic proteins, including food allergens, intestinal flora, skin flora, and vaccines. It is interesting to note that dust mite did not fall into this pattern. However, the Th2 cytokines IL-5 and IL-13 responses to house dust mite were more frequent in patients with atopic dermatitis. The authors concluded that the increased Th2 response to aeroallergens (house dust mite) in children with atopic dermatitis was coupled with a decrease in Th1-type cytokine response to other environmental stimuli. A clinical study of 14 patients with severe atopic dermatitis treated with recombinant interferon-gamma for 6 weeks showed marked improvement in clinical symptoms and signs in 8 of the 14 patients [109]. Four patients had continued improvement even after cessation of therapy. A placebo-controlled study of 83 patients with atopic dermatitis demonstrated that interferon-gamma was successful in improving the clinical status of atopic dermatitis and eosinophilia. Subjects were treated with either 50 µg/m² recombinant interferon-gamma or placebo by daily subcutaneous injection for 12 weeks. Parameters evaluated included both physician and patient overall responses, body surface area improvement, laboratory parameters, and clinical severity scores. In the treated group, 45% of treated subjects had a greater than 50% improvement in physician's overall evaluations in contrast to 21% in the placebo group. There were also improvements in erythema, excoriations and erosions, and in peripheral blood eosinophil count. Side effects noted included headaches, myalgias, chills, granulocytopenia, and elevated serum transaminases [110].

Infliximab

Infliximab is a chimeric IgG1 monoclonal antibody to the Th1 cytokine, tumor necrosis factor-alpha. Infliximab has been studied in the treatment of Th1-type diseases, such as rheumatoid arthritis or psoriasis. In some cases, infliximab has actually been associated with the emergence of atopic dermatitis, presumably by downregulation of Th1 cytokines and disruption of the Th1–Th2 balance [111]. On the other hand, a trial of infliximab in nine patients with severe, recalcitrant atopic dermatitis showed initial improvement, although it was not sustained throughout the entire 46-week study period. Whereas this study was not placebo-controlled or blinded, it suggests that further investigation may

be warranted to clarify if infliximab improves or causes atopic dermatitis and to elucidate the mechanism of action of whatever effect is found [112].

Alternative and Complementary Medicine Techniques for Treating Eczema

The use of alternative and complementary medicine is widespread in the Western Hemisphere [113]. These measures include homeopathy, dietary supplements, biofeedback, relaxation training, massages, acupuncture, and hypnosis. Whereas it is often assumed by health care practitioners and patients alike that these measures are at the very least, harmless, this may not be universally true. Most of these modalities have not been subject to the rigors of scientific testing and clinical trials [114]. Because they frequently are not marketed as “drugs”, they do not fall under the auspices of regulatory agencies such as the Food and Drug Administration in the United States or its foreign equivalents. It is important to realize that some of these measures carry risks.

Probiotics and Eczema

Probiotics are preparations containing microbial cells or components of microbial cells. These products are thought to be of benefit to overall human health. When administered concomitantly with breast-feeding, probiotics may confer additional protection against atopic dermatitis. In 62 breast-fed mother–infant pairs studied, the incidence of eczema was significantly reduced in those mothers who consumed probiotics over placebo (15% vs 47%). The effect was most significant in those infants with elevated cord blood IgE, and the immunomodulatory effect was illustrated by an approximately twofold increase in transforming growth factor beta 2 in breast milk [115]. The study was extended to 4 years of age, and the protective effect of the probiotic *Lactobacillus rhamnosus* was persistent [116].

Dietary Supplements and Dietary Manipulation

Obviously, what we ingest has a great deal to do with this. In addition to our daily diet, consumers now use a myriad of vitamins, minerals, supplements, and other cofactors. With or without scientific evidence, taking supplements has been utilized as a way to fight off almost any conceivable type of illness, including heart disease, asthma, infection, neoplasms, allergic disorders, and rheumatologic conditions. The case is no different for atopic dermatitis.

Fish Oil

It has been postulated that there is a role of antiinflammatory *n*-3 polyunsaturated fatty acids in preventing atopic derma-

titis or asthma in early life. In one double-blind study of atopic pregnant women, subjects were given either fish oil capsules or placebo between 20 weeks of gestation and childbirth. Cord blood was analyzed for CD34+ cell expression of various cytokines. The infants were reassessed at 1 year of age for atopic disease and skin tests. The authors found that the proportion of CD34+ cells increased in the *n*-3 PUFA group compared with placebo [117]. There were also more IL-5 responsive cord blood eosinophil/basophil colony-forming units in the fish oil group. The study demonstrated that fish oil supplementation altered neonatal progenitors at birth in infants at risk for atopy. An earlier study demonstrated that maternal dietary supplementation with fish oil during pregnancy led to higher *n*-3 PUFAs in neonatal erythrocyte membranes in the treated group compared to the placebo group [118]. Infants in the fish oil group were evaluated by skin testing at 1 year of age, they were found to be three times less likely to be positive to egg. The frequency of atopic disease in the two groups was not different, but the fish oil group had less severe disease. Another study evaluating the effect of fish oil on neonatal cytokines found an inverse relationship between levels of *n*-3 PUFAs in neonatal cell membranes and plasma IL-13 [119].

Evening Primrose Oil

The association of low essential fatty acid levels and reduced levels of delta-6-desaturase metabolites of linoleic acid in atopic eczema patients suggested the use of evening primrose oil in the treatment of this disease. Evening primrose oil or Efamol contains these metabolites and its efficacy was studied in 24 children who were divided into two groups receiving either Efamol or olive oil as a placebo. The authors noted significant improvement in clinical status after 4 weeks of treatment in the essential fatty acid group over placebo. Fatty acid composition in plasma, neutrophil, and lymphocyte was also studied. Plasma fatty acid composition was affected but not neutrophil or lymphocyte composition [120]. On the other hand, an earlier study did not show any significant improvement in eczema in 123 patients who received oral doses of primrose oil (children received 2–4 gm/day, whereas adults received 6–8 g/day) [121].

Borage Oil

Borage oil has a higher percentage of gamma-linolenic acid than primrose oil. However, a study of 160 patients randomized to receive either 500 mg of borage oil-containing capsules per day or bland lipid miglyol as a placebo over a period of 24 weeks failed to demonstrate any significant difference in overall response, although several clinical symptoms did improve with borage oil [122]. This study confirmed earlier

negative results associated with the use of borage oil in atopic eczema [123] and it was further established that borage oil has no beneficial effect in atopic dermatitis in a subsequent study in 2003, which showed that 920 mg/day of gamma linolenic acid in adults and 460 mg/day in children over 12 weeks had no significant effect on atopic dermatitis scores, topical corticosteroid requirement, global assessment of response by subjects, and adverse events and tolerability [124].

Pyridoxine

A report of the benefit of pyridoxine in atopic eczema [125] prompted investigators to examine the effect on 50 mg of pyridoxine hydrochloride on clinical severity scores in eczema. Investigator examination and subject reports were reviewed in children randomized to receive either pyridoxine hydrochloride or a placebo in a double-blind placebo-controlled trial. There was no significant difference in all parameters at the end of the study [126].

Vitamins C and E

Naturally occurring antioxidants include vitamins C and E, selenium, and β -carotene. Selenium intake in adults has been associated with a reduced asthma rate. Vitamins C and E are associated with positive health effects. A study seeking to establish a connection between maternal diet consumption of these vitamins, breast milk composition, and risk of atopy during the first year of life was conducted [127]. Mother and infant pairings were analyzed for skin prick reactivity during the perinatal period and at 12 months of age, respectively. The results showed a link between maternal intake of vitamin C in diet (but not as supplement) and the concentration of vitamin C in breast milk. Concentration of vitamin C in turn was inversely related to the risk of developing skin prick reactivity in the infant. There was no such association with alpha-tocopherol. In a prospective study of 2,000 healthy, pregnant women, maternal dietary records were analyzed for intake of vitamins C and E during pregnancy and correlated with risk of atopy during the first 2 years of life. The authors found no association between maternal dietary vitamins C and E intake and wheezing or eczema in the first year of life, but in the second year of life there was a paradoxical pattern. There was a negative association between vitamin E intake and wheeze in the absence of a cold, and also a negative association between vitamin E intake and eczema in those mothers who were atopic. However, there was a positive association between vitamin C intake and wheeze and eczema in the second year of life.

A placebo-controlled single-blind clinical study of the effect of vitamin E versus placebo on subjective symptoms of atopic dermatitis and serum IgE levels was conducted on 96

subjects with atopic dermatitis [128]. Of the subjects, 50 were given vitamin E orally and 46 were given placebo for a period of 8 months. RAST, antinuclear antibody (ANA) levels, serum IgE levels, and a complete blood count were obtained every 15 days during the course of the study. Subjective clinical status was monitored by a questionnaire administered at 8 months. Results showed that a greater proportion of subjects in the vitamin E-treated group experienced a significant improvement compared to the placebo group (23 subjects vs 1). In seven of the subjects in the vitamin E group, there was complete remission. None of the patients in the control group had complete remission. Serum IgE levels decreased by 62% in the vitamin E treated group and by only 34% in the placebo group. Patients reported improvements in lichenification, facial erythema, and appearance of normal skin. In contrast, a study of the effects of a 12-week period of supplementation with 600 μ g/day of selenium and 600 IU/day of vitamin E or 600 μ g/d of selenium alone compared with placebo showed no improvement in severity of atopic dermatitis in 60 adults [129]. It appears that although antioxidant intake can modulate atopic disease, the mechanism by which this occurs is still a mystery. Further studies are warranted to clarify this effect.

Zinc Supplementation

Zinc is a cofactor required for the biological activity of a number of immunomodulatory agents. It is an antiinflammatory antioxidant, which can reduce IL-1 beta, tumor necrosis factor (TNF), and IL-6 secretion. Zinc has been found to restore interferon-alpha levels in the elderly to the levels comparable to younger subjects [130]. Studies on the effect of dietary zinc supplementation on atopic dermatitis have yielded mixed results. It has been demonstrated that children with atopic dermatitis had lower serum levels of zinc [131, 132]. The clinical significance of this observation is not known. Another study showed that an increase in dietary zinc, calcium, retinol along with probiotics reduced the incidence of eczema [133]. The study did not separate out the effects of the individual components. Increased ascorbic acid intake had the opposite effect. This beneficial effect of zinc in the diet was not supported by a double-blind placebo-controlled study of 50 children between the ages of 1 and 16 who had eczema. In this study, zinc had no effect on surface area affected, symptoms scores of itch, degree of erythema, effects on sleep, and the amount of topical therapy used [134].

Homeopathic Medicine

Eczema is one of the most common conditions in which homeopathy is used, despite the lack of evidence supporting its use. At this time, there is no place for homeopathy in the treatment of eczema [135, 136].

Chinese Herbal Therapy

Chinese herbal medicines have been around for centuries. They have been passed down from one generation to the next and have provided relief in many diseases throughout history. There have been little or no studies to determine the exact composition of these herbal preparations. Only recently has this been brought to the foreground, in part because of the extensive use of alternative and complementary medicine by the Western world. However, some components in Chinese herbal medicines are similar to those used in Western medicine. The most well-known example of this is the use of Ma Huang to treat asthma. The active ingredient in Ma Huang is actually ephedrae, a precursor of the stimulant and bronchodilator ephedrine. This phenomenon has also been observed in atopic dermatitis. Chinese herbal medications can be effective in treating atopic dermatitis. An example of such an herbal preparation is Yunbutang. Yunbutang has been found to have inhibitory effects on mast cell-dependent immediate-type allergic reactions. Effects of Yunbutang include inhibition of histamine release from mast cells activated by compound 48/80, inhibition of antidinitrophenyl IgE antibody-induced passive cutaneous anaphylaxis reaction, and inhibition of tumor necrosis factor secretion from stimulated mast cells. Another study of 47 children showed that treatment with a standardized formulation of Chinese herbal therapy was more effective than placebo. After 1 year of treatment, 18 children showed a 90% or greater reduction in eczema scores. Seven were able to discontinue treatment without relapse [137, 138]. Liver enzyme elevation was observed in two of the children. The active ingredient is unknown, but again, may have antimicrobial, antiinflammatory or corticosteroid-like activity. Indeed, a separate study of 11 Chinese herbal creams used in the treatment of atopic dermatitis showed that eight contained measurable amounts of dexamethasone. The range of concentrations was from 64 to 1,500 µg/g of cream, with a mean of 456 µg/g [139]. By comparison, triamcinolone acetonide, a commonly used topical corticosteroid, is commonly applied at a concentration of 0.1% or 1,000 µg/g of cream.

Acupuncture

Whereas acupuncture has been used in the treatment of allergic rhinitis and asthma, there is a lack of well-designed clinical studies examining the effectiveness of these measures. In atopic dermatitis, there is nothing in the literature to support the use of acupuncture as a treatment modality.

Biofeedback, Massage Therapy, and Hypnotherapy

The issue of whether stress exacerbates atopic dermatitis is not known. It is particularly difficult to conduct studies of this

type because of the lack of objective measurements of stress levels. Typical stressors may include trauma and abuse, major life events, work and personal relationships, and illness, but individuals react to stressors differently. Stress may also lead to a failure of conventional methods of therapy, such as in the form of a glucocorticoid resistance. As a result, various psychological interventions and alternative medicine techniques have been used to treat patients with allergic diseases. These measures have also been specifically attempted in atopic dermatitis patients but the studies conducted were small and in most cases, lacked a control group [140–142]. Large-scale studies must be designed and conducted to demonstrate not only effectiveness, but also the safety of these measures.

Prognosis

The Natural History of the Disease

The prognosis of atopic dermatitis is unpredictable. In children who develop atopic dermatitis early, there is often clearing within the first few years of life, but atopy frequently persists in the form of asthma or allergic rhinoconjunctivitis. Children with severe atopic dermatitis tend to have high levels of serum IgE. Positive skin prick tests were present early on in 47% of children with atopic dermatitis; the prevalence increased to 100% in subsequent testing of those children with severe disease.

Patient Resources

With the advent of the Internet, patients are able to obtain a great deal of medical information. It is important for patients with a chronic disease such as eczema to understand the nature of the disease, what the triggers are for exacerbation, and the treatment options. Physicians and other health care providers should provide patients literature and a detailed written management plan. Frequent monitoring of disease course should be implemented and

Table 6 Web-based resources on atopic dermatitis for the professional and the patient

Web-based resources on atopic dermatitis	
National Eczema Society	http://www.eczema.org
American Academy of Dermatology	http://www.aad.org
American Academy of Allergy, Asthma and Immunology	http://www.aaaai.org
American College of Allergy, Asthma and Immunology	http://www.acaai.org
National Eczema Association	http://www.nationaleczema.org/home.html

treatment should be adjusted accordingly. A list of web-based resources on atopic dermatitis is shown in Table 6.

Conclusions

Topical corticosteroids have been the gold standard for the treatment of atopic dermatitis for many decades. The emergence of the immunomodulatory drugs tacrolimus and pimecrolimus represented the first major advance in the treatment of this disease in 40 years. Numerous other therapeutic modalities have been studied and whereas some have been found to have beneficial effects, none have exceeded the efficacy of topical corticosteroids. Less severe forms of eczema are generally treated successfully with topical steroids or immunomodulatory drugs, however, steroid-resistant eczema presents a problem because most of the other adjunctive treatments do not completely resolve the condition. In addition to pharmacologic agents, environmental management and the use of moisturizers are important aspects of the overall care of atopic dermatitis. For this reason, patients need to be educated on skin care and written instructions provided, as there are such a variety of products available for purchase in pharmacies and grocery stores. As we understand more about the mechanism and pathogenesis of atopic dermatitis, including the roles of Th1–Th2 balance, regulatory and stimulatory cytokines, and genetic influences, the prospects of being able to control atopic dermatitis are promising. As to which new treatment will bring significant advances in the treatment of eczema, current studies have not yet identified such a product. As shown above, numerous trials and studies have been conducted on agents that theoretically should provide relief in this chronic condition. Until a cure for atopic dermatitis is found, management of the disease should be focused on reducing associated morbidity and improving patient's quality of life. Morbidity issues include infection, chronic scarring, and associated atopic illness. Quality of life issues include effects of the disease on the patient's personal and professional life, including lack of sleep, changes in mental disposition, discomfort, inability to concentrate or function, and many others. Reducing symptoms results in improvement in quality of life [143].

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