NCC Pediatrics Continuity Clinic Curriculum: **Atopic Dermatitis**

Pre-Meeting Preparation:

Please read/review the following enclosures:

- "Atopic Dermatitis and Ichthyosis" *(PIR 2010)*
- "Mechanisms of Atopic Disease" *(cartoons from NEJM 2011)*
- "Treatment of Atopic Dermatitis":
  - Atopic Dermatitis Action Plan
  - Prescribing Tips: Steroids & Moisturizers on Formulary, FTUs
  - Home Remedies: ("Management of Atopic Dermatitis" Pediatrics, 2008)

Conference Agenda:

- *Review* Atopic Dermatitis Quiz
- Complete Atopic Dermatitis Cases
- Round table: Compare moisturizers and topical corticosteroids on formulary. **Discuss potential benefits and drawbacks.** **Samples will be provided**
- Optional Video: http://www.nationaleczema.org/videos/video-starting-scratch

Post-Conference: *Board Review Q&A*

Extra-Credit:

- "Management of Atopic Dermatitis in the Pediatric Population" (Pediatrics, 2008)
- "Effects of Early Nutritional Interventions on the Development of Atopic Disease . . ." (2008)
- "Complementary, Holistic, and Integrative Medicine: Atopic Dermatitis" (PIR, 2007)
- **Resources for Patients/Parents:**
  - http://www.nationaleczema.org (educational videos, support group, etc.)
  - http://www.skincarephysicians.com/eczemanet/index.html (AAD)

Atopic Dermatitis and Ichthyosis

Roselyn E. Epps, MD*

Author Disclosure
Dr Epps has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

After completing this article, readers should be able to:

1. Identify the characteristic features of atopic dermatitis and the factors that worsen it.
2. Understand that children who have atopic dermatitis are prone to recurrent infections, particularly with *Staphylococcus aureus* and herpes simplex virus.
3. Know the signs of Wiskott-Aldrich syndrome.
4. Plan the appropriate treatment of atopic dermatitis (emollients, corticosteroids, antibiotics, and allergen elimination when appropriate).
5. Recognize ichthyosis vulgaris and know that ichthyosis commonly occurs in children who have atopic dermatitis.
6. List the effective therapies in the management of ichthyosis vulgaris.
7. Distinguish between tinea pedis and atopic dermatitis.
8. Discuss the relationship of atopic dermatitis and food allergies and how to evaluate a patient who has both.
9. Explain why children who have one component of atopy syndrome (allergic rhinitis, asthma, atopic dermatitis) have a threefold greater risk of developing a second component.

Atopic Dermatitis

Atopic dermatitis (AD) is a chronic, relapsing dermatosis that features dry skin (xerosis), pruritus, and a personal or family history of eczema, allergic rhinitis or allergies, or asthma. Children who have one component of the atopic triad (AD, asthma, allergic rhinitis) are three times as likely to develop a second component. There is no sex predilection, and the onset frequently is in infancy. Although many affected children outgrow the condition by age 5 years, AD may persist into adolescence and adulthood. A smaller percentage of patients experience the onset of AD as older children or in adulthood.

The incidence and prevalence of AD have increased in the United States and worldwide, particularly in developed nations. Fewer than 10% of children were affected in the 1970s, but recent epidemiologic studies estimate that 15% to 20% of children are diagnosed with AD. The reason for the increased rate is unknown. The "hygiene hypothesis" proposes that decreased exposure to infectious and biologic antigens may result in an increased response to environmental antigens or perhaps to decreased immune suppression. Additional research must be conducted to determine the reasons for the increased prevalence and to address the trend.

Pathophysiology

Manifestations of AD are believed to be due to the interaction of certain genes, the environment, and immunologic response to the environment and specific trigger factors. Patients who have AD may be considered to have systemic changes, not just manifestations in the skin. Susceptible individuals can react to internal and environmental triggers in certain target organs, not only resulting in skin eruptions, but also in asthma and allergic rhinitis. Patients may exhibit extrinsic immunoglobulin E (IgE)-mediated sensitization due to external antigens, with allergenic signs and elevated allergen-specific IgE, or intrinsic sensitization, without IgE-mediated sensitization.

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In acute AD lesions, T-helper 2 (TH2) cells are present in larger numbers than normal and have increased expression of specific cytokines that, in turn, stimulate B cells to produce IgE, resulting in peripheral eosinophilia. Cytokines and chemokines are released from cells in the skin, attracting other inflammatory cells and producing inflammatory mediators and reactions. Keratinocytes, Langerhans cells, endothelial cells, monocyte-macrophages, and eosinophils all play roles in the acute and chronic inflammation of AD.

Clinical Manifestations

Generally, the primary lesion is a red, rough, poorly defined dry papule or plaque. Scaling may be seen. There is no central clearing. In children of color or deep pigmentation, plaques can be papular or follicular, especially on the trunk or over the extensor areas of joints.

AD is diagnosed clinically and manifests particular patterns at different ages. Frequently, infants present with rough patches or plaques on the cheeks, the dorsa of the wrists, the ankles, and the lateral extremities. The perioral and diaper areas customarily are spared. After infancy, children develop flexural involvement, and the cheek areas improve. The neck, antecubital and popliteal fossae, and gluteal folds frequently are involved (Fig. 1).

Teenagers are more likely to experience eyelid eruptions. With age, the hands and feet also become more problematic, and AD may present as dyshidrotic eruptions. Any part of the body, from the scalp to the soles and including the lips and genitalia, may be affected at any age. Eruptions occur whether or not an offending factor or trigger is identified. Exacerbations and remissions are common and to be expected.

Secondary skin changes occur frequently. Oozing, weeping, and crust formation can develop, which may represent secondary infection. Hyperpigmentation as well as hypopigmentation and depigmentation (loss of pigmentation) can occur. Normal color of the skin usually returns when the signs and symptoms of AD resolve. Weeks to months may be required for the hyperpigmentation and hypopigmentation to resolve. If excoriations are deep or the inflammation is severe, scarring or depigmentation can be permanent.

Lichenification, a hallmark of AD, is thickening and accentuation of skin markings due to chronic scratching. Lichenified skin on the hands and feet is more likely to fissure. Excoriations are common, and some patients create erosions and deeper wounds by unrelenting, intense, repeated trauma. Repeated friction and trauma promote inflammation and trigger inflammatory reactions and pathways in affected skin. Lichenification also may occur in other dermatologic conditions that feature chronic scratching and pruritus.

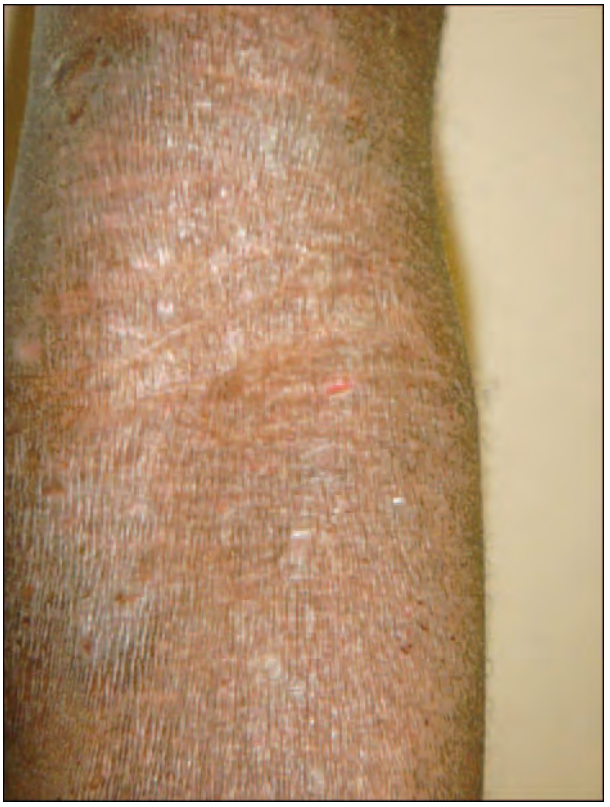

Figure 1. Atopic dermatitis often involves the antecubital fossa. Lichenification and excoriations are evident in this example.

Friction on the skin and scratching the skin are known to exacerbate pruritus and can initiate the "itch-scratch cycle," in which the child scratches, itching in the involved area increases, the child continues to scratch, and the cycle continues. Plaques, papules, and nodules can result because of the escalating "itch-scratch cycle."

Secondary Infection

Patients who have AD are more likely to develop skin and possibly systemic infections. One reason superinfection occurs more easily is due to altered skin barrier function, including apparent and imperceptible excoriations, fissures, and skin defects (Fig. 2). For patients who have AD, seemingly uninvolved skin is not normal. In addition to greater irritancy and dryness, there are immunologic differences in the type of TH2 cells and an increase in the number of TH2 cells within the skin. *Staphylococcus aureus* is an important cause of superinfection. *S aureus* colonization by age 6 months, with frequent

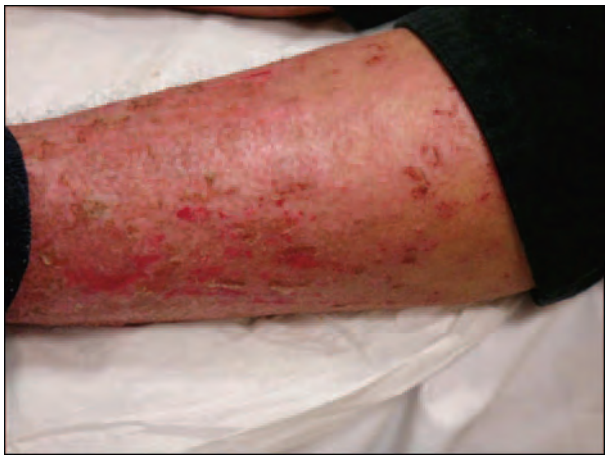

Figure 2. Atopic dermatitis of this leg shows erythema, excoriations, and scaling consistent with superinfection.

colonization during the first year after birth, is associated with an increased prevalence and severity of AD. Impaired skin barrier function, a defective host immune response, and increased synthesis of extracellular matrix adhesion substances promote *S aureus* colonization.

Exotoxins secreted by *S aureus* penetrate the skin barrier and stimulate T cells and antigen-presenting cells, thereby exacerbating and contributing to persistent skin inflammation. *S aureus* overgrowth and superinfection can result in flares, impetigo, folliculitis, cellulitis, abscesses, bacteremia, and sepsis. Methicillin-resistant *S aureus*, now more common in the community, can be particularly problematic for patients who have AD and their families. The patient's infection must be treated, and treating the family may be necessary to minimize the risk of AD exacerbation in the patient. The clinician should consider culturing the atopic patient who is febrile, is unresponsive to therapy, or shows an inadequate response to maximized treatment that includes antibiotic therapy. Other bacteria also may be cultured from the AD patient's wounds and should be treated accordingly.

Although patients who have AD develop bacterial infections, they also may acquire viral and fungal infections. Eczema herpeticum occurs when AD is superinfected with a herpesvirus, either herpes simplex virus or varicella-zoster virus. Vesicles develop on affected and apparently unaffected skin and can be very painful. When disseminated, there may be associated viremia, fever, and lymphadenopathy, and patients can become very ill. Ocular involvement may occur innocuously when the patient rubs his or her eyes. Acyclovir should be administered intravenously in critical disseminated infections or orally for localized, recurrent infections in patients who have AD. If herpesvirus infection involves the eye or periocular area, ophthalmology consultation is essential to manage herpes keratitis and to prevent permanent loss of vision.

Dermatophytes and yeast also can superinfect the skin. Patients who have AD can develop tinea capitis and tinea pedis, and it can be difficult at times to distinguish AD from tinea infection because both may involve pruritus, scaling, and inflammation. On physical examination, unlike AD, tinea pedis frequently develops in the toe web spaces (particularly the third and fourth). Tinea lesions frequently feature expanding plaques with central clearing and peripheral papules and scale. Potassium hydroxide slide examination of a sample taken from the skin from any affected body area, including the skin, the scalp, and hair, can help make the diagnosis.

Allergy and Environment

Allergic contact dermatitis can exacerbate AD. Common contact triggers include fragrances and preservatives in personal care products such as soaps, cleansers, shampoos, detergents, and certain emollients. Among other materials and substances that commonly elicit symptoms of allergic contact dermatitis are wool, nickel, synthetics, dyes, and rubber.

Physical and environmental factors also can play a role. Temperature changes between cold and hot environments (as when moving from an air conditioned enclosure to hot outdoor weather) or change of season can be problematic. Some children prefer warm or cool temperatures. Therefore, their dermatitis is milder in the summer or winter, respectively. Other environmental variables such as dust and mites, pollen, and ambient humidity can have an impact. Because sweating can produce pruritus and skin eruptions for some patients, treatment of AD may require modifying exercise regimens. Clothing tags, coarse fabrics, snug clothing, and footwear can worsen symptoms in a localized distribution. Emotional factors such as stress, anger, sleepiness, and boredom often increase pruritus.

The role of foods in causing AD can be significant for some children; food allergies can be present in up to 40% of patients who have AD. Symptoms include pruritus, urticaria, contact dermatitis, and exacerbation of AD as well as wheezing, asthma, and anaphylaxis. The symptoms can be immediate or delayed. Among the leading allergenic foods are milk and dairy products, eggs, wheat, soy, and peanuts. Some children outgrow allergies to particular foods, but peanuts and eggs are often the exception. Although some foods are difficult to avoid, the improved availability of nutritional information, di-

etary counseling, and food labeling helps families make proper dietary choices for children who have food allergies.

Allergy skin prick testing usually is more reliable after age 2 years; specific radioallergosorbent testing can be performed in infancy. The patient must not take oral antihistamines or steroid medications for several days before skin prick allergy testing; AD should be controlled as much as possible to allow proper evaluation while minimizing patient discomfort. Avoidance of allergenic substances identified by allergy testing occasionally benefits the patient who has AD, but AD can be exacerbated by unrelated factors while allergies are present. Allergy testing may be repeated and expanded if the patient does not improve after avoidance therapy.

Management

Treatment of AD requires a coordinated plan aimed at moisturizing dry skin, decreasing inflammation, treating any infections, and avoiding irritants and other factors associated with dermatitis flares. The regimen must be discussed with the family, patient, and clinicians to ensure compliance.

Bathing is an important aspect of general skin care for patients who have AD. Baths and showers should be brief and the water comfortably warm, never hot. After exposure to water, the skin should be patted or excess water brushed off of the skin before applying medication and moisturizer. Some patients improve and are maintained with daily or twice-daily bathing. Other patients experience drying and increased pruritus or discomfort with water contact, making infrequent bathing the required approach. In addition, during flares, some patients are unable to bathe or shower due to discomfort and pain. Bathing may be resumed when symptoms decrease.

Although not necessary, a variety of commercial products, including cleansers, soaps, oils, and oatmeal powders, can be combined with bath water. Fragrance-free soaps and cleansers are preferred, but which product benefits or is tolerated by each patient differs. The use of bubble bath, shampoo, and dishwater detergent to cleanse the body should be avoided. For some, dilute chlorine bleach baths are beneficial, particularly for children whose AD improves after swimming in chlorinated pools. One-quarter to one-half cup of bleach in the bathtub (24 gallons or a standard tub filled 4 to 6 inches) should create a sufficient concentration without bleaching or damaging linens. Dilute white vinegar, extra light olive oil, and other products also have been used for bathing.

Because the skin of patients who have AD is dry, the use of emollients is a cornerstone of therapy. Even without visible lesions, dry skin often is pruritic. Many products are available; no single emollient provides relief, moisturizes the skin, and improves skin barrier function for all patients. The medication vehicle (eg, cream versus ointment) and the presence of fragrance, preservatives, or other additives can affect the patient's response. Lotions, creams, ointments, and oils are composed of varying amounts of oil and water. Ointments are composed of more petroleum jelly, creams contain more water than oil, and lotions contain more water than cream. If the skin is excoriated or fissured, stinging or pain can occur from products containing more water. An optimal time for moisturizer application is immediately after the bath or shower. Many patients benefit from several emollient applications per day.

Topical corticosteroids have been a mainstay of AD therapy for approximately 50 years. Hydrocortisone (up to 1%) is available over the counter, and numerous prescription preparations are available (Table). Ointments, creams, lotions, gels, foams, and oil preparations are available. Different preparations deliver corticosteroid through the skin in varying potencies. If preparations are used sparingly and appropriately, adverse effects should be minimized. Adverse effects include skin atrophy, telangiectasias, striae, and systemic absorption. The use of potent and fluorinated corticosteroids on the face and intertriginous and diaper areas should be avoided due to increased absorption through thinner or occluded skin. Middle-strength to more potent corticosteroid medications may be required for treating lichenified areas or on the hands and feet due to the increased skin thickness and keratin of the skin layers.

Several clinical trials of topical corticosteroid use in the pediatric age group have been performed or are in progress; some topical corticosteroids are approved specifically for use in children and some infants. Many practitioners find topical corticosteroids useful to break the itch-scratch cycle, treat acute flares, and minimize symptoms of inflammation. When signs and symptoms improve, the frequency of topical corticosteroid application should be reduced while moisturizer use is continued. Continuous, prolonged application of topical corticosteroids also can produce tachyphylaxis or decreased effectiveness of the medication.

Oral corticosteroid therapy has limited use in treating AD. Although helpful for some severe flares, once therapy is discontinued, the rebound or subsequent flare that may occur might be more severe than the initial exacerbation and more difficult to control. Some patients become oral corticosteroid-dependent in their attempt to

Table. Topical Corticosteroids Ranked Strongest (Class I) to Weakest (Class VII)

	Medication	Available Formulation
Class I	Clobetasol propionate 0.05%	Cream, ointment, gel, foam
	Betamethasone dipropionate augmented 0.05%	Ointment
	Diflorasone diacetate 0.05%	Ointment
	Fluocinonide 0.01%	Ointment
	Halobetasol propionate 0.05%	Cream, ointment
Class II	Amcinonide 0.01%	Ointment
	Betamethasone dipropionate 0.05%	Ointment
	Betamethasone dipropionate augmented 0.05%	Cream
	Desoximetasone 0.25%	Cream, ointment
	Desoximetasone 0.05%	Gel
	Fluocinonide 0.05%	Cream, ointment, gel, solution
	Halcinonide 0.1%	Cream, ointment, solution
	Mometasone furoate 0.1%	Ointment
Class III	Amcinonide 0.1%	Cream, lotion
	Betamethasone valerate 0.1%	Ointment
	Desoximetasone 0.05%	Cream
	Fluocinonide emollient 0.05%	Cream
	Fluticasone propionate 0.005%	Ointment
	Halcinonide 0.1%	Solution
	Triamcinolone acetonide 0.1%	Ointment
Class IV	Betamethasone valerate 0.12%	Foam
	Fluocinonide acetonide 0.025%	Ointment
	Flurandrenolide 0.05%	Ointment
	Fluticasone propionate 0.05%	Cream
	Hydrocortisone valerate 0.2%	Ointment
	Mometasone furoate 0.1%	Cream, lotion
	Triamcinolone acetonide 0.1%	Cream, ointment
Class V	Betamethasone dipropionate 0.05%	Lotion
	Betamethasone valerate 0.1%	Cream
	Clocortolone pivalate 0.1%	Cream
	Desonide 0.05%	Ointment
	Fluocinolone acetonide 0.025%	Cream
	Flurandrenolide 0.05%	Cream
	Fluticasone propionate 0.01%	Oil
	Fluticasone propionate 0.05%	Cream
	Hydrocortisone butyrate 0.1%	Cream, ointment
	Hydrocortisone valerate 0.2%	Cream
	Prednicarbate 0.1%	Cream
	Triamcinolone acetonide 0.1%	Lotion
Class VI	Alclometasone 0.05%	Cream, ointment
	Betamethasone valerate 0.1%	Lotion
	Desonide 0.05%	Cream
	Fluocinolone acetonide 0.01%	Cream, lotion
	Hydrocortisone butyrate 0.1%	Solution
	Triamcinolone acetonide 0.1%	Cream
	Triamcinolone acetonide 0.025%	Cream, lotion
Class VII	Hydrocortisone acetonide, dexamethasone	Cream, ointment, lotion

Note: Vehicle affects medication potency for several products.

prevent flares and are more likely to develop adverse systemic effects such as hypothalamic-pituitary axis suppression, growth retardation, and cushingoid features.

Chronic, high-dose, or high-potency oral corticosteroid use has been shown to cause osteopenia or osteoporosis in children and adults. It is not known whether chronic intermittent topical corticosteroid use affects the bones of children. Some physicians give vitamin D and calcium supplementation to patients who have AD. Of note, the American Academy of Pediatrics has released new recommendations regarding vitamin D supplementation in children; the recommended minimum dose was doubled to 400 IU daily for infants and children. Clearly, corticosteroid use in children who have AD, the impact of therapy on bone health, and the role of vitamin D and calcium supplementation merit additional scientific study.

Topical calcineurin inhibitors are newer elements of the therapeutic armamentarium. Pimecrolimus 1% cream is approved for mild-to-moderate AD. Tacrolimus ointment is available in 0.03% and 0.1% strengths and is targeted for moderate-to-severe AD. Tacrolimus 0.03% and pimecrolimus are approved by the United States Food and Drug Administration for those ages 2 years and older; tacrolimus 0.1% is intended for those ages 15 years and older. Both medications can be used on any part of the body and are particularly beneficial for the eyelids, face, and intertriginous areas.

The most common adverse effects reported are burning at the site of application, headache, upper respiratory tract symptoms, cough, and pyrexia. In addition, exacerbation of viral infections, including herpesvirus infection, verrucae, and molluscum contagiosum, may be more likely in patients who use these products. A black box warning was placed on both medica-

tions, stating that long-term safety of topical calcineurin inhibitors has not been established and that these medications are not recommended for use in children younger than age 2 years. Additional therapeutic trials in children who have AD are planned and needed.

Several prescription topical nonsteroidal moisturizing creams have been approved for use in AD. Their purpose is to improve the hydrolipid layer and barrier function, relieve AD symptoms, and promote wound healing. They may be used alone or in combination with topical corticosteroids and calcineurin inhibitors. The nonsteroid creams Atopiclair® Nonsteroidal Cream (Graceway Pharmaceuticals, Bristol, Tenn.), Eletone® Cream (Ferndale Laboratories, Ferndale, Mich.), Epiceram® Skin Barrier Emulsion (Promius Pharmaceuticals, Bridgewater, NJ), and MimyX® Cream (Steifel Pharmaceuticals, Bristol, Tenn.) are approved for all ages, for use on any area of the body, and may be used two to three times a day. Zetania® cream (Tiber Laboratories, Suwanee, Ga.) is approved for children 2 years of age and older. Patients allergic to any components of the creams should avoid their use.

Oral antihistamine drugs have been prescribed for patients who have AD. Although not statistically proven to be useful for treating pruritus generally, oral antihistamines can be helpful for children who have an urticarial component or decreased or altered sleep patterns due to pruritus.

Wiscott–Aldrich Syndrome

Wiskott-Aldrich syndrome is one important condition to consider in patients who have AD. This X-linked recessive disorder features eczematous eruptions in association with thrombocytopenia and recurrent infections. Thrombocytopenic purpura and hemorrhagic events may occur. The identified Wiskott-Aldrich syndrome protein (*WASP*) gene codes for a cytoplasmic protein that has multiple functions. The impaired humoral immune response to polysaccharide antigens seen in patients who have Wiskott-Aldrich syndrome makes patients susceptible to bacteria such as *Streptococcus pneumoniae* and *Pneumocystis jiroveci* and, later, to viruses. After the second decade of life, these patients are at risk for developing leukemia and lymphoma.

Job Syndrome

Another important condition to consider is Job syndrome, or hyperimmunoglobulin E syndrome (HIES), which is defined by eczematous eruptions associated with IgE concentrations greater than 2,000 IU/mL and repeated skin and sinopulmonary infections. The classic autosomal dominant form is due to a mutation in the signal transducer and activator of the transcription 3 (*STAT3*) gene. Skin eruptions appear during the newborn period, with onset of infections during the first 3 postnatal months. Although the type of skin infection can vary, "cold" abscesses are typical and feature slight redness, no or low-grade fever, little systemic involvement, and minimal signs and symptoms, unlike abscesses seen in patients unaffected by HIES. Paronychiae and candidal infections are common. Although the eczematous symptoms usually resolve, the recurrent pulmonary infections due to *S aureus* and *Haemophilus influenzae* progress to chronic lung infections and subsequent lung changes. Of note, children who have AD can have very high concentrations of IgE; conversely, patients who have HIES can have normal IgE concentrations.

Ichthyosis

Ichthyosis represents a group of disorders that involves abnormal epidermal skin barrier function, keratinization, and desquamation. Multiple types of ichthyosis have been described. Initially defined descriptively, the disorders now can be distinguished by genetic, histologic, biochemical, and molecular methods.

Ichthyosis vulgaris (IV) is the most common type, with an incidence of 1 in 250. The onset is during infancy or childhood, not at birth. Inheritance can be autosomal dominant or sporadic, so patients have a varied presentation. IV usually presents as fine white scales on the skin, sparing the antecubital and popliteal fossae. Scaling is most obvious on the lateral lower legs (Fig. 3). Hyperlinearity is noted on the palms and soles. IV can be innocuous and appear as an isolated finding. The histopathology may show a thinned-to-absent granular layer and a compact superficial stratum corneum. However, a skin biopsy may not be diagnostic; microscopically, IV can look like normal skin. IV often improves with age, and manifestations in adulthood may be minimal.

There are many forms of ichthyosis, most of which are rare. Ichthyosis can be inherited in autosomal or X-linked patterns or by spontaneous mutation. Although IV is rather common, X-linked ichthyosis, lamellar ichthyosis, and harlequin fetus are rare, well-described forms (Fig. 4). Several syndromes and related conditions of note include ichthyosis as part of the clinical picture. KID syndrome is defined as keratitis, ichthyosis, and deafness. Netherton syndrome, also called ichthyosis linearis circumflexa, features congenital erythroderma as well as atopic dermatitis, hair shaft abnormalities, and high IgE concentrations.

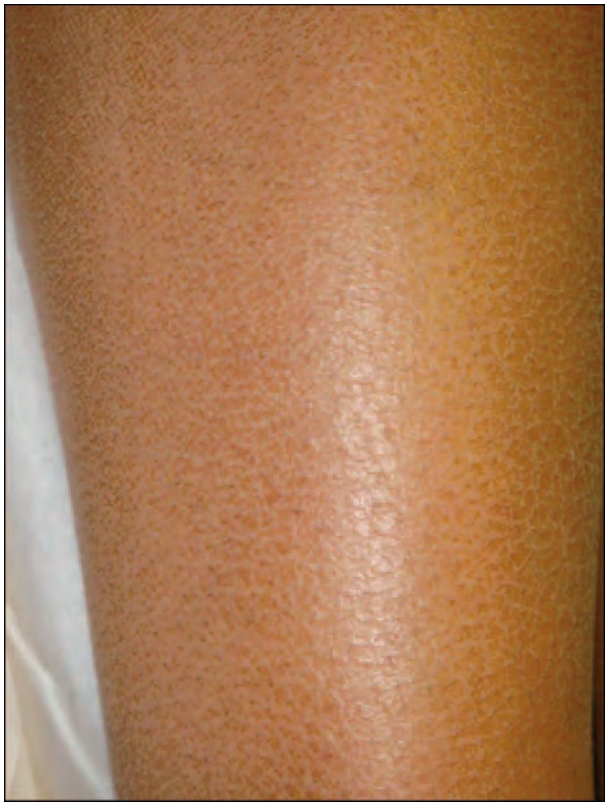

Figure 3. Ichthyosis vulgaris demonstrates fine, white scales.

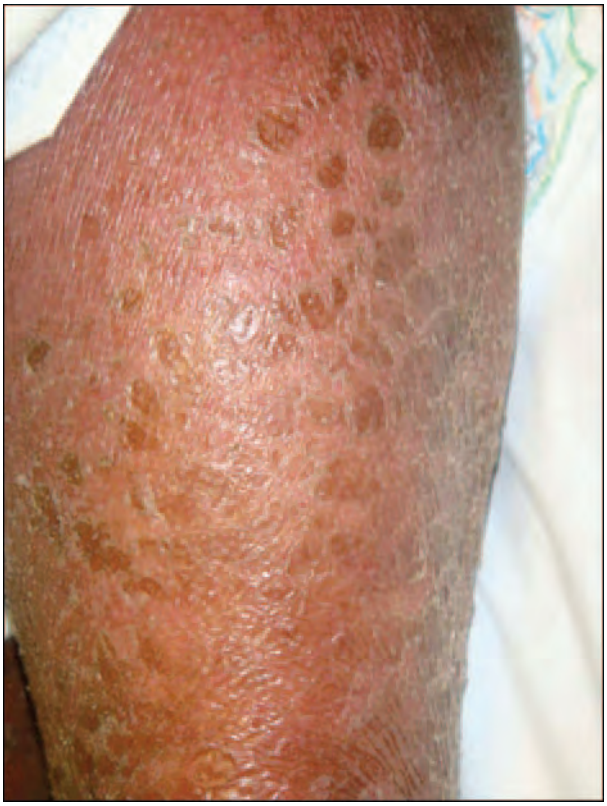

Figure 4. Lamellar ichthyosis features larger, platelike scales.

Management

Treatment of IV usually involves the use of topical salicylic acid; lactic acid; or urea in lotion, cream, or ointment form. These products moisturize, soften the skin, and aid in desquamation. For patients who have both IV and AD, these products are more likely to cause irritation. The products should be used cautiously in children because total body application can result in systemic absorption and serious adverse effects. Salicylic acid, in particular, should be used in children after 1 year of age and then with caution due to risks of salicylate toxicity.

Research

Significant research has been performed in IV, AD, and related disorders. IV often coexists with AD, and research has shown a genetic basis for this association in certain populations. Gene mutations in keratin proteins alter skin barrier function. Most important, the *FLG* gene produces profilaggrin, and filaggrin is critical for AD expression. Multiple international and familial studies have shown that *FLG* mutations in patients who have AD alter normal skin formation, function, and hydration and result in severe AD, as well as asthma associated with AD.

The mutation for IV also has been identified. Studies have shown that Northern European patients who have IV have a statistically significant increased risk for developing AD as well. Also, patients who have both IV and AD have a statistically significant increased risk for developing asthma. Overall, there is strong evidence for a genetic and molecular basis for the association of IV and AD. More studies are in progress and are necessary for elucidating the role of altered cutaneous barrier function.

Summary

- Based on strong research evidence and consensus, a multifaceted, individualized approach to treatment benefits patients who have atopic dermatitis and includes bathing, emollients, topical anti-inflammatory medications, allergen avoidance, and the use of antistaphylococcal antibiotics and antihistamines when clinically indicated. (1)(2)
- Based on strong research evidence, mutations in the *FLG* gene cause ichthyosis vulgaris, resulting in alterations in the skin protein filaggrin. (3)(4)
- Based on strong research evidence, atopic dermatitis is associated with certain populations who have ichthyosis vulgaris. (5)(6)(7)

Mechanisms for Atopic Disease

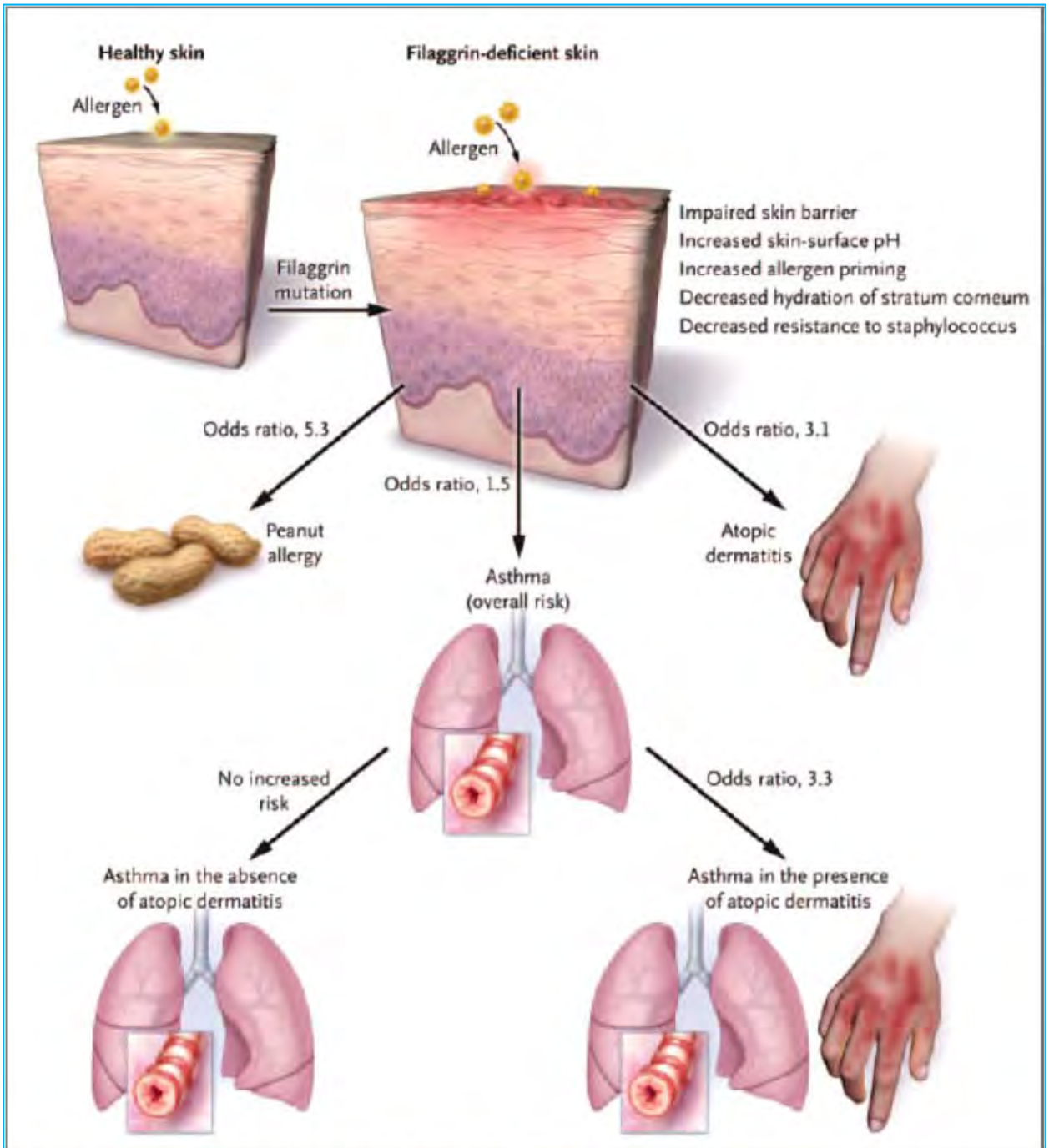

Figure 4. Filaggrin Haploinsufficiency and Increased Risk of Several Complex Traits.

Filaggrin haploinsufficiency is defined as a 50% reduction in the expression of the filaggrin protein. The odds ratios are for the risk of peanut allergy, asthma, or atopic dermatitis as compared with the risk in the absence of filaggrin mutation. The odds ratios listed for atopic dermatitis and asthma are from meta-analyses involving several thousand patients. *FLG* mutations confer an overall risk of asthma of 1.5, but this risk is restricted to patients with atopic dermatitis. The odds ratio for the complex phenotype of asthma plus atopic dermatitis is 3.3. The odds ratio for peanut allergy is based on the only available data, from a single study.

Statistics Review: *Odds ratio:* *Odds of Atopic Disease with Filaggrin MUTATION (Disease/No Disease)*
Odds of Atopic Disease with NORMAL Filaggrin (Disease/No Disease)

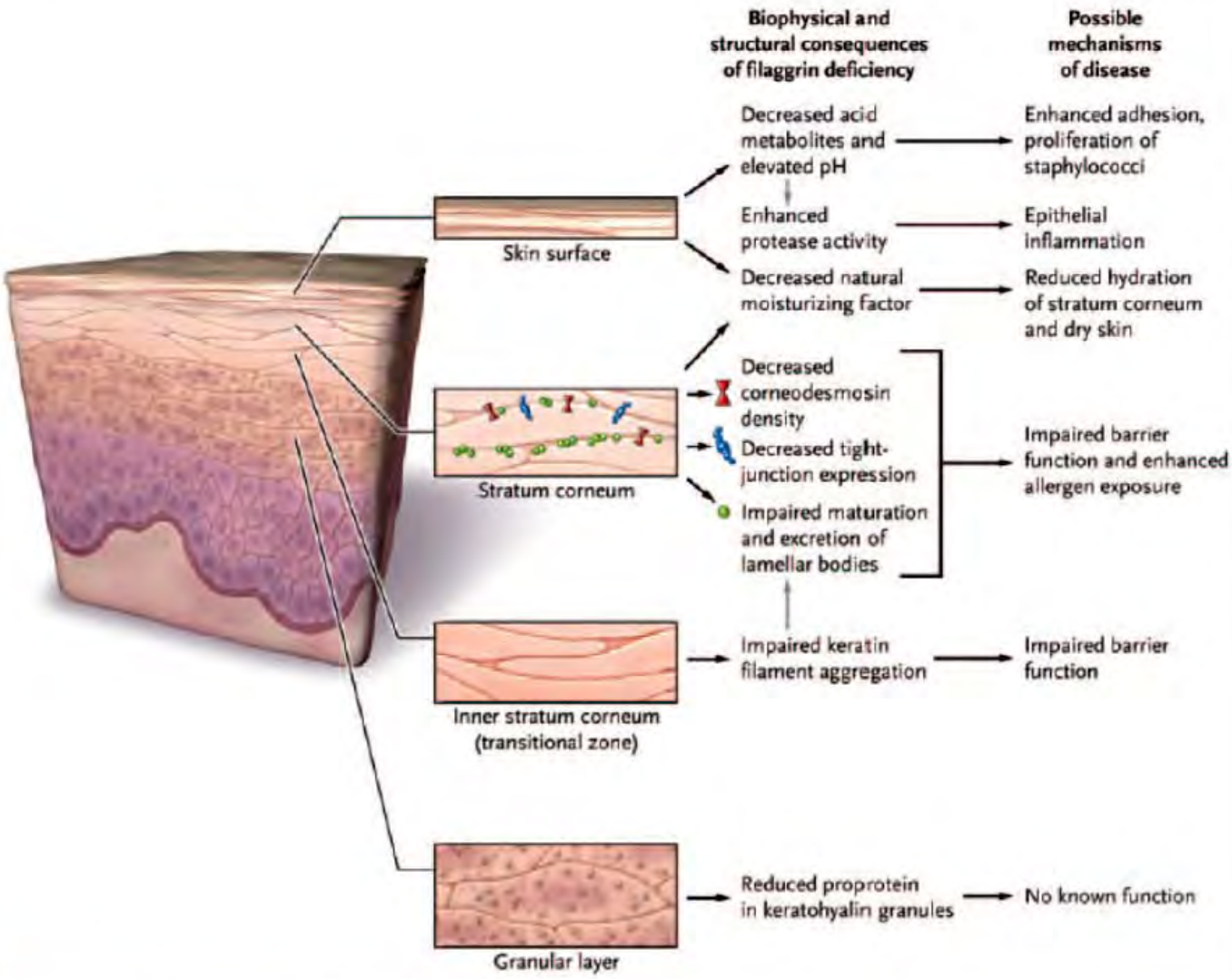

Figure 5. Filaggrin Deficiency and Possible Mechanisms of Disease.

Filaggrin haploinsufficiency results in a number of differentiation-specific structural, biophysical, and functional changes within the stratum corneum that are likely to be directly related to disease pathogenesis in ichthyosis vulgaris and atopic dermatitis. In the granular layer, the proprotein profilaggrin is stored within the keratohyalin granules, where it is thought to be functionally inert. At the interface of the inner stratum corneum and the stratum granulosum, impaired aggregation of keratin filaments causes impaired excretion of lamellar bodies, with resultant impairment in barrier function. In the stratum corneum, filaggrin deficiency is associated with multiple structural changes, including decreased corneodesmosome density, decreased expression of tight-junction proteins, and — most important — impaired maturation and secretion of lamellar bodies. These changes may be mediated by increased pH within the residual cytoplasm of squames due to a lower concentration of acidic filaggrin breakdown products. All these changes contribute to impaired barrier function and increased ease of allergen presentation to epidermal dendritic cells. Finally, on the skin surface, decreased levels of natural moisturizing factor cause the skin to lose hydration and feel dry; reduced levels of urocanic acid and pyrrolidone carboxylic acid on the skin surface impair *Staphylococcus aureus* adhesion and proliferation through pH-dependent and possibly pH-independent mechanisms. Elevated skin-surface pH increases the activity of several proteases that cleave proforms of interleukin-1, possibly contributing to epithelial inflammation and further barrier destruction.

Filaggrin Mutations Associated with Skin and Allergic Diseases

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Treatment of Atopic Dermatitis

National Jewish Atopic Dermatitis Program Step-Care "AD Action" Plan

MAINTENANCE OR DAILY CARE
Take at least one bath or shower per day; use warm water, for 10-15 minutes.
Use a gentle cleansing bar or wash in the sensitive skin formulation as needed such as Dove® or Oil of Olay®.
Pat away excess water and immediately (within 3 minutes) apply moisturizer, sealer, or maintenance medication if directed. Fragrance-free moisturizers available in one pound jars include Aquaphor® Ointment, Eucerin® Crème, Vanicream®, CeraVe® Cream or Cetaphil® Cream. Vaseline® is a good occlusive preparation to seal in the water; however, it contains no water so it only works effectively after a bathing. Use moisturizers liberally throughout the day. Moisturizers and sealers should not be applied over any topical medication.
Avoid skin irritants and proven allergens.
MILD-TO-MODERATE ATOPIC DERMATITIS
Bathe as above for 10-15 minutes, once (and possibly twice) daily.
Use cleansers as above.
Use moisturizers as above to healed and unaffected skin, twice daily especially after baths and at mid-day total body.
Apply to affected areas of face, groin and underarms twice daily especially after baths _____ (low-potency topical corticosteroid), or_____ (topical calcineurin inhibitors), or other topical preparation as directed _____ (topical barrier repair cream, eg., Atopiclair® three times daily).
Apply to other affected areas of the body twice daily especially after baths _____(low to mid- potency topical corticosteroid), or _____(topical calcineurin inhibitors), or other topical preparation as directed _____.
MODERATE-TO-SEVERE ATOPIC DERMATITIS
Bathe as above for 10-15 minutes, two times a day, once before bedtime.
Use cleansers as above or consider an antibacterial cleanser (eg., Lever 2000®)
Use moisturizers as above to healed and unaffected skin, twice daily especially after baths and at mid-day total body.
Apply to affected areas of face, groin and underarms twice daily especially after baths _____(low-potency topical corticosteroid), or_____ (topical calcineurin inhibitors), or other topical preparation as directed _____ (topical barrier repair cream, eg., Atopiclair® three times daily).
Apply to other affected areas of the body twice daily especially after baths _____ (mid-to-high-potency topical corticosteroid), or _____ topical calcineurin inhibitors), or other topical preparation as directed.
Use wet wraps to involved areas selectively as directed.
Add other medications as directed: _____(eg., oral sedating antihistamines, topical or oral antimicrobial therapy)
Pay close attention to things that seem to irritate the skin or make condition worse.
Contact your health care provider for additional evaluation or therapies. Oral steroids are not usually recommended.
Step down to moderate plan above as the skin heals.
REDUCE SKIN IRRITATION
Wash all new clothes before wearing them. This removes formaldehyde and other irritating chemicals.
Add a second rinse cycle to ensure removal of detergent. Residual laundry detergent, particularly perfume or dye, may be irritating when it remains in the clothing. Changing to a liquid and fragrance-free, dye-free detergent may be helpful.
Wear garments that allow air to pass freely to your skin. Open weave, loose-fitting, cotton-blend clothing may be most comfortable.
Work and sleep in comfortable surroundings with a fairly constant temperature and humidity level.
Keep fingernails very short and smooth to help prevent damage due to scratching.
Carry a small tube of moisturizer/sunscreen at all times. Daycare/school/work should have a separate supply of moisturizer.
After swimming in chlorinated pool or using hot tub, shower or bathe using a gentle cleanser to remove chemicals, then apply moisturizer.

Steroids on Formulary at WR-B (Jan 2014)

Potency Group	Generic Name	Percentage Strength	Brand Name (Alt Brand Name)	Size
Class I	Augmented Betamethasone Dipropionate	0.05% lotion	Diprolene	30 ml
	Clobetasol Proprionate	0.05% ointment	Temovate (Cormax)	15 g, 30 g
	Clobetasol Proprionate	0.05% cream	Temovate-E (Cormax)	15 ml, 30 ml, 45 ml
	Clobetasol Proprionate	0.05% solution	Temovate Scalp (Cormax)	25 ml, 30 ml
	Flurandrenolide	4mcg/cm tape	Cordran	200 cm
Class II	Augmented Betamethasone Dipropionate	0.05% cream	Diprolene AF	15 g
	Betamethasone Dipropionate	0.05% ointment	Diprosone	15 g
	Fluocinonide	0.05% cream	Lidex	15 g, 60 g
	Fluocinonide	0.05% gel	Lidex	15 g, 60 g
	Fluocinonide	0.05% ointment	Lidex	15 g, 60 g
	Fluocinonide	0.05% solution	Lidex	60 ml
Class III	Amcinonide	0.1% cream	Cyclocort	15 g, 60 g
	Betamethasone Dipropionate	0.05% lotion	Diprosone	60 ml
	Fluocinonide Emollient	0.05% cream	Lidex-E	15 g, 60 g
Class IV	Hydrocortisone Valerate	0.2% ointment	Westcort	15 g, 60 g
	Triamcinolone Acetonide	0.1% ointment	Kenalog	15 g, 80 g, 454 g
	Triamcinolone Acetonide	0.2% aerosol	Kenalog	63 g
Class V	Betamethasone Valerate	0.1% cream	Valisone	15 g
	Betamethasone Valerate	0.1% lotion	Valisone	60 ml
	Desonide	0.05% ointment	Tridesilon (DesOwen)	15 g, 60 g
	Flurandrenolide	0.05% lotion	Cordran	60 ml
	Hydrocortisone Valerate	0.2% cream	Westcort	15 g, 60 g
	Triamcinolone Acetonide	0.1% cream	Kenalog (Aristocort EQ)	15 g, 80 g, 454 g
	Triamcinolone Acetonide	0.025% ointment	Kenalog	15 g
Class VI	Desonide ☺	0.05% cream	Tridesilon (DesOwen)	15 g, 60 g
	Fluocinolone Acetonide	0.01% oil	Dermasmooth (Capex)	120 ml
	Triamcinolone Acetonide	0.025% cream	Kenalog	15 g, 80 g
Class VII	Hydrocortisone	2.5% cream	(Hytone)	28 g
	Hydrocortisone (OTC) ☺	1% cream		30 g
		0.5% cream		30 g
		1% lotion		118 ml
		1% ointment		30 g

☺ Safe for facial use

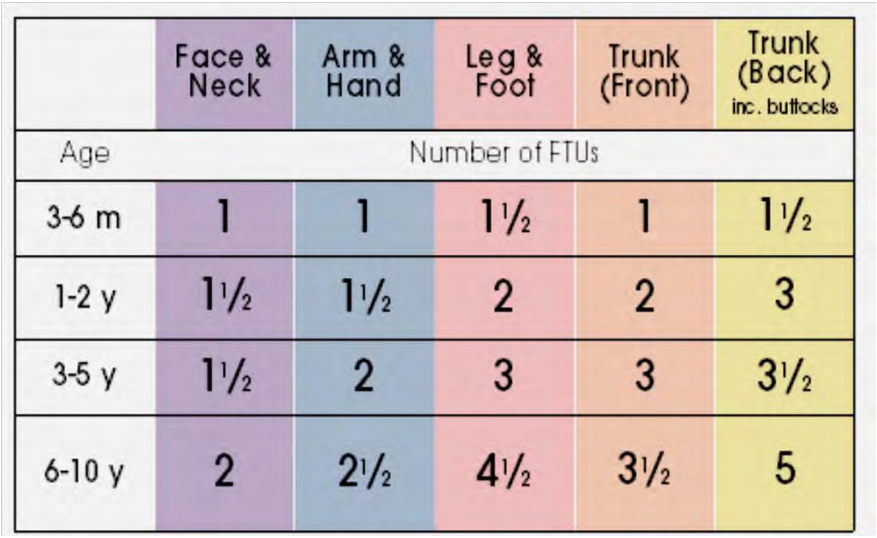
Moisturizers on Formulary at WR-B (Jan 2014)

Aquaphor (mineral oil/petroleum)	454 g jar
Cetaphil cream	454 g jar
Hydrocerin lotion	480 ml
Vanicream	454 g jar

Finger Tip Units (FTUs)

- Amount of ointment/cream product that extends from the tip of an adult finger to the first flexural crease of the DIP, when dispensed from a tube with the standard 5mm nozzle.
- Used to gauge the amount of topical steroid to use on a given area of affected skin.
- Provides guide to the appropriate size of tube that should be prescribed for a patient.

- **1 FTU = 0.5 g = treats an area 2x the size of an adult's hand with fingers together,**
- **2 FTUs = 1g = treats an area equivalent to 4 adult handprints (10 x 10cm), etc.**
- *30 g of product is necessary to fully cover an adult patient.*



	Face & Neck	Arm & Hand	Leg & Foot	Trunk (Front)	Trunk (Back) inc. buttocks
Age	Number of FTUs				
3-6 m	1	1	1½	1	1½
1-2 y	1½	1½	2	2	3
3-5 y	1½	2	3	3	3½
6-10 y	2	2½	4½	3½	5

"Home Remedies"

TABLE 6 A Bleach Bath Primer

Explain to patients that their skin may benefit from "swimming in pool water." Then, give them these instructions for making a pool right in their very own bathroom.

- Add lukewarm water to fill the tub completely (about 40 gallons of water).
- Depending on the size of the tub/amount of water used, add ¼ to ½ cup of common bleach solution to the bath water. Any sodium hypochlorite 6% solution will do (for example, Chlorox liquid bleach); the goal is to make a modified Dakin's solution with a final concentration of about 0.005%.
- Stir the mixture to ensure that the bleach is completely diluted in the bath water.
- Have patients soak in the chlorinated water for 5 to 10 minutes.
- Thoroughly rinse skin clear with lukewarm, fresh water at the end of the bleach bath to prevent dryness and irritation.
- As soon as the bath is over, pat the patient dry. Do not rub dry, as this is the same as scratching.
- Immediately apply any prescribed medications/emollients.
- Repeat bleach baths 2–3 times a week or as prescribed by the physician.

The following restrictions apply

- Do not use undiluted bleach directly on the skin. Even diluted bleach baths can potentially cause dryness and/or irritation.
- Do not use bleach baths if there are many breaks or open areas in the skin (for fear of intense stinging and burning).
- Do not use bleach baths in patients with a known contact allergy to chlorine.

Additional Types of Baths (www.nationaleczema.org)

Vinegar Baths: Referred to as the "pickle the patient" treatment. Add one cup to one pint of vinegar to the bath. Can be used as a wet dressing too as it kills bacteria.
Bath Oil Baths: Oils in the bath are a favorite of some providers and patients. Bath oils can leave the tub slippery – be careful. They can also leave a hard-to-clean film. See if they work for you.
Salt Baths: When there is a significant flare the bath water may sting or be uncomfortable. Add one cup of table salt to the bath water to decrease this side effect.
Baking Soda Baths: Added to a bath or made into a paste it can be used to relieve the itching.
Tar Baths: Tar baths can sooth inflammation and itch. Tar bath oil or tar shampoo can be used. Warning: if the skin is open or excoriated the tar baths can sting.
Oatmeal baths: Added to a bath or made into a paste it can be used to relieve the itching.

TABLE 7 Keeping Eczema Under Wraps: Recommendations for Applying Wet Wraps

Gather your supplies.

- Topical steroid ointment and/or emollient prescribed by your physician.
- The wraps themselves consist of a bottom (wet) and top (dry) layer. Gauze wrap (eg, Kerlex) or cotton sleepers, pajamas, or long johns may be used. It will be necessary to have two of the material chosen. Alternatively, it is possible to use the "daddy sock" method for wrapping extremities. Simply cut a small hole in the toes of any adult-sized pair of 100% cotton socks to create a pair of tubular cotton bandages that fit easily over an extremity, can be moved up or down as needed, and can be washed and reused.
- Warm water in a sink or a basin.

Apply the steroid ointment directly to the patient's inflamed skin using tongue depressors or popsicle sticks (similar to how a spatula is used in cooking). Using a "spatula" helps to avoid direct contamination of the medication supply, allows large areas to be covered quickly and evenly, and prevents the caregiver from being unnecessarily exposed to topical corticosteroids.

Apply emollient to the rest of the patient's skin.

Take a layer of the wrap (e.g., gauze or one sock) and soak it in warm water.

Wring out any excess water until this bottom wet layer is only very slightly damp.

Wrap the affected area with the wet layer material. Make sure the wet layer is not too tight.

Immediately put the dry layer over the wet layer. Do not use plastic as the dry layer (it is too occlusive and may be a choking hazard).

Make sure the wrapped patient remains in a warm environment, which helps to promote a higher degree of humidity and ensures that the child does not get too cold as the evaporation process occurs.

Wet wraps are generally left in place overnight and may be applied for 5 to 7 days in a row. As always, follow the advice of the physician for frequency of change and duration of use.

Maintain close contact with the physician while undergoing the use of wet wraps. Report any suspected adverse effects immediately.

Atopic Dermatitis Quiz

1. The atopic triad includes: _____. Children with one atopic disease are _____ more likely to develop a second atopic disease.

2. Describe the **underlying etiology** of atopic dermatitis.

3. List the **sites** *typically* affected by atopic dermatitis depending on age:

Infants	
Children	
Teenagers	

4. **True** or **False**: Atopic dermatitis can develop on *any* part of the body regardless of age.

5. Place the following topical corticosteroids in or order of **decreasing potency**:

Desonide 0.05% ointment
Fluocinonide 0.05% cream
Fluocinonide 0.05% ointment
Flurandrenoloide Tape
Hydrocortisone 2.5% cream
Triamcinolone Acetonide 0.1% ointment
Desonide 0.05% cream
Fluocinonide 0.05% emollient cream
Fluoocinolone Acetonide 0.01% oil
Hydrocortisone Valerate 0.2% ointment
Triamcinolone Acetonide 0.025% ointment
Triamcinolone Acetonide 0.1% cream

6. List **adverse effects** of topical corticosteroids. Consider local and systemic.

Atopic Dermatitis Cases

Case 1:

Colton is a 15 month old male infant who presents for a routine well visit. He is the only child of well-educated parents who live in the suburbs. His height and weight have been stable at the 50th percentile. He was breastfed for the first year of his life and continues to breastfeed at night. He was introduced to solid foods at 6 months of age and has fully transitioned to table foods. His mother boasts that he has "never had a runny nose in his life" and that she uses hand sanitizer "all the time, of course". Her only concern is for a red, dry, itchy rash that keeps recurring on his cheeks, arms, and legs. She has not noticed any triggers.

Based on history, what are protective and predisposing factors for Colton developing AD?

On exam, Colton's rash appears consistent with a mild-to-moderate eczema flare, with large dry erythematous plaques covering his cheeks and chin. His arms and legs have multiple papules and vesicles in the flexural surfaces with scratch marks.

What treatment would you recommend?

His mother is wary of starting topical steroids and asks about alternatives or homeopathic treatments that are available. **What would you recommend or advise against?**

Prior to leaving, you obtain additional family history to better delineate his risk for additional atopic disease. His mother notes that she and all her sisters struggled with asthma as kids. His father is adopted so family history is unknown, but he does have a h/o anaphylaxis to peanuts.

How would you counsel Colton's mother regarding his risk, particularly for food allergies?

Case 2

Sarah is a 9 year old female brought in by her mother with the complaint of worsening eczema. The family just moved to the DC area from Arizona after her father was injured in Afghanistan. She is currently living in an apartment in Building 72 with her parents and two younger sisters. She has had eczema since infancy that has been controlled with periodic use of moisturizers and topical steroids. Her eczema today is the worse it has ever been, completely involving her arms, legs, and neck with patches on her trunk. She has been unable to sleep because of the pruritis and has little interest in going outside to play because of discomfort with walking.

What further history would you like to know?

Her mother, accustomed to these visits, brings in multiple half used 15 g tubes of steroids that were prescribed or purchased from the drugstore. She says she has tried all of them for 1-2 days with no relief. The only one that has helped was a new script for Desonide 0.05% cream, that is now half-full. She has been using it once a day for the past week on all of Sarah's affected areas.

Has the Desonide been used appropriately? What clues can you use to answer this question, other than Sarah's clinical symptoms?

On exam, you notice that some of Sarah's lesions appear impetiginous. You also learn she has a history of abscesses and that her father is receiving home IV antibiotics for MRSA osteomyelitis.

How does this history and exam affect the treatment for Sarah's eczema flare?

What are additional types of super-infections that can occur in patients with AD?

You ultimately decide to treat Sarah with an oral antibiotic for secondary bacterial infection, decolonize her with daily bleach baths for a week and nasal mupirocin, decrease inflammation with a low potency corticosteroid for her face and a medium potency corticosteroid for her extremities, and start her on a regular bathing and moisturizing regimen.

She returns in one week with no further signs of infection. History and medication tubes support compliance. She continues, however, to complain of pruritis and pain and there has been only moderate improvement. There is no concern for secondary viral or fungal infection.

What would else could you recommend?

Atopic Dermatitis Board Review

1. A 7-year-old girl presents in September with an intensely itchy rash of several weeks' duration. During the summer she had many mosquito bites and one area of ringworm, but otherwise she has had no prior skin conditions. She has had no fever, joint pain, myalgias, fatigue, or change in appetite or activity. Antihistamines helped when she had the insect bites, but now they have little effect. No other family members have a rash. On physical examination, the rash is apparent on exposed areas and consists of papules, vesicles, and wheals, some in a linear array or in triangular clusters. There are also numerous hyperpigmented macules. The scalp is involved, but the palms and soles are spared.

Of the following, the MOST likely cause of this rash is:
A. Atopic dermatitis
B. Id reaction to recent fungal infection
C. Hypersensitivity reaction to insect bites
D. Recurrent impetigo with post-inflammatory changes
E. Scabies

2. A 6-year-old boy presents with a 2-year history of frequent pruritic, erythematous eruptions on his arms and legs. The rash usually worsens during winter but occurs intermittently throughout the year. His mother has tried various moisturizers, but they have not been effective in controlling the rash. On physical examination, you note erythematous patches on his antecubital and popliteal regions bilaterally.

Of the following the MOST appropriate initial step in management for this patient is:
A. food allergy skin testing
B. oral antibiotic therapy
C. oral antihistamine therapy
D. topical calcineurin inhibitor therapy
E. topical corticosteroid therapy

3. A 12-month-old girl presents with a 3-month history of a pruritic rash that involves her cheeks, neck, anterior trunk, and antecubital and popliteal areas. The rash improves after use of an over-the- counter topical steroid cream but still is present most days, and the infant often wakes up at night scratching. On physical examination, you observe a raised erythematous rash that has areas of lichenification.

Of the following, the MOST helpful intervention is to:
A. eliminate fruit and acidic juices from the diet
B. eliminate milk, eggs, soy, and wheat from the diet
C. perform aeroallergen allergy testing
D. perform food allergy testing
E. recommend a skin biopsy

4. A 2-year-old boy presents for evaluation of a chronic pruritic eruption. His medical history is remarkable for recurrent epistaxis, otitis media, and pneumonia. Physical examination reveals erythematous, slightly scaling patches on the trunk and in the antecubital and popliteal fossae. Petechiae are present profusely.

Of the following, these findings are MOST suggestive of:
A. Acrodermatitis enteropathica
B. Ataxia telangiectasia
C. Atopic dermatitis
D. Langerhans cell histiocytosis
E. Wiskott-Aldrich syndrome