142 Eczematous Skin Disorders and Atopic Dermatitis in Childhood

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Definition and Epidemiology

Atopic dermatitis (AD) is a genetically inherited papulosquamous skin disease most commonly seen in children. Seventy to ninety-five percent of cases present before the age of 5 years. The prevalence of AD in the western world is now between 10% and 20%, with the ratio of girls to boys being 1.3:1. Additionally, it is more likely for a child to inherit atopic dermatitis from a mother with atopy than from a father with atopy. This prevalence has steadily increased in North America and Europe since World War II. There are many theories that attempt to explain this increase ranging from environmental factors to the "Hygiene Hypothesis," many of which will be discussed later on in this chapter. The prevalence of AD varies worldwide. One very large study which looked at over 700,000 children in over 150 centers across the world showed the lowest prevalence in 6–7 year olds to be 2% in Iran and the highest prevalence in this age group to be 16% in Japan. In children 13–14 years of age, the lowest prevalence was 1% in Albania and the highest was over 17% in Nigeria.

Atopic dermatitis is commonly associated with asthma and allergic rhinitis, and the three together have historically been referred to as the "atopic triad." More recently, the finding of eosinophilic enteritis associated with severe food allergies has also been linked to these diseases. Food allergies can be seen in 40% of infants and children with moderate to severe AD. Eighty percent of individuals with AD will go on to develop either asthma or allergic rhinitis later on in life.

Etiology and Pathogenesis

From an etiologic perspective, AD is a multifactorial disease. First, there are several aspects of immune dysregulation. Seventy to eighty percent of patients with AD show elevated levels of IgE and eosinophilia. Biopsies of active skin lesions show a predominance of TH2 lymphocytes. Additionally, the skin of patients with AD produces lower levels of two families of antibacterial peptides known as B-defensins and cathelicidins. This is just one reason why atopics are much more susceptible to viral and bacterial infections than are non-atopics. Up to 90% of patients with AD will grow pathogenic *Staphylococcus aureus* from swab cultures taken from exudative skin lesions. *Staphylococcus* proteins can act as superantigens that can also flare AD.

Another pathomechanism, and another reason why atopics are so prone to infection, is that they have deficient epidermal skin barrier function. The stratum corneum of the skin of atopics contains much lower levels of ceramide proteins and filagrin than does the skin of non-atopics. Ceramides and filagrin are proteins that function to help the skin retain its moisture content. A hydrated epidermis keeps transepidermal water loss to a minimum, and also provides the best barrier against infection. There are many new topical products now available, both over the counter and by prescription, which contain both ceramides and filagrin. Their appropriate use as part of an overall treatment regimen for AD will be discussed at length in the treatment section to follow.

Clinical Manifestations

Clinically AD usually manifests itself in three phases, infantile, childhood, and an adolescent/adult phase. Infantile AD usually presents with a diffuse red scaly dermatitis mainly limited to the face and scalp (*Fig. 142.1*). Within the first 6–12 months of life, AD can overlap clinically with Seborrheic Dermatitis, also known as cradle cap. Usually, sometime between 12 and 18 months, the rash of AD leaves the face and scalp, and becomes more prominent on the popliteal (*Fig. 142.2*) and antecubital fossas (*Fig. 142.3*). This phase usually persists up through the early teenage years, by which point approximately 60% of patients will have grown out of their disease. In the up to 40% of atopics who carry their skin disease into adulthood, a number of different clinical patterns can be seen. These can include a chronic hand dermatitis, eyelid or neck eczema, or nipple eczema in young women. Many other clinical features can be seen

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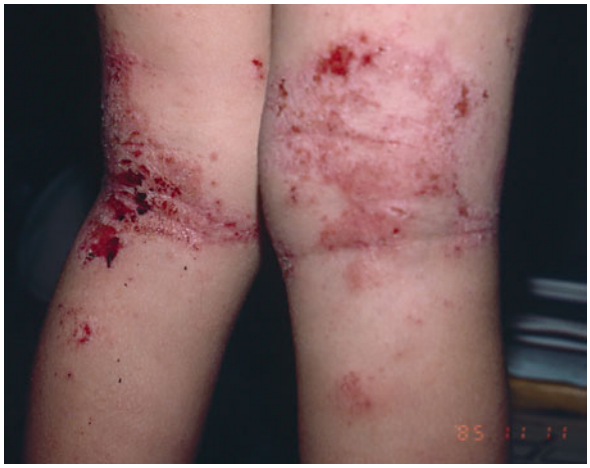

Figure 142.1
Facial atopic dermatitis in an infant

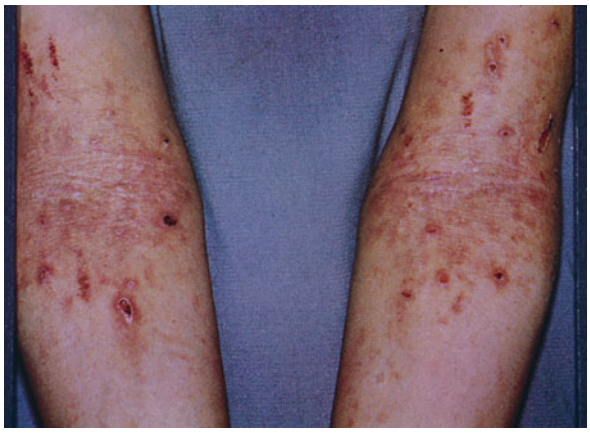

Figure 142.2
Popliteal fossa atopic dermatitis

at any age and make up a number of the minor criteria used to diagnose atopic dermatitis (see list below). From a morphological perspective, clinical lesions at each phase can also present in three different stages, acute, subacute, and chronic, which vary both clinically and histologically.

Major and minor criteria for the diagnosis of atopic dermatitis (adapted from Hanifin and Rajka's article) are as follows:

Major features

Pruritus
Typical morphology/distribution
Chronic and relapsing
Personal or family history

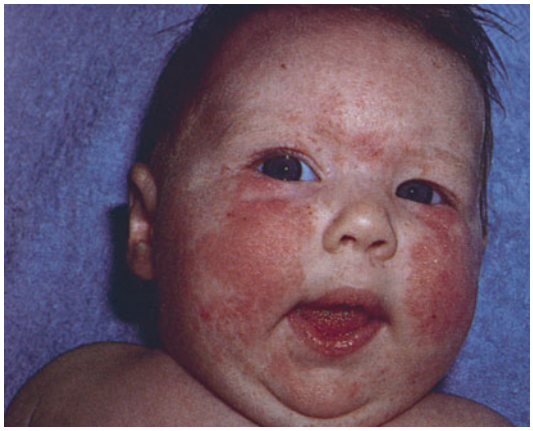

Figure 142.3
Antecubital fossa atopic dermatitis

Minor features

Xerosis
Ichthyosis/keratosis pilaris
Immediate Type 1 hypersensitivity
Elevated serum IgE
Early age of onset
Increased skin infections
Non-specific hand foot dermatitis
Nipple eczema
Chelitis
Recurrent conjunctivitis
Dennie–Morgan folds
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor/erythema
Pityriasis alba
Anterior neck folds
Pruritus with sweating
Intolerance to wool
Perifollicular accentuation
Food intolerance
Influenced by environment
White dermatographism

Pathology

Histopathology varies at each stage. Acute eczema shows intraepidermal edema with microvesicles, also known as spongiosis. There is a perivascular lymphocytic infiltrate predominantly composed of CD4+ T cells extending from

the upper dermis into the epidermis. Langerhans cells and macrophages may also be seen in the infiltrate of acute eczema. Subacute eczema still shows some spongiosis and a less prominent lymphocytic infiltrate. Additionally, some epidermal thickening may be noted at this stage. Chronic eczema, which clinically appears as lichenification, shows only sparse to absent inflammation and spongiosis, with psoriasiform epidermal hyperplasia. Even the normal skin of patients with atopic dermatitis can show abnormal pathology, including a sparse perivascular infiltrate of T lymphocytes, eosinophils, and macrophages.

Differential Diagnosis

The differential diagnosis of AD is quite broad and is different for each phase, infantile, childhood, and adult. The differential includes other chronic dermatosis, infections and infestations, immunodeficiency syndromes, metabolic, genetic and autoimmune disorders, drug eruptions, and malignancies (*Table 142.1*).

Table 142.1
Differential diagnosis of atopic dermatitis (adapted from Bolognia)

Chronic dermatosis	
Seborrheic dermatitis	C
Contact dermatitis	B
Psoriasis	B
Nummular eczema	B
Asteatotic eczema	A
Lichen simplex chronicus	B
ID reaction	B
Infections and infestations	
Scabies	B
Tinea	B
Impetigo	B
Mucocutaneous candidiasis	C
Congenital syphilis	C
Primary immunodeficiencies	
Wiskott–Aldrich syndrome	C
Hyper IgE syndrome	C
Genetic syndromes	
Netherton syndrome	C
Ectodermal dysplasias	C
Autoimmune disorders	
Dermatitis herpetiformis	A>>C
Pemphigus foliaceus	A> > C
Dermatomyositis	B
Lupus	A>>C
Malignancies	
Cutaneous T cell lymphoma	A>> > C
Langerhans cell histiocytosis	C
Other	
Drug eruptions	B

A = adults, *B* = both, *C* = children

Treatment

Once the diagnosis is made, the treatment of AD varies based on the patient's age, the location of the eczematous lesions, and their morphology. Treatment of infantile AD, which mainly involves the face and scalp, should begin with mild soap-free cleansers, known as syndets, and with moisturizers which contain ceramides and/or filaggrin. If those are not effective, very mild topical steroids should be added. There are seven classes of topical steroids available to treat all types of skin disease in patients of all ages. Class 1 steroids are the strongest and Class 7 steroids are the weakest. Several agents in Classes 5–7 are approved for use as young as 3 months of age in the United States, including certain strengths of hydrocortisone, desonide, and fluticasone. These are the agents that should be used to treat eczema in young infants. The topical steroids should be used for no more than 2 weeks without taking a break to minimize their side effects, including the possibility of hypothalamic–pituitary–adrenal (HPA) axis suppression. They should be used in conjunction with the above cleansers and moisturizers. Pruritus can be seen in association with AD at any age. If numerous excoriations are noted, or the parents report poor sleep hygiene, a low nightly dose of a sedating antihistamine, such as hydroxizine, should be considered. Sometimes there is a clinical overlap between AD and seborrheic dermatitis. If this overlap is suspected, the addition of ketoconazole shampoo applied three times per week can be very helpful.

At some point between 12 and 18 months, most facial and scalp AD resolves, and many young children are left with a flexural dermatitis involving the popliteal and antecubital fossas. These skin lesions often exhibit accentuation of the skin lines, a clinical finding known as lichenification. Once lichenification is noted, it will probably become necessary to increase the strength of the topical steroid to one of mid potency, such as triamcinolone. As above, it continues to be important to use

soap-free cleansers and ceramide and filaggrin containing moisturizers. As the strength of the topical steroid use is increased, it is especially important to find ways to give the skin a break from steroid use. Twice daily use of a Class 4 steroid for only 2 weeks on greater than 10% of the body surface area of a child can be associated with statistically significant HPA axis suppression. If, as a clinician, one finds patients for whom the moisturizers and cleansers are not enough to allow the patient to not use topical steroids for at least 1 week per month, that patient may be a candidate for the use of one of the two calcineurin inhibitors/topical immunomodulators (TIMs), pimecrolimus or tacrolimus. In the United States, these two agents carry a Black Box Warning against the theoretical increased malignancy risk of using these agents in children under 2 years of age. This warning stems from the fact that the transplant patients taking oral tacrolimus for more than 5 years have an increased risk of malignancy, especially skin cancers and lymphomas. No malignancies have been definitively causally linked to the use of either topical pimecrolimus or topical tacrolimus.

For a very small percentage of patients who do not respond to aggressive moisturization, mid to high potently topical steroid use, oral antihistamines, and the addition of one of the TIMs, systemic therapy is sometimes necessary. Systemic therapy may also be appropriate for those patients with such a large percentage of body surface area involved (i.e., >20%) that topical therapy is not a tenable option. There are numerous systemic therapies ranging from oral antibiotics and oral steroids, threw light therapy, and up to other oral and injectable immunosuppressive agents such as Cyclosporin, Azathioprine, Methotrexate, Mycophenolate mofetil (MM), Intravenous immunoglobulin (IVIG), and Interferon gamma.

Prospective clinical trials evidence exists only for Cyclosporin, Azathioprine, Interferon gamma, Broadband UVB, and PUVA. Evidence at the level of retrospective clinical trials or large case series exists for systemic steroids, narrowband UVB, methotrexate, mycophenolate mofetil (MM), and intravenous immunoglobulin (IVIG). Although the scientific evidence for oral prednisone is not as strong as for some other agents, based on decades of clinical experience, many pediatric dermatologists will first try a 2–3 week taper of oral prednisone from a starting dose of 1 mg/kg/day. It is often necessary to overlap a 10–14-day course of a penicillin or cephalosporin antibiotic with the prednisone in these patients with severe atopic dermatitis due to their high risk of secondary bacterial infection. If the prednisone is either not effective or significant rebound in disease activity is noted rapidly, one of the steroid sparing agents should be considered.

Cyclosporin is the most effective of these other agents and should be given at a dose of 3–5 mg/kg/day for 3–6 months. Close monitoring of patients on cyclosporine is very important, and includes monthly blood pressure checks, complete blood counts, lipid profiles, BUN, creatinine, magnesium, and urinalysis. Azathioprine can also be very effective, but produces a slower clinical response. Dosing should be determined based on the patient's level of thiopurine methyl transferase. It is necessary to follow hepatic function tests and complete blood counts monthly. If cyclosporine and azathioprine are either ineffective or too toxic for a given individual, either methotrexate or MM can be given. Methotrexate is dosed weekly at 0.2–0.8 mg/kg/week, while MM is given daily at a dose of 10–30 mg/kg/day. It is important to follow hepatic function and complete blood counts monthly in patients on both of these drugs. Although there is a good evidence for the efficacy of several different types of light therapy in the treatment of atopic dermatitis, the technical difficulties involved in providing it to young children usually puts it far down the therapeutic ladder. Lastly, Interferon gamma and IVIG, although both effective, must be considered treatments of last resort due to their extremely high costs.

Prognosis and Prevention

Approximately 60% of individuals with AD will grow out of it by the early teenage years. Unfortunately, a small percentage of these patients will carry their tendencies toward asthma and food and environmental allergies into adulthood. Prevention can be viewed as either keeping the disease from ever developing or minimizing the level of disease activity once it has developed. Complete prevention has only been reported in a few small trials in the British medical literature that looked at the use of probiotics in pregnant and nursing mothers, and the incidence of AD in their infant children. From the point of view of prevention of active disease, once the diagnosis has been made, ceramide and filaggrin containing moisturizers have been shown in numerous studies to fill this roll.

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