



Atopic Dermatitis

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Practice Essentials

Atopic dermatitis (AD) is a pruritic disease of unknown origin that usually starts in early infancy, though an adult-onset variant is recognized. That it is the first disease to present in a series of allergic diseases—including food allergy, asthma, and allergic rhinitis, in order—has given rise to the “atopic march” theory, which suggests that AD is part of a progression that may lead to subsequent allergic disease at other epithelial barrier surfaces.^[1, 2]

Essential update: Methotrexate polyglutamate assay helps guide dosing in late responders

A retrospective study of 46 children with atopic dermatitis, psoriasis, or psoriasis-eczema overlap found that a commercial methotrexate polyglutamate assay (Avisé PG, Exagen Diagnostics) reflected the treatment efficacy of methotrexate.^[3, 4] In all, 38 of the 46 (83%) exhibited a good-to-excellent response, 27 within 12 weeks and 11 after dosage was adjusted. Mean maximum polyglutamate levels were 31.5 nmol/L for responders and 18.1 nmol/L for nonresponders ($P = .035$). This difference was also significant for the subset with atopic dermatitis.

Whereas the maximum assay level did not reflect the efficacy of methotrexate treatment among most patients who responded within 12 weeks, it did help guide dosing modifications in those who did not show improvement within this initial period.^[4] After dosage adjustment, late responders ultimately achieved a significantly higher mean maximum methotrexate polyglutamate level (41.9 nmol/L) than nonresponders did ($P = .002$).

Signs and symptoms

Incessant pruritus is the only symptom of AD. The disease typically has an intermittent course with flares and remissions occurring, often for unexplained reasons.

Primary physical findings include the following:

- Xerosis
- Lichenification
- Eczematous lesions

The eczematous changes and its morphology are seen in different locations, depending on the age of the patient (ie, infant, child, or adult).

The following is a constellation of criteria commonly used for the diagnosis of atopic dermatitis:

- Pruritus
- Eczematous changes that vary with age
- Chronic and relapsing course
- Early age of onset
- Atopy (IgE reactivity)
- Xerosis
- Personal history of asthma or hay fever or a history of atopic diseases in a first-degree relative in patients younger than 4 years
- Onset younger than age 2 years (not used if the child is younger than 4 years)

A firm diagnosis of AD depends on excluding conditions such as the following:

- Scabies
- Allergic contact dermatitis
- Seborrheic dermatitis
- Cutaneous lymphoma
- Ichthyosis
- Psoriasis
- Immunodeficiency

See [Clinical Presentation](#) for more detail.

Diagnosis

The following considerations apply to workup for suspected AD:

- No chemical marker for the diagnosis is known
- Laboratory testing is seldom necessary; a swab of infected skin is sometimes helpful
- Allergy and radioallergosorbent testing is of little value.
- A platelet count for thrombocytopenia and testing to rule out other immunodeficiencies may be helpful
- Scraping to exclude tinea corporis is occasionally helpful
- Biopsy shows an acute, subacute, or chronic dermatitis, without specific findings

See [Workup](#) for more detail.

Management

Pharmacologic agents typically used to treat AD include the following:

- Moisturizers: Petrolatum, Aquaphor, or newer agents such as Atopiclair and Mimyx (superior but more expensive and requiring further evaluation)
- Topical steroids (current mainstay of treatment; commonly used in conjunction with moisturizers): Hydrocortisone, triamcinolone, or betamethasone; ointment bases are generally preferred, particularly in dry environments
- Immunomodulators: Tacrolimus and pimecrolimus (calcineurin inhibitors; to be considered second-line therapy and used only as indicated); omalizumab (monoclonal antibody that blocks immunoglobulin E [IgE] function)

Other treatments that have been tried include the following:

- Probiotics
- Ultraviolet (UV)-A, UV-B, a combination of both, psoralen plus UV-A (PUVA), or UV-B1 (narrow-band UV-B) therapy
- Acyclovir
- In severe disease, phototherapy, methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil^[5]
- Hydroxyzine and diphenhydramine hydrochloride
- Ketotifen
- Everolimus^[6, 7]
- Antibiotics for clinical infection caused by *Staphylococcus aureus* or flares of disease
- Intranasal mupirocin ointment and diluted bleach (sodium hypochlorite) baths^[8]

Nonmedical measures that may be helpful include the following:

- Using soft clothing (eg, cotton) next to the skin; wool products should be avoided
- Maintaining cool temperatures, particularly at night
- Using a humidifier (cool mist) in both winter and summer
- Washing clothes in a mild detergent, with no bleach or fabric softener
- Avoiding specific foods as appropriate

See [Treatment](#) and [Medication](#) for more detail.

Image library



Flexural involvement in childhood atopic dermatitis.

Background

Atopic dermatitis (AD) is a pruritic disease of unknown origin that usually starts in early infancy (an adult-onset variant is recognized); it is characterized by pruritus, eczematous lesions, xerosis (dry skin), and lichenification (thickening of the skin and an increase in skin markings).

AD may be associated with other atopic (immunoglobulin E [IgE]–associated) diseases (eg, acute allergic reaction to foods, asthma, urticaria, and allergic rhinitis).^[9] AD has enormous morbidity, and the incidence and prevalence appear to be increasing. Further, AD is the first disease to present in a series of allergic diseases such as food allergy, asthma, and allergic rhinitis (in order), provoking the “atopic march” theory, which suggests that early or severe AD and cutaneous sensitization to environmental allergens may lead to subsequent allergic disease at other epithelial barrier surfaces (eg, gastrointestinal or respiratory tract). This hypothesis is supported by cross-sectional and longitudinal studies.^[1]

Pathophysiology

Despite recent advances in the understanding of the genetics of atopic dermatitis (AD), the pathophysiology remains poorly defined. Two main hypotheses have been proposed regarding the development of inflammation that leads to AD. The first suggests a primary immune dysfunction resulting in IgE sensitization and a secondary epithelial-barrier disturbance. The second proposes a primary defect in the epithelial barrier leading to secondary immunologic dysregulation and resulting in inflammation.

In healthy individuals, balance exists between important subsets of T cells (eg, T_h 1, T_h 2, T_h 17). The primary immune dysfunction hypothesis invokes an imbalance in the T-cell subsets, with T_H 2 cells predominating; this results in the production of T_h 2 cytokines such as interleukin (IL)–4, IL-5, and IL-13, causing an increase in IgE from plasma cells and diminished interferon-gamma levels. Later, in persons with chronic AD, the T_h 1 cells predominate.

More recently, T_h 17 cells have been found to be elevated in patients with acute AD.^[10] Though primarily considered to be a T_h 2-mediated disease, the precise contribution of T_h 1 and T_h 17 cell responses remain to be fully defined. In addition to the role of T and B cells in AD, other innate immune cells are also implicated in the pathogenesis of AD, including basophils, eosinophils, and mast cells.^[11, 12, 13, 14]

The epidermal barrier dysfunction hypothesis suggests that AD patients develop AD as a result of skin barrier defects that allow for the entry of antigens, resulting in the production of inflammatory cytokines. Some authors question whether such antigens can also be absorbed from the gut (eg, from food) and/or the lungs (eg, from house dust mites). Xerosis and ichthyosis are known to be associated signs in many AD patients. Clinically, 37-50% of people with *ichthyosis vulgaris* have atopic disease and up to 37% of people with AD have clinical evidence of *ichthyosis vulgaris*.^[15] Mutations in the gene encoding filaggrin, a key epidermal barrier protein, cause *ichthyosis vulgaris* and are the strongest known genetic risk factors for the development of AD.^[16]

In fact, filaggrin mutations are associated with early-onset AD and with airway disease in the setting of AD.^[17] One mechanism by which filaggrin defects may influence inflammation is by the release of a family of epithelial cytokines including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which are all known to be up-regulated in the context of epithelial barrier disruption.^[18] All of these cytokines are potent promoters of T_h 2 cytokine responses.^[19] Although filaggrin is strongly linked to AD, mutations are only found in 30% of European patients, begging the question of whether other genetic variants may also be responsible for some of the findings in the pathogenesis of AD.

In AD, transepidermal water loss is increased. Whether the primary immune dysregulation causes secondary epithelial barrier breakdown or primary epithelial barrier breakdown causes secondary immune dysregulation that results in disease remains unknown. However, given the fact that filaggrin is critical for epithelial integrity, it is now thought that loss of filaggrin function leads to increased transepidermal penetration of environmental allergens, increasing inflammation and sensitivity and potentially leading to the atopic march.^[20]

Epidemiology

Frequency

United States

The prevalence rate for atopic dermatitis is 10-12% in children and 0.9% in adults. More recent information examining physician visits for atopic dermatitis in the United States from 1997-2004 estimates a large increase in office visits for atopic dermatitis occurred. In addition, blacks and Asians

visit more frequently for atopic dermatitis than whites. Note that this increase involves all disease under the umbrella of atopic dermatitis and it has not been possible to allocate which type has increased so rapidly.^[21]

International

The prevalence rate of atopic dermatitis is rising, and atopic dermatitis affects 15-30% of children and 2-10% of adults. This figure estimates the prevalence in developed countries. In China and Iran, the prevalence rate is approximately 2-3%. The frequency is increased in patients who immigrate to developed countries from underdeveloped countries.^[22]

Mortality/Morbidity

Incessant itch and work loss in adult life is a great financial burden. A number of studies have reported that the financial burden to families and government is similar to that of asthma, arthritis, and diabetes mellitus. In children, the disease causes enormous psychological burden to families and loss of school days. Mortality due to atopic dermatitis is unusual.

- **Kaposi varicelliform eruption** (eczema herpeticum) is a well-recognized complication of atopic dermatitis.
 - It usually occurs with a primary herpes simplex infection, but it may also be seen with recurrent infection. Vesicular lesions usually begin in areas of eczema and spread rapidly to involve all eczematous areas and healthy skin. Lesions may become secondarily infected. Timely treatment with acyclovir ensures a relative lack of severe morbidity or mortality.
 - Another cause of Kaposi varicelliform eruption is vaccination with vaccinia for the prevention of small pox, but because this is no longer mandatory, patients with atopic dermatitis do not develop the sequelae of eczema vaccinatum that has been seen in the past. It was usually contracted by the patient from the vaccination of themselves or their close relatives. This condition had a high mortality rate (up to 25%). In the current climate of threats of bioterrorism, vaccination may once again become necessary, and physicians should be aware of eczema vaccinatum in this setting.
 - Note that chickenpox vaccine does not carry the same risk as herpes simplex and vaccinia.
- Bacterial infection with *Staphylococcus aureus* or *Streptococcus pyogenes* is not infrequent in the setting of atopic dermatitis. The skin of patients with atopic dermatitis is colonized by *S aureus*. Colonization does not imply clinical infection, and physicians should only treat patients with clinical infection. The emergence of methicillin-resistant *S aureus* (MRSA) may prove to be a problem in the future in these patients. Eczematous and bullous lesions on the palms and soles are often infected with beta-hemolytic group A *Streptococcus*.
- Urticaria and acute anaphylactic reactions to food occur with increased frequency in patients with atopic dermatitis. The food groups most commonly implicated include peanuts, eggs, milk, soy, fish, and seafood. In studies in peanut-allergic children, the vast majority were atopic.
- Latex and nickel allergy is more common in patients with atopic dermatitis than in the general population.
- Of atopic dermatitis patients, 30% develop asthma and 35% have nasal allergies.

Race

- Atopic dermatitis affects persons of all races. Immigrants from developing countries living in developed countries have a higher incidence of atopic dermatitis than the indigenous population, and the incidence is rapidly rising in developed countries

Sex

- The male-to-female ratio for atopic dermatitis is 1:1.4.

Age

- In 85% of cases, atopic dermatitis occurs in the first year of life; in 95% of cases, it occurs before age 5 years. The incidence of atopic dermatitis is highest in early infancy and childhood. The disease may have periods of complete remission, particularly in adolescence, and may then recur in early adult life.
- In the adult population, the rate of atopic dermatitis frequency is 0.9%, but onset may be delayed until adulthood.