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The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

Atopic dermatitis (**AD**), also known as **atopic eczema**, is a long-term type of inflammation of the skin (dermatitis). It results in itchy, red, swollen, and cracked skin. Clear fluid may come from the affected areas, which can thicken over time. AD may also simply be called eczema, a term that generally refers to a larger group of skin conditions.

Atopic dermatitis affects about 20% of people at some point in their lives. It is more common in younger children. Females are slightly more affected than males. Many people outgrow the condition.

While the condition may occur at any age, it typically starts in childhood, with changing severity over the years. In children under one year of age, the face and limbs and much of the body may be affected. As children get older, the areas on the insides of the knees and folds of the elbows and around the neck are most commonly affected. In adults, the hands and feet are commonly affected. Scratching the affected areas worsens the eczema and increases the risk of skin infections. Many people with atopic dermatitis develop hay fever or asthma.

The cause is unknown but believed to involve genetics, immune system dysfunction, environmental exposures, and difficulties with the permeability of the skin. If one identical twin is affected, the other has an 85% chance of having the condition. Those who live in cities and dry climates are more commonly affected. Exposure to certain chemicals or frequent hand washing makes symptoms worse. While emotional stress may make the symptoms worse, it is not a cause. The disorder is not contagious. A diagnosis is typically based on the signs, symptoms and family history. **"DISEASE DIAGNOSIS"** segment highlights AD for you.

As skin disorders need to rule out allergic phenomena, IgE plays an important role. **"INTERPRETATION"** outlines IgE and how to understand the same. **"TROUBLE SHOOTING"** talks about Immunoglobulins in general. **"BOUQUET"** needs no reminder. It does find its place within.

DISEASE DIAGNOSIS

ATOPIC DERMATITIS

Background

Atopic dermatitis (AD) is a pruritic skin condition 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). 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.

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, allergic inflammation, 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, Th1, Th2, Th17, Th22). The primary immune dysfunction hypothesis invokes an imbalance in the T cell subsets, with Th2 cells predominating; this results in the production of type 2 cytokines such as interleukin (IL)–4, IL-5, and IL-13, causing an increase in IgE from plasma cells. Later, in persons with chronic AD, the Th1 cells have been shown to predominate. More recently, Th17 cells have been found to be elevated in patients with AD. Although primarily considered a Th2 cell associated cytokine-mediated disease, the precise contributions of Th1 and Th17 cell responses remain to be fully defined. In addition to the role of T and B cells in AD, other innate immune cells have also been implicated in the pathogenesis of AD, including eosinophils and mast cells. More recently, basophils and newly identified innate immune cells called group 2 innate lymphoid cells (ILC2s) have been shown to underlie the pathogenesis of AD. Together, basophils and ILC2s are critical sources of the type 2 cytokines IL-4, IL-5, and IL-13. Further, these cells appear to be potently regulated by a family of epithelial cell derived cytokines directly released from damaged keratinocytes, including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. Taken together, these studies highlight a new paradigm in which, in addition to classical adaptive Th2 cells, innate type 2 immune cells play critical roles in the etiology of AD through interactions with epidermal-derived cytokines. In terms of AD-associated itch, Th2 cells are known to be significant sources of the itch-inducing cytokine or pruritogen IL-31. Emerging clinical trials data indicate that blocking this pathway may be a key mechanism by which atopic itch can be treated clinically. Additionally, a 2017 study identified that neuronal, rather than immune, signaling of the type 2 cytokines IL-4 and IL-13 critically regulate AD-associated itch. Indeed, the dual IL-4 and IL-13 blocker, dupilumab, has emerged as a highly effective treatment for AD, which received FDA approval in March of 2017. Thus, blocking cytokine-nerve interactions with targeted biologic therapies has emerged as a novel therapeutic strategy in AD. 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. 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. Further, filaggrin mutations are associated with early-onset AD and with airway disease in the setting of AD. One mechanism by which filaggrin defects may influence inflammation is by the release of epithelial cell derived cytokines, including TSLP, IL-25, and IL-33, which are all known to be up-regulated in the context of AD. TSLP has been shown to be a potent promoter of basophil and ILC2 responses in the skin, while IL-25 and IL-33 preferentially elicit ILC2s.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. Indeed, genetic variants of TSLP have been shown to interact with mutations in filaggrin to influence AD disease persistence in patients. 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.

Etiology of Atopic Dermatitis

Genetics

A family history of atopic dermatitis (AD) is common. The strongest known genetic risk factor for developing AD is the presence of a loss-of-function mutation in filaggrin. More recently, genome-wide association studies (GWAS) have identified susceptibility loci at 11q13.5 in European populations, at 5q22.1 and 1q21.3 in a Chinese Han population, and at 20q13.33 in both Chinese Han and German populations. A recent meta-analysis of GWAS studies in European populations identified SNPs rs479844 near *OVOL1*, rs2164983 near *ACTL9*, and rs2897442 in intron 8 of *KIF3A*. Many of these loci contain genes that encode proteins involved in epidermal proliferation and differentiation or inflammatory cytokines.

Infection

The skin of patients with AD is colonized by *S aureus*. Clinical infection with *S aureus* often causes a flare of AD, and *S aureus* has been proposed as a cause of AD by acting as a superantigen. Similarly, superinfection with herpes simplex virus can also lead to a flare of disease and a condition referred to as eczema herpeticum.

Hygiene

The hygiene hypothesis is touted as a cause for the increase in AD. This attributes the rise in AD to reduced exposure to various childhood infections and bacterial endotoxins.

Climate

AD flares occur in extremes of climate. Heat is poorly tolerated, as is extreme cold. A dry atmosphere increases xerosis. Sun exposure improves lesions, but sweating increases pruritus. These external factors act as irritants or allergens, ultimately setting up an inflammatory cascade.

Food antigens

The role of food antigens in the pathogenesis of AD is controversial, both in the prevention of AD and by the withdrawal of foods in persons with established disease. Because of the controversy regarding the role of food in AD, most physicians do not withdraw food from the diet. Nevertheless, acute food reactions (urticaria and anaphylaxis) are commonly encountered in children with AD.

Probiotics

The role of probiotics in the diet of patients with AD remains controversial.

Aeroallergens

A role for aeroallergens and house dust mites has been proposed, but this awaits further corroboration.

Tobacco

A study by Lee et al suggested a correlation between early and/or current exposure to cigarette smoking and adult onset of AD. The study also determined that exposure to tobacco smoke in childhood is linked to adult onset of AD.

Epidemiology of Atopic Dermatitis

Frequency

International

The prevalence rate of AD is rising, and AD 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.

Race

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

Sex

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

Age

In 85% of cases, AD occurs in the first year of life; in 95% of cases, it occurs before age 5 years. The incidence of AD 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 AD frequency is 3% or higher, but onset may be delayed until adulthood.

Prognosis

Most patients with this skin condition improve; this can occur at any age. While the frequency of atopic dermatitis (AD) is as high as 20% in childhood, it is 0.9% in adults. One third of patients develop allergic rhinitis. One third of patients develop asthma. In a longitudinal study of 7157 children and adolescents with AD from the Pediatric Eczema Elective Registry, researchers found that symptoms of mild to moderate AD are likely to persist into the teen years or beyond. Approximately two-thirds of the patients were followed for at least 2 years and the rest were followed for at least 5 years. From ages 2 to 26 years, more than 80% of patients reported having continued symptoms and/or use of topical medications to control symptoms. By age 20, approximately half of the patients had experienced at least one 6-month symptom- and medication-free period. Living in southern states, having a relative with an atopic illness, and exposure to pollen, wool, pets, cigarettes, fumes, some foods or drinks, and soaps/detergents were linked to persistent symptoms.

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. Sleep disturbance is common in AD patients, owing to the incessant pruritus. Sleep disturbances can significantly impact quality of life. Mortality due to AD is unusual. Kaposi varicelliform eruption (eczema herpeticum) is a well-recognized complication of AD. 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 AD 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 *S aureus* or *Streptococcus pyogenes* is not infrequent in the setting of AD. The skin of patients with AD 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 AD. 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 AD than in the general population.Of AD patients, 30% develop asthma and 35% have nasal allergies.

Clinical Presentation

History

Incessant pruritus (itchiness) is the central and most debilitating symptom of atopic dermatitis (AD); children often scratch themselves uncontrollably. Although pruritus may be present in the first few weeks of life, parents become more aware of the itch as the itch-scratch cycle matures when the patient is aged approximately 3 months. This skin condition typically has an intermittent course with flares and remissions occurring, often for unexplained reasons. Data from a study by Garmhausen et al indicate that the natural course of the disease can be divided into subgroups with different clinical features. The most frequent

course type (31.1% of the sample) was characterized by an early disease onset (before age 2 years) and a chronic persisting course through adulthood. Of the 607 patients in the study, 85.7% were categorized into 5 main different course types. The greatest differences in the number of sensitizations, total immunoglobulin E serum levels, and predilection of skin lesions were seen between subjects with early-onset disease and a chronic persisting course until adulthood and those with late-onset AD developing after age 20 years. AD patients often present with a personal or family history of type I hypersensitivity, allergic rhinitis, and asthma.

Essential historical features (must be present) are as follows:

- Pruritus
- Chronic or relapsing history of disease

Important historical features (supports the diagnosis) are as follows:

- Early age of onset
- Atopy: Personal and/or family history.

Physical Examination

Perform a routine skin examination to look for features associated with atopic dermatitis (AD). In younger patients, examine for dermatographism as many patient may have acute urticaria in the setting of AD. Primary findings of AD include xerosis, lichenification, and eczematous lesions. Excoriations and crusting are common and some patients exhibit prurigo nodularis like lesions. The eczematous changes and its morphology are seen in different locations depending on the age of the patient.

Essential features (must be present) are as follows:

- Pruritus
- Eczema (acute, subacute, chronic): (1) Typical morphology and age-specific patterns (facial/neck/extensor involvement in children, flexural involvement in any age group, sparing the groin and axillary regions); (2) chronic or relapsing history

Important features (supports the diagnosis) are as follows:

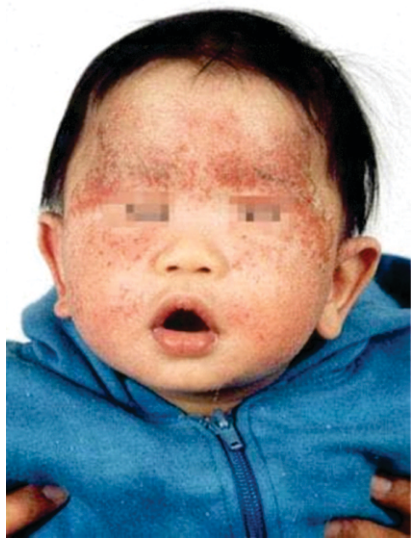
- Early age of onset
- Atopy: (1) Personal and/or family history; (2) IgE reactivity
- Xerosis

Associated features (nonspecific but suggest the diagnosis of AD) are as follows:

- Atypical vascular responses (eg, facial pallor, delayed blanch response)
- Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
- Ocular/periorbital changes
- Other regional findings (eg, perioral changes/periauricular lesions)
- Perifollicular accentuation/lichenification/prurigo

Infancy

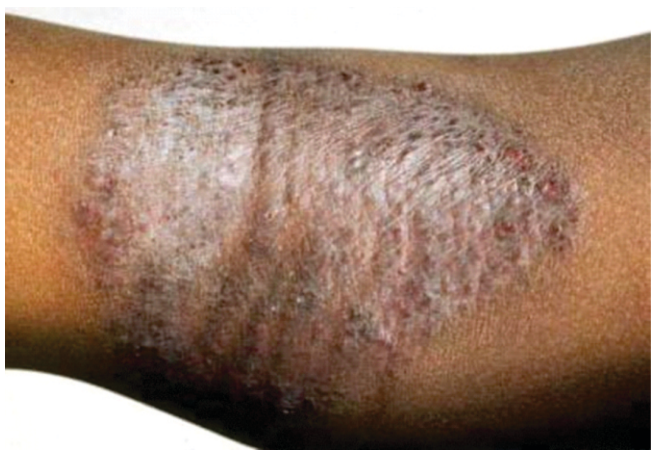
AD is usually noticed soon after birth. Xerosis occurs early and often involves the whole body; the diaper area is usually spared. The earliest lesions affect the creases (antecubital and popliteal fossae), with erythema and exudation. Over the following few weeks, lesions usually localize to the cheeks, the forehead and scalp, and the extensors of the lower legs; however, they may occur in any location on the body, usually sparing the diaper area and the nose. Lesions are ill-defined, erythematous, scaly, and crusted (eczematous) patches and plaques. Lichenification is seldom seen in infancy. A typical presentation is shown in the following image.



Atopic dermatitis. Typical atopic dermatitis on the face of an infant.

Childhood

Xerosis is often generalized. The skin is flaky and rough. Lichenification is characteristic of childhood AD. It signifies repeated rubbing of the skin and is seen mostly over the folds, bony protuberances, and forehead. Lesions are eczematous and exudative. Pallor of the face is common; erythema and scaling occur around the eyes. Dennie-Morgan folds (ie, increased folds below the eye) are often seen. Flexural creases, particularly the antecubital and popliteal fossae, and buttock-thigh creases are often affected. See the image below.

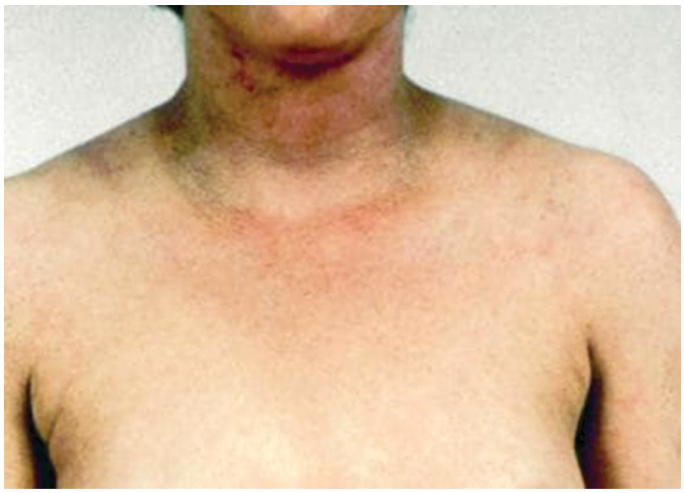


Atopic dermatitis. Flexural involvement in childhood atopic dermatitis.

Excoriations and crusting are common. The crusting with AD should not be confused with infection because both may manifest oozing and crusting. Children with AD are likely to experience symptoms into their teens and beyond.

Adulthood

Lesions become more diffuse with an underlying background of erythema. The face is commonly involved and is dry and scaly. Xerosis is prominent. Lichenification may be present. A brown macular ring around the neck is typical but not always present. It represents localized deposition of amyloid. See the image on next page.



Atopic dermatitis. Dirty neck sign in chronic atopic dermatitis.

Diagnostic criteria

Until Hanifin and Rajka developed diagnostic criteria for the diagnosis of AD in 1980, no standardized methods were available to make the diagnosis. Since then, numerous other experts have developed different criteria suitable for their own environment, and varying with age. The original criteria of Hanifin and Rajka have been modified many times. Efforts to develop practical clinical criteria have not been successful, and those available are not suitable for all geographic areas and age groups. The lack of a good biomarker for diagnosing the disease is an enormous obstacle to the study of AD.

Exclusionary conditions (conditions that should be excluded) are as follows:

- Scabies
- Seborrheic dermatitis
- Contact dermatitis
- Ichthyoses
- Cutaneous T-cell lymphoma
- Psoriasis
- Photosensitivity dermatoses
- Immune deficiency diseases
- Erythroderma of other causes

Severity assessment

Several tools have been developed to assess the severity of atopic dermatitis. No one is considered the criterion standard, but some validated tools are listed below :

- Eczema Area and Severity Index (EASI) - Based solely on objective clinician assessment; primarily used in clinical trials
- SCORing Atopic Dermatitis (SCORAD) - Combines objective clinician assessment and subjective patient assessment; primarily used in clinical trials
- Patient-Oriented Eczema Measure (POEM): Based solely on subjective patient assessment; may be more convenient in clinical practice
- Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD): Based solely on subjective patient assessment; may be more convenient in clinical practice

The Numerical Rating Scale is a subjective tool in which patients are asked, “On a scale of 0 to 10, with 0 being 'no itch' and 10 being 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?'”.

Differential Diagnoses

Diagnostic Considerations

Atopic dermatitis (AD) is indistinguishable from other causes of dermatitis. In infancy, the most common difficulty is distinguishing it from seborrheic dermatitis (SD). This entity is not seen with the same frequency as a decade ago. Both AD and SD are associated with cradle cap (a retention hyperkeratosis) found on the vertex of the scalp, which is greasy and yellow in individuals with SD and dry and crusted in individuals with AD. Other areas of involvement in SD are the intertriginous areas and diaper area; erythema and a greasy scale can be seen over the eyebrows and the sides of the nose. In AD, xerosis of the skin and pruritus occur, which are not usually features of SD. Both conditions should be distinguished from psoriasis. Scabies manifests in infancy or childhood as a pruritic eruption. Other members of the family are usually itchy, and the primary sites of involvement are moist, warm areas. The eruption is polymorphic with a dermatitis, nodules, urticaria, and 6-10 burrows. Pustules on the hands and feet are almost diagnostic of scabies in infancy. Facial involvement is rare, and xerosis does not occur. Allergic contact dermatitis from nickel in infants and children is sometimes difficult to distinguish from AD. A central area of dermatitis on the chest from nickel snaps in undershirts or around the umbilicus from snaps in jeans is helpful for making the diagnosis, although a dermatitic eruption may occur as an id reaction in other areas, particularly the antecubital fossae. Xerosis and facial involvement are absent. AD usually starts earlier than contact dermatitis. Infants with a severe itch and generalized dermatitis in the setting of recurrent infections should be investigated for evidence of an immunodeficiency. Failure to thrive and repeated infections help distinguish the eruption from AD. In Wiskott-Aldrich syndrome, bleeding may be prominent with the dermatitis, because of the associated thrombocytopenia. A population-based cohort study by Schmitt J et al. suggested a possible link to the development of mental health issues in patients who experienced infant eczema and concurrent sleeping problems. In older children, mycosis fungoides (a form of T-cell lymphoma) often presents with hypopigmented patches associated with a dermatitis. This entity is being recognized with increased frequency as physicians become more aware of the disease, and it is sometimes difficult to distinguish between the 2 entities. Tinea corporis usually manifests as a single lesion, but inappropriate treatment with steroids may cause a widespread dermatitis. Facial involvement, the presence of xerosis, the age of appearance, and an early onset (in AD) help distinguish between the two conditions. One report describes localized varicella lesions developing in preexisting infectious or inflammatory dermatitis; no clear evidence of full-blown chickenpox was seen. The authors suggest viral testing may be needed if vesicular or ulcerative lesions develop within a preexisting dermatitis.

Differential Diagnoses

- Allergic Contact Dermatitis
- Immunodeficiency
- Irritant Contact Dermatitis
- Lichen Simplex Chronicus
- Mollusca contagiosa with dermatitis
- Mycosis fungoides
- Nummular Dermatitis (Nummular Eczema)

- Plaque Psoriasis
- Relative zinc deficiency
- Scabies
- Seborrheic Dermatitis
- Tinea Corporis

Workup

Laboratory Studies

- No biomarker for the diagnosis of atopic dermatitis (AD) is known. Laboratory testing is seldom necessary.
- A swab of infected skin may help with the isolation of a specific organism (eg, *Staphylococcus or Streptococcus)* and antibiotic sensitivity. Allergy and radioallergosorbent testing is of little value.
- A swab for viral polymerase chain reaction (PCR) may help identify superinfection with herpes simplex virus and identify a diagnosis of eczema herpeticum.
- A complete blood cell count for thrombocytopenia helps exclude Wiskott-Aldrich syndrome, and testing to rule out other immunodeficiencies may be helpful. This also helps identify peripheral eosinophilia, which may help to support the diagnosis.
- A serum IgE level can be helpful to support the diagnosis.
- Scraping to exclude tinea corporis is occasionally helpful.

Histologic Findings

Biopsy shows characteristic acute, subacute, or chronic spongiotic dermatitis, but findings are not specific.

Management of atopic dermatitis

Agents typically used to treat AD include the following:

- Moisturizers: Petrolatum, Aquaphor, or newer agents such as Atopiclair and Mimyx
- 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
- Broad immunomodulators: Tacrolimus and pimecrolimus (calcineurin inhibitors; generally considered second-line therapy)
- Targeted biologic therapies
  - Dupilumab (anti-IL-4Ra monoclonal antibody)
  - Tralokinumab (anti-IL-13 monoclonal antibody)

See the list below:

- Janus kinase (JAK) inhibitors
  - Abrocitinib
  - Upadacitinib
  - Ruxolitinib topical

Other treatments that have been tried include the following:

- Ultraviolet (UV)-A, UV-B, a combination of both, psoralen plus UV-A (PUVA), or UV-B1 (narrow-band UV-B) therapy
- In severe disease, methotrexate, azathioprine, cyclosporine, and mycophenolate mofetil
- Everolimus
- Probiotics
- Antibiotics for clinical infection caused by *S aureus* or flares of disease
- Intranasal mupirocin ointment and diluted bleach (sodium hypochlorite) baths

Nonmedical measures that may be helpful include the following:

- Using soft clothing (eg, cotton) next to the skin; wool products should be avoided
- Maintaining mild 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 if there is concomitant food allergy.

INTERPRETATION

IgE

What is immunoglobulin E?

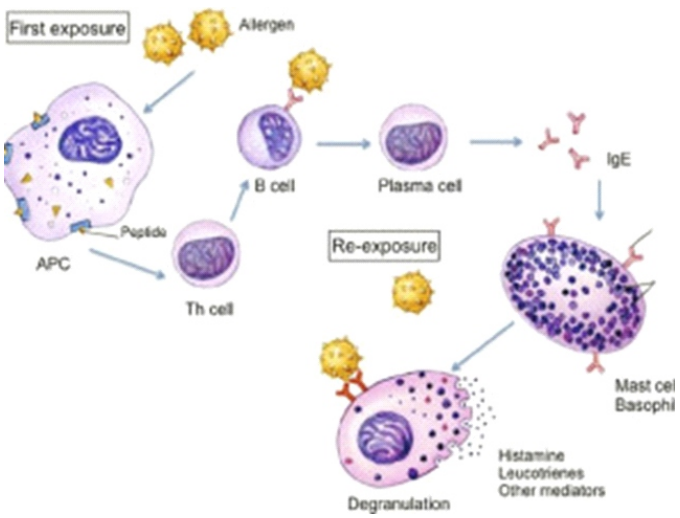
Immunoglobulin E (IgE) is an antibody produced during a type I hypersensitivity reaction to an allergen. A schematic for the type I reaction pathway is shown below.

IgE antibodies are normally found in small amounts in the blood. A higher level than normal infers an allergic disorder may be present

What is a type I hypersensitivity reaction?

Following exposure and re-exposure to an antigen (allergen) in susceptible individuals, a type I, or immediate, allergic reaction involves antigen-presenting cells, the activation of T-helper (Th) cells, the stimulation of B cells that release specific IgE, and the release of various pharmacological mediators (such as histamine, cytokines, leukotrienes, and others) from mast cells and basophils. The release of the mediators causes symptoms such as sneezing, wheezing, and weals.

Type 1 IgE-mediated hypersensitivity reaction pathway



Type 1 hypersensitivity reaction

What is an IgE test?

An IgE test is a blood test that detects circulating IgE. The test includes two types of test:

1. Testing for total IgE — the total level of IgE in the blood.
2. Testing for specific IgE — the level of specific IgE against a particular allergen.

Total IgE and specific IgE tests can be ordered at the same time or independently.

IgE levels can be measured using one of several methods. The use of the radioallergosorbent test (RAST) to measure IgE has been superseded by the use of enzyme-linked immunosorbent assays (ELISA), fluorescent enzyme immunoassays (FEIA), and chemiluminescent immunoassays (CLIA).

What are the indications for IgE testing?

An IgE test is indicated when the taking of a careful patient history and an examination lead to a suspicion of type I allergy.

An IgE test can also be used for monitoring a patient with a known allergic condition, such as:

- Anaphylaxis
- Allergic rhinitis (hay fever)
- Allergic conjunctivitis
- Asthma
- Chronic rhinosinusitis.

IgE tests are also useful to determine whether a patient is allergic to a specific protein, such as:

- Types of food allergy (eg, peanuts)
- House dust mites
- Grass, weed or tree pollens
- Animal dander or fur
- Certain drugs and cosmetics
- Moulds
- The venom of a bee or wasp.

An IgE test can be used when skin prick testing is not available or is unsuitable; for example, in an individual with dermographism, extensive skin disease, recent use of antihistamines or systemic steroids, or when there is concern that prick testing could cause an anaphylactic reaction.

IgE testing is rarely indicated in atopic dermatitis, allergic contact dermatitis, chronic spontaneous urticaria, or angioedema as the relevance of elevated IgE is uncertain in these diseases.

Choosing Wisely recommendations

- Don't perform an indiscriminate battery of IgE tests in the evaluation of allergy.
- Food-specific IgE testing should not be performed without a clinical patient history that is suggestive of IgE-mediated food allergy.
- Specific IgE testing for inhalants or foods is not indicated in urticaria unless there is a clear history implicating an allergen as a provoking or perpetuating factor for the urticaria.
- Indiscriminate batteries of IgE tests for foods are expensive and not useful, potentially leading to erroneous diagnoses and inappropriately restrictive diets.

Which specific allergens can be tested?

The specific allergens that can be tested can be classified as follows:

- Aeroallergens (inhalants)
- Indoor allergens — including house dust mites, animal dander (eg, cat, dog, and cockroach), mould, and fungal spores
- Outdoor allergens — such as pollens (from grasses, rye, weeds, and trees) and polluted air (smoke)
- Food allergens — including milk, eggs, peanuts, tree nuts, wheat, soy, codfish, and shellfish
- Venoms — including bee, wasp, hornet, ant venoms
- Dust mites (*Dermatophagoides*)
- Medicines — such as penicillin, aspirin, and others
- Latex
- Metals (especially nickel, cobalt, chromium, and zinc)
- Household chemicals
- Cosmetics.

IgE tests are also available to test different mixes of allergens. These include a:

- Food mix (ie, egg white, milk, codfish, wheat, peanut, and soybean)
- Cereal mix (ie, wheat, oat, corn, sesame seed, and buckwheat)
- Fruit mix (ie, banana, pear, peach, and apple)
- Seafood mix (ie, codfish, shrimp, mussel, tuna, salmon)
- Grass mix (ie, Bermuda, rye, Timothy, meadow, Johnson, and Bahia grasses)
- Tree mix (ie, olive, willow, eucalyptus, white pine, Melaleuca)
- Nut mix — routine (ie, peanut, hazelnut, brazil nut, almond, and coconut)
- Nut mix — extra (ie, pecan nut, cashew nut, pistachio, and walnut)
- Mould mix (ie, *Penicillium*, *Aspergillus fumigatus*, *Cladosporium*, *Candida albicans*, and *Alternaria*).

How are IgE levels reported?

The total IgE reference range depends on the age of the individual (it ranges from 0 to 4 kU/L in a newborn and 0 to ~148 kU/L in an older child or adult).

The result of a specific IgE test is reported for a grouped allergen mix or an individual allergen. The table below shows how the results are typically rated and interpreted.

Table. IgE level test ratings and interpretations

Rating of specific IgE level (kUA/L)	Grade/ Class	Interpretation
Absent or undetectable (< 0.35)	0	Unlikely
Low (0.35–0.69)	I	Doubtful significance
Moderate (0.70–3.49)	II	Possible
High (3.50–17.49)	III	More possible
Very high (17.50–49.99)	IV	More likely
Very high (50.00–100.00)	V	Very likely
Extremely high (> 100.00)	VI	Extremely likely

How are IgE test results interpreted?

IgE test results should be carefully interpreted in the context of a patient's presentation. High levels of total IgE can occur in allergic conditions, parasitic infections, certain immune-related disorders, and malignancies.

The sensitivity of specific IgE tests ranges from 60% to 95% and the specificity from 30% to 95%, depending upon the type of allergen and the age of the patient [3]. There is a good predictive value (> 90%) for food (cow's milk, egg, fish, and peanuts), pollens (grass and trees) and dust mites. Tests for some medicines, latex, moulds, and venom have poor sensitivity but greater specificity.

Note:

- A positive test result means sensitisation to an allergen.
- The indicated level of IgE may not correlate with the extent or severity of symptoms when exposed to the allergen.
- A normal level of IgE may not exclude allergic disorders.
- A result may be misleading. False-positive and false-negative results can be due to cross-reactivity, the age of the patient, or the type and duration of exposure to the allergen.

Further evaluation can be done by skin prick testing or by challenging the patient to a specific allergen in vivo.

How does IgE testing compare with skin prick testing?

Skin prick testing is more specific than IgE testing and gives a rapid result (often within 30 minutes), but it requires a trained practitioner and is not always tolerated by young children.

Specific IgE blood tests are simple and safe. They can be expensive, depending on the number of allergens tested. Caution is required when interpreting the results.

TROUBLESHOOTING

IMMUNOGLOBULINS

What Is an Immunoglobulin Test?

This test checks the amount of certain antibodies called immunoglobulins in your body.

Antibodies are proteins that your immune cells make to fight off bacteria, viruses, and other harmful invaders. The immunoglobulin test can show whether there's a problem with your immune system.

Some conditions cause your body to make too many or too few immunoglobulins.

Having too few immunoglobulins in your blood gives you a greater chance of getting infections. Having too many could mean you have allergies or an overactive immune system.

Types of Immunoglobulin

Your body makes a few different types of immunoglobulin antibodies, including these:

Immunoglobulin A: IgA antibodies are found in the mucous membranes of the lungs, sinuses, stomach, and intestines. They're also in fluids these membranes produce, like saliva and tears, as well as in the blood.

Immunoglobulin G: IgG is the most common type of antibody in your blood and other body fluids. These antibodies protect you against infection by "remembering" which germs you've been exposed to before.

If those germs come back, your immune system knows to attack them. Your doctor can test for IgG to figure out whether you've been infected by certain kinds of bacteria or viruses.

Immunoglobulin M: Your body makes IgM antibodies when you are first infected with new bacteria or other germs.

They are your body's first line of defense against infections. When your body senses an invader, your IgM level will rise for a short time. It will then begin to drop as your IgG level kicks in and increases to protect you long-term.

Immunoglobulin E: Your body makes IgE antibodies when it overreacts to substances that aren't harmful, such as pollen or pet dander. Your doctor will likely measure your IgE levels if you have a blood test to check for allergies.

Why You Might Need This Test?

Your doctor might order an immunoglobulin test if you get a lot of infections -- especially infections of the sinuses, lungs, stomach, or intestines.

They may also order the test if you have:

- Diarrhea that doesn't go away
- Unexplained weight loss
- Fevers that can't be explained by another cause
- Skin rashes
- Allergies
- Sickness after traveling
- HIV/AIDS or multiple myeloma (a type of cancer), or another condition that needs to be monitored.

How the Test is Done?

Doctors often measure IgA, IgG, and IgM together to get a snapshot of your immune function. A lab tech will usually take a sample of your blood by inserting a needle into a vein in your arm. The blood collects in a tube or vial.

Another way to do this test is with a sample of what's called cerebrospinal fluid (CSF).

CSF surrounds your brain and spinal cord. The doctor will take a sample of this fluid with a lumbar puncture (often called a "spinal tap").

For this, you go to an outpatient facility or a hospital. A technician will give you a shot in your back to help numb any pain.

You will likely lie on your side with your knees pulled up to your chest, or you sit on a table. The technician inserts a hollow needle between two vertebrae in your lower spine and removes a small amount of fluid so it can be tested.

What Do My Results Mean?

The sample will be sent to a lab for testing. This might take a few days.

Depending on your results, the doctor might need to do other tests, such as a:

- Complete blood count (CBC)
- Protein blood test
- Urine test to check for kidney problems

If your immunoglobulin level is high, it might be caused by:

- Allergies
- Chronic infections
- An autoimmune disorder that makes your immune system overreact, such as rheumatoid arthritis, lupus, or celiac disease
- Liver disease
- Inflammatory bowel disease
- Cancer, such as multiple myeloma, lymphoma, or leukemia

Low levels of immunoglobulins mean your immune system isn't working as well as it should. This can be caused by:

- Medicines that weaken your immune system, such as steroids
- Diabetes complications
- Kidney disease or kidney failure
- A weakened immune system that you were born with or developed (as with HIV/AIDS)

Just because your immunoglobulin level is high or low doesn't mean you have one of these conditions.

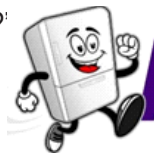
Each person's test can differ based on the method the lab uses to check the results. Talk to your doctor about your test results, and find out what you should do next.

BOUQUET

In Lighter Vein

Wrong Number:

Naughty Kid : "Hello! Do you have a refrigerator?"
Man : "Yes, I have. Who are you?"
Naughty Kid : "Is It Running?"
Man : "Yes"
Kid : "Get Hold of it… Otherwise it might run away."
The man Slams down the phone !!!



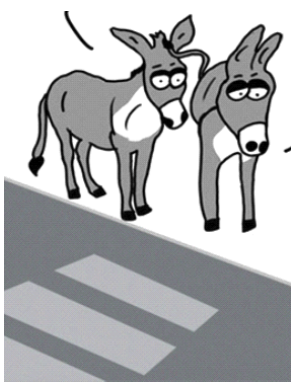
After a few Minutes the phone bell rings again.
Naughty Kid : "Hello! Do you have a refrigerator?"
Man (Angrily) : "No I don't have."
Naughty Kid : "Didn't I tell you to hold it?"

****

1 million copies of a new book sold in just two days due to typing errors of just one Alphabet in the title.
TITLE OF BOOK: "An Idea can change your **WIFE**"

****

Two Donkeys are standing on roadside...
One Donkey to other : Shall we cross the road?
Other Donkey: No way, Look at what happened to Zebra.



Wisdom Whispers

"We cannot solve our problems with the same thinking we used when we created them."

****

"While we may not be able to control all that happens to us, we can control what happens inside us".

****

"In the end, it's not the years in your life that count. It's the life in your years."

****

"Just as a snake sheds its skin, We must shed our past over and over again."

Brain Teasers

1. **Which immunoglobulin can cross the placental barrier?**
   A. IgG
   B. IgM
   C. IgA
   D. IgE.
2. **Which immunoglobulin is the least prevalent?**
   A. IgA
   B. IgD
   C. IgE
   D. IgM
3. **IgM comprises ___ % of all serum immunoglobulins.**
   A. 2–5
   B. 7–10
   C. 11–15
   D. 16–20
4. **Which is the major immunoglobulin found on mucosal surfaces?**
   A. IgG
   B. IgM
   C. IgA
   D. IgE

ANSWER: 1: A, 2: C, 3: B, 4: C

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