

# Atopic Dermatitis

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## Abstract

Atopic dermatitis (AD) together with asthma and allergic rhinitis, is the most typical manifestation of an atopic constitution. Atopic dermatitis has been known since ancient times: Job probably suffered from it. Aetius de Amida in 534BC was the first to report a skin condition closely resembling AD. But the first 'scientific' description of childhood AD, together with advice on its treatment, is found in the first textbook of Pediatrics of the Western world "Libellus de Aegritudinibus Infantium" (Handbook of Diseases of children) by the Italian doctor Paolo Bagellardo, published in 1472. In a chapter on the skin, the author advises physicians to lubricate the skin and prevent scratching in children affected by this skin disorder.

Atopic dermatitis is associated with patchy, characteristically distributed areas of cutaneous eczema, with intense itching and subsequent lichenification of the skin. Cutaneous autonomic dysfunction (increased vasoconstriction) and xerosis (dryness of the skin) commonly occur in the affected patients. In addition, profound immunological dysregulation with various immune alterations has been described in affected patients. Most patients produce IgE antibodies to a number of food and inhalants allergens.

## Epidemiology

Infants and children are principally affected by AD, adults less often. Atopic dermatitis occurs more commonly in children of atopic parents, and genetic predisposition appears to be a prerequisite in the majority of cases. Atopic Dermatitis has never been reported at birth, and rarely starts in the first 6 weeks of life.

Recent surveys indicate a significant increase in the prevalence of AD and estimations of prevalence of AD in childhood vary between 8 and 14% [1]. In children of atopic parents the estimated prevalence of AD in the first years of life is about 50% [2].

Several studies on the natural history of AD have shown that AD in early childhood usually resolves in about 60% of the children within the 6 years of life. Studies have been carried out to investigate the factors that may significantly affect AD outcome and predictive unfavorable factors are: late onset of the disease, atypical or widespread skin lesions, persisting food hypersensitivity. Prevalence of respiratory allergy in children with AD has been estimated about 60% [3].

## Clinical Features

The clinical features can be arbitrarily divided into three stages which usually occur in sequential order:

- Infantile stage (birth through two years): Although seborrheic dermatitis may precede and coexist with AD, the disease typically occurs after 8 weeks, appearing as eczema on the face, scalp, and extensor surfaces of the extremities. It may involve the trunk, thighs, buttocks, and anogenital region, or develop into a generalized exfoliation. In most infants, AD clears over months to years, whereas the most severely affected patients frequently have more persistent symptoms.
- Childhood stage (2 to 12 years): Atopic dermatitis often occurs as a continuation and extension of the infantile phase, or occurs between 3 and 6 years. It is characterized by erythema, papules, xerosis, and lichenification of the flexural folds of the arms, legs, ankles, wrists, hands, face and neck. A "reverse pattern" of AD has been described in children, which primarily affects the elbows and knees.
- Adolescent stage: Atopic dermatitis begins at about age 12, although it may be a continuation of the earlier childhood phase. Clinical features include large lichenoid plaques surrounded by crusted papules, erythema, and xerosis, predominantly involving the antecubital and popliteal fossae. The face, eyelids, neck, wrists, hands and feet can also be involved.

## Triggering Factors

Emotional stress, contact irritants, cutaneous infections and overheating are important contributory factors to AD once established. In addition to foods, recent evidence suggests that environmental allergens such as house dust mites and pollens can trigger AD [4].

## The Role of Food Allergy

The role of Food Allergy (FA) in AD was first suggested by Grulee and Sandford in 1936. These authors reported that cow's milk (CM) feeding early in life was a significant contributory factor in AD and the prevalence of AD was 7 times higher in CM-fed babies than in breast-fed babies [5]. In 1955 Glaser [6] reported that skin rashes and urticaria frequently occurred in babies up to 3 months of age with egg white in the diet, and the prevalence of such disorders was significantly reduced when egg white was given after 6 months. Other data supporting the role of FA in AD are provided by the finding of food-induced contact urticaria, which may frequently occur in children with AD. In addition, children with AD may experience food-induced systemic hypersensitivity reactions of rapid onset, both cutaneous and noncutaneous, such as vomiting, diarrhoea, respiratory symptoms and even anaphylactic shock after challenge test with the offending food. Another indirect evidence of the role of FA in AD is the significant improvement of the skin lesions after institution of an appropriate elimination diet. The elegant cross-over double-blind study by Atherton [7] demonstrated a marked improvement of AD in children receiving an egg- and CM-free diet (soy protein-based formula as CM substitute). In particular, it was noted that 14/20 children on this diet showed a significant improvement of the skin lesions, whereas only one had a favorable response when they received egg and CM in the diet. On the other hand, Fergusson et al. [8] showed that babies who received solid foods (vegetables, meat, fruits, dairy products, etc.) in the first 4 months of life had a significantly increased risk of eczema compared with babies who did not receive solid foods at this age. In addition, the rates of eczema increased in almost direct proportion to the number of different types of solid foods given to the baby in the first 4 months of life; babies given 5 or more different solid foods had over twice the risk of eczema compared with children given no solid food [8].

Other indirect support for the role of the type of feeding early in life and the onset of AD is provided by the encouraging results obtained in high-risk babies with some dietary manipulations. A significant reduction in both the prevalence and severity of AD was shown by several groups of investigators using prolonged breastfeeding supplemented by extensively Hydrolysed Formulae or Soy-protein Formulae [9-11].

Several data suggest that the role of foods in AD appears to be more relevant in infants and in pre-school children. The majority of children (75%) develop the disease within the first year of life when the food antigenic load is prominent, especially in bottle-fed babies. Positive skin test responses to foods are significantly higher in infants with AD than in children with asthma. Immunoglobulin (IgE) antibodies to a large variety of foods are frequently detected in infants and in pre-school children with AD [12]. In the last decade, double-blind placebo-controlled food challenges (DBPCFC) have definitively confirmed the role of food allergy in children with AD. In particular, it has shown that almost 50% of children with AD, attending an allergic clinic, have food hypersensitivity. Eggs, peanuts, CM, wheat, fish

and soybeans accounted for 90% of the positive reactions [13]. Employing two foods for challenges, we obtained a similar percentage of positive reactions [14]. Children with AD are frequently reported to be allergic to a wide variety of foods, an opinion supported by the high number of positive skin and RAST tests to foods found in children with AD. Although children eat a wide variety of different foods, CM, eggs and wheat - the most common foods consumed in the Italian diet - accounted for more than 93% of the positive responses. These data should be taken into account to eliminate the nutritional problems of too restrictive a diet. Foods frequently reported to induce hypersensitivity such as citrus fruit, chocolate or strawberries did not elicit positive responses in our patients. In conclusion, food hypersensitivity is an important triggering factor in almost 50% of the children with AD and the most common of ending foods are cow milk and egg.

## Pathophysiology

It has been suggested that the ingestion of the offending food(s) would lead to release of the mediators as a consequence of an IgE reaction, and high levels of serum histamine have been shown in children with AD after a positive DBPCFC response [15]; but histamine release only (at the gastrointestinal and/or skin level) cannot completely explain the histology of the eczematous lesion. An important role is played by the late phase of IgE-mediated hypersensitivity, and evidence is accumulating that eosinophils actively participate in late phase-allergic reactions in different tissues, including the skin. When the ingested food antigen comes in contact with the skin mast cells, histamine and other chemo-attractants are released into local tissue. Consequently, neutrophils and eosinophils infiltrate the skin, thus contributing to the skin pathology by releasing cationic proteins and various pro-inflammatory mediators. Eosinophilia is frequently associated to AD, and generally its degree correlates with the severity of the disease. Although the pathophysiology of AD is not fully understood, there is evidence that eosinophils may play an important role in this process (Table 1). Recent studies indicate a role for eosinophil disruption and degranulation in inducing tissue destruction. Several potent, toxic and cationic proteins have been described in the eosinophil granules. These include major protein (MBP), eosinophil-derived neurotoxin (EDN), eosinophil cationic protein (ECP) and eosinophil peroxidase (EPO).

It has been shown that some of these cationic proteins are elevated in the peripheral blood of patients with AD [16]. There is also evidence for eosinophil disruption and degranulation in the affected skin [17]. Finally, an active participation of eosinophils in patch-test reactions to inhalant allergens has been shown in patients with AD [18]. Eosinophils are not only active in mediating allergic inflammation but interact in cellular networks with antigen-presenting cells, mast cells, and T lymphocytes. These other cells influence eosinophil maturation, mobilization, tissue localization and activation. In agreement with other authors, we found elevated serum levels of ECP in children with AD. It seems likely that elevated ECP serum levels in patients with AD may reflect the activation of eosinophils in the skin. It has been reported that *in vitro* ECP can induce an increased histamine release [19] and can suppress T-lymphocyte function via non-toxic mechanisms [20]. It is therefore tempting to speculate that ECP, besides having noxious effects for the skin, may contribute to the profound immunologic abnormalities described in patients with AD.

Table 1: Properties of Soya-proteins-based Formulas

Properties of Soya-proteins based on formulae	<ul style="list-style-type: none"> <li>• No minute amount of cow milk proteins</li> <li>• No cross reactivity with cow milk protein</li> <li>• Lower immunogenicity (IgE Abs) than cow milk proteins</li> <li>• Lower allergenicity than cow milk proteins</li> <li>• Similar antigenicity (IgG Abs) to cow milk proteins</li> <li>• Nutritional adequacy similar to cow milk formulas</li> <li>• Better palatability than highly Hydolysate Formulas</li> <li>• Less expensive than highly Hydolysate Formulas</li> </ul>
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The detection of elevated ECP levels in the serum of AD patients represents only an indirect measure of the pathological process taking place in the skin [21]. In our experience, measurement of ECP might represent a noninvasive tool to assess the activity of AD in relation to eosinophil involvement in this disease.

Other possible factors involved in the eosinophils degranulation are platelet-activating factor (PAF) and cytokines interleukin (IL-3) IL-5 and GM-CSF. An aggravating factor is the demonstration in AD and food-sensitive patients of histamine releasing factors (HRF) produced by mononuclear cells as a consequence of continuous food challenge; these HRF are able to promote a continuous histamine release from mast cells and basophils. It has been shown that spontaneous basophil histamine release (SBHR) is high in children with food induced AD while they are not on an restricted diet but it is close to normal when these children are on an elimination diet [22]. Spontaneous basophil histamine release correlates to the HRF production from peripheral blood mononuclear cells and HRF may activate or decrease the activation threshold of both basophils and mast cells and could explain the high SBHR described in patients with AD.

It is noteworthy to stress that the mediators and cytokines that can be released by various mechanisms induce pruritus, the main symptom of AD; this provokes scratching which, in turn, produces the skin lesions.

### Diagnosis of Food Allergy in AD

It is well known that clinical history of FA in AD usually is rather unreliable

[23]. Only in a few cases does the patient note a worsening of skin lesions and pruritus after the ingestion of the offending food. In addition, the triggering foods usually are common items in the diet and cannot therefore be identified easily. Of course, in infants it is important to collect data or breast-feeding, the time and type of weaning, and the relationship between the first ingestion of a given food and the onset of skin lesions.

A “diagnostic” oligoantigenic elimination diet should be given for no more than 4 weeks since there are so far no laboratory tests for the diagnosis of FA which obviate the need for careful clinical assessment. The elimination diet can be adapted to the suspected sensitivities of the single patient. We use, with good results, a home-made meat diet as suggested by Rezza (Table 2). The formula is prepared as follows: fresh or frozen lean lamb’s meat (free from fat and tendons) is cut into small pieces, boiled and minced, then mixed with the other components of the diet. This formula is nutritionally adequate, has a pleasant taste, and is economical. Once clinical improvement is achieved, wheat and saccharose are reintroduced into the diet, then various foods in sequence, with the obvious exception of CM. This diet provides 740 calories per liter and the distribution of nutrient and the energy provided by this diet are in agreement with the European Society of Paediatric Gastroenterology and Nutrition guidelines on infant nutrition. Among the advantages of this diet is the possibility of adapting it to the individual patient; that is, vegetables, fruit and meat, wheat flour and other nutrients can be added to the diet according to the age and weight of the child, and the doctor’s judgement.

Table 2: Immunogenicity and cross-reactivity of HFs and SPFs

	HFs Casein		SPF Whey	
	Highly	Partially	Highly	Partially
Immunogenicity (IgE)	-	+	-	+
Antigenicity (IgG)	-	+	-	+
Allergenicity	+	+++	-	+
Cross-reactivity with IgE Abs to CM	+	+++	+	-

Although diagnostic elimination diets are considered the most suitable procedure to detect the offending foods, several factors may contribute to the lack of reliability of elimination diets in AD due to FA, since small quantities of triggering allergens may be heedlessly or inadvertently ingested by, or may reach food-allergic children [24]. Cross-reactions may sometimes occur between closely related foods (eggs of different birds such as chicken, turkey, duck, and goose, milk of various species such as CM and goat milk, veal meat and cow milk, chicken meat and egg). Cross-reactions also may occur between CM proteins and CM proteins hydrolysate formulas, especially partially hydrolyzed [25-27].

When a child shows a clear-cut improvement after the 4-week diet, a challenge test should be performed. This test, although time-consuming and sometimes even hazardous, is necessary because of the lack of any other reliable in vivo or in vitro test for the diagnosis of food hypersensitivity.

It is generally agreed that the diagnosis of FA should be always confirmed by DBPCFC. Usually the offending food is hidden in gelatin capsules. However there exists no general agreement on the amount of food, fresh or lyophilized, to be administered or on the procedure of administration to be followed when children or infants are unable to ingest the capsule, nor how to mask the taste of the offending food [23].

The procedure is not risk-free and severe reactions may occur. Therefore equipment for the management of anaphylaxis should be at hand.

The clinical accuracy of Skin prick-test depends on the standardization of food-allergen extract. Since variations in food allergen extract may influence the results, it is necessary that the preparations of allergen extract be purified and standardized to minimize the risk of questionable results. However the positive predictive accuracy of skin test to foods is about 60%, therefore the challenge test is imperative for the diagnosis of FA [13,23].

Since history is unreliable especially regarding the prediction of immediate reactions, challenge tests in children with positive ST and/or RAST should always be done with caution. The pretty good negative predictive accuracy of skin test permits exclusion of immediate reactions following the challenge test.

Methods for the detections of IgE antibodies to foods suffer from the same limitations of the skin test [12].

## Treatment

### Elimination of the Offending Food

The elimination of the offending food(s) is mandatory in children with food induced AD. The most common offending foods are cow milk and egg. Hypersensitivity to cow's milk (CM) is an important contributory factor in atopic dermatitis. CMA peaks in infancy, when CM is an important source of nutrients. In the first year of life, CM provides almost the entire dietary supply of a 2-year-old ml of CM provides 100% of the daily requirement of calcium, 50% of the protein, 100% of the 24% of energy. Therefore the appropriate choice of a CM substitute is imperative for feeding babies with CMA.

In (Table 1 and 2) we have reported the main properties of SPFs [28]. Contrary to hydrolysate formulas (HFs) which may contain native proteins from which the product is derived, no minute amount of intact CM proteins are present in SPFs. Soy proteins are immunogenic, but according to experimental and clinical studies, they are less immunogenic and allergenic than CM proteins. Soy Proteins Formulas do not cross-react with CM proteins, while HFs do. As we first reported, whey and partially HFs can trigger anaphylactic reactions, which may be even life threatening, in infants and children with IgE mediated CMA [25-27]. Due to residual allergenic epitopes and contamination with minute amount of intact proteins, these products are not safe for children with IgE mediated CMA, while extensively HF are safer and useful in young babies with CM and/or soy enteropathy. Soy proteins are antigenic as CM proteins, but as previously pointed out this should not be regarded as harmful. SPFs are nutritionally adequate, the taste is well accepted by most infants and, although SPFs are expensive, they are cheaper in comparison to HFs [28].

Therefore SPFs should be the preferred choice in children with IgE-mediated CMA and casein highly HFs should be tried when there is definitive evidence that the child is allergic to Soy. Whey partially HFs should never be used in infants with IgE-mediated CMA and due to the very good negative predictive value prick test to highly HFs should be performed before giving this product to babies with CMA.

### Counselling

As with any chronic disorder, it is most important to counsel the parents about the cause and natural history of the disorder. This is usually the most important aspect of treatment.

Standard management of AD include: judicious use of low or mild potency topical steroids (no more than 2-3 times a day), lubricants, frequent bathing, avoidance of harsh soap and wollens, parenteral antibiotics.

### Elimination of Irritants

It is not necessary to avoid woolen clothing, soap, bathing or exposure to the sun unless they aggravate the eczema. If sensitivity to wool is present, contact should be avoided with wool in clothing, carpets, car seats, sheepskins and furniture. If soap aggravates the eczema emulsifying ointment may be used as a soap substitute. If bathing is irritant it should be reduced to the least amount that keeps the infant socially acceptable, with explanation to mother that frequent bathing is more for aesthetic than health reasons. Appropriate sun exposure and bathing in the sea is helpful to most children with eczema.

### Topical Corticosteroids

The most effective symptomatic treatment is the application of a topical corticosteroid. Hydrocortisone one percent is safe for long term use on all areas. Nothing stronger should be used on the face, flexures or napkin area. If hydrocortisone gives satisfactory control it can be used for all areas of eczema. Parents should be instructed to apply the topical steroid as evenly and thinly as possible, one to three times a day. No benefit is achieved by applying it more frequently.

Treatment with systemic steroids should be avoided and widespread, long-term use of potent topical steroids, especially under occlusion, can induce adrenal suppression.

## Infection

Secondary infection of eczema should be suspected when there is increasing erythema, oozing or pustulation, especially if the eczema becomes resistant to treatment. Diagnosis of secondary bacterial infection is important because control of the infection gives dramatic improvement of previously unresponsive eczema.

Oral antibiotics are useful for the management of acute, weeping flares of AD. The most common recovered organism is *Staphylococcus aureus* and a ten-day course of erythromycin is usually effective. Topical antibiotic preparations should be avoided since they are non effective and potentially sensitizing.

## Itch and Scratching

Measures to reduce itch and scratching are very important. Topical steroids are the most effective local treatment, but keeping the infant well covered with clothing is a more effective measure. Itch and scratching increase when infants with eczema are undressed, and decrease or stop when they are dressed. This can be observed regularly during consultations. Also, excoriations cannot be produced by finger nail scratching when this is done through a layer of clothing. When the eczema is active, a second person should restrain the infant's hands during bathing.

Pruritus is the most important symptom which afflicts patients with AD. Among antihistamine drugs, hydroxyzine is the most useful antipruritic agent due to its tranquilizer effect.

## Pharmacological Treatment of Food Allergy

The treatment of choice for AD due to food allergy is to avoid the offending food(s). This is easy if the child is allergic to foods which are not basic components of the diet such as strawberries, seafood, citrus fruit, peaches, etc., or when the offending food is not an important nutrient such as apples, nuts or chocolate. Problems arise when the child is allergic to basic food(s) or food with high nutritional value like CM, eggs or fish.

In these cases a drug which can prevent symptoms would be useful in order to avoid a strict diet free from such important nutrients. Sodium cromoglycate is now widely used for the management of respiratory allergy. But conflicting results of its use in food allergy have been reported by different investigators since the first report which showed that sodium cromoglycate pretreatment of a soy allergic patient gave no protection when the drug was inhaled whereas oral pretreatment with 400mg blocked both immediate and late reactions. We have reviewed 12 papers on the use of sodium cromoglycate in the management of children with AD. These covered a total of 281 children aged 0.5-15 years (11\$) (Table 2). Five of the studies were open trials, 1 single-blind and 6 double-blind. Four of the 5 open studies concluded that sodium cromoglycate was effective and three found it ineffective.

As already reported by previous studies, there are several explanations for the varying effectiveness of sodium cromoglycate in food allergy. Factors influencing the outcome include different selection criteria of patients, wide variations in daily dosage of sodium cromoglycate, different amounts of food antigen ingested during the trials, different ways of evaluating efficacy and problems of patient compliance. But overall sodium cromoglycate appears to be a safe drug and the reports of adverse effects are few.

## Conclusion

Scientific evidence accumulated in recent years indicates that food and inhalant allergens can trigger AD. As a consequence, a state of skin hyperreactivity, similar to bronchial hyperreactivity described in allergic patients with asthma, frequently occurs. Nonspecific stimuli can therefore trigger and worsen the skin lesions. Eosinophils, as in asthma, seem to play an important role in inducing and maintaining the skin lesions.

Taken together, these data suggest that in AD there exists a vicious circle, by which immunologic and non immunologic factors act in various ways and at different levels triggering different, though synergistic, reactions to initiate, amplify and maintain the chronic skin lesions characteristic of the condition. It may be hypothesized that, also in AD, the allergens could induce a cutaneous hyper-reactivity analogous to the bronchial hyperreactivity seen in patients with asthma (17°). This in turn could lower the pruritus threshold for a wide range of nonspecific stimuli such as irritants, heat, humidity, stress, and the like.

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