

Role of immediate food hypersensitivity in the pathogenesis of atopic dermatitis

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Twenty-six children with atopic dermatitis and markedly elevated serum IgE concentrations were evaluated for clinical evidence of hypersensitivity to foods with double-blind placebo-controlled food challenges. Selection of foods for challenges was based on positive prick skin tests (>3 mm wheal) or a convincing history. At least one positive skin test to a food antigen was found in 24/26 patients. A total of 111 double-blind placebo-controlled challenges were performed in these children after suspect foods were eliminated from their diets for 10 to 14 days. There were 23 positive challenges in 15 children, 21 of which manifested as cutaneous symptoms, primarily pruritus and an erythematous macular and/or maculopapular rash involving 5% (or greater) of the body surface. In all, 14 children (54%) developed cutaneous symptoms after food challenges. All symptoms occurred within 10 min to 2 hr of challenge; nasal symptoms, mild wheezing, and gastrointestinal symptoms were seen in some children. No symptoms occurred in 104 placebo challenges. There were 86/111 clinically insignificant positive skin tests (77%) and three false-negative skin tests. These studies demonstrate that in some children with atopic dermatitis, immediate food hypersensitivity can provoke cutaneous pruritus and erythema, which leads to scratching and subsequent eczematoid lesions. (J ALLERGY CLIN IMMUNOL 71:473, 1983.)

Several lines of evidence suggest a role for immediate hypersensitivity in the pathogenesis of AD: (1) the fact that serum IgE concentrations are elevated in approximately 80% of children with AD,¹ (2) the presence of positive immediate skin tests and RAST to various dietary and environmental allergens in most children so affected,^{2, 3} (3) a positive family history for atopic disease in two thirds of eczema patients,⁴ and (4) the eventual development of allergic rhinitis and/or asthma in 50% to 80% of such patients.^{5, 6} A large body of anecdotal information has accumulated in the literature, citing the efficacy (or lack of it) of various elimination diets in the treatment of AD. However, the debate continues, primarily due to a lack of controlled studies. Diagnostic procedures have often been imprecise, clinical correlation with laboratory data has been poor, and responses to treatment have been highly variable. At a symposium on infantile

AD sponsored by the Academy of Pediatrics in 1965, a consensus of opinion was reached that results of food extract skin tests were not useful either as a diagnostic tool or as a guide in formulating elimination diets for children with AD.⁷ Investigators further argued that provocative testing did not elicit typical eczematoid skin lesions. However, the role of "scratching" in the genesis of eczema lesions was demonstrated by Engman et al.,⁸ and AD is commonly referred to as "the itch that rashes." If food challenges could be shown to incite distinct episodes of pruritus, it follows that frequent ingestion of the offending antigens would result in intermittent pruritus, secondary scratching, and subsequent development of eczematoid skin changes. Therefore the purpose of this study was to determine whether immediate food hypersensitivity plays a part in the pathogenesis of AD in a pediatric population and, if so, whether skin testing is useful in diagnosing that hypersensitivity in these patients.

MATERIALS AND METHODS

Subjects

Twenty-six children, ranging in age from 16 mo to 19 yr (median 11 yr), fulfilled the following preestablished criteria and were included in the study: (1) diagnosis of AD as defined by the criteria of Hanifin and Lobitz,⁹ (2) serum IgE concentration greater than 1000 U/ml (normal range 5

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Abbreviations used

AD: Atopic dermatitis
RAST: Radioallergosorbent test

to 621 U/ml), (3) history of possible food hypersensitivity, and (4) capability of cooperating with challenge procedures.

Procedures

Before admission of children to the Duke University Clinical Research Unit (RR-30), medical histories and previous skin-test and/or RAST results were reviewed. On the basis of this review, parents were instructed to eliminate totally up to four to six suspected food allergens from the child's diet for a 1 to 2 wk period before admission. Diet information sheets were mailed in advance to assist parents in identifying all sources of particular food antigens. Elimination diets were maintained during the hospitalization. Patients were also instructed to discontinue all antihistamines for 5 to 7 days before admission and all beta agonists for 12 hr before admission. No patient entering the study had been on systemic steroids within 1 mo before admission.

Skin tests

Shortly after admission, all children underwent skin testing to a battery of 28 different food antigens (see Table I). Standard glycerinated extracts (1:20 w/v; Greer Laboratories, Lenoir, N. C.) were applied by the prick technique. All skin tests were applied and measured by the same technician; mean diameters of erythema and wheal reactions were recorded. Wheal reactions 3 mm greater than the negative control were considered positive.¹⁰

Food challenge

Double-blind placebo-controlled food challenges were performed in a manner similar to that described by Bock et al.¹⁰ and May.¹¹ The selection of foods for administration was based on a positive skin test and history of possible clinical reactivity or a strongly suggestive history despite a negative skin test. No patient with a convincing history of a major anaphylactic reaction (laryngeal edema, severe wheezing, hypotension, etc.) requiring emergency therapy was tested with that food.

Foods for testing were placed in size "0" tartrazine-free opaque capsules (Eli Lilly & Co., Indianapolis, Ind.) with 400 to 500 mg of dehydrated powdered food per capsule or were disguised in a broth or juice. Dehydrated foods were obtained from camping stores (Richmoor, Van Nuys, Calif.) or local health food stores. Up to 8 gm of dehydrated food was administered in capsules (up to 18 capsules per challenge) or up to 10 gm was administered in a broth or juice (up to 150 ml per challenge) over a 1 hr period. Two challenges were performed each day, one at 8 A.M. and one at 1 P.M. One of the daily challenges was always with a placebo (sucrose or corn starch) and the other with one of the suspected foods. Dieticians in the Clinical Research Unit randomized all challenges so that nursing staff, patients, par-

ents, and the investigator were unaware of the contents of any given challenge. If any symptoms secondary to the challenge were suspected, the challenge was interrupted and the patient was examined by the investigator. If the investigator felt a significant reaction had occurred, the challenge was terminated. If no symptoms developed, the code was broken the following day and the patient was given the food in an open fashion. Equivocal reaction or those that occurred in individuals with negative skin-test results were repeated at least one time.

Symptom scores

A standard sheet was used to score all studies (Fig. 1). All potential reactions were scored as to the type, time of onset, severity, and duration. With a modification of the "rule of nines" burn chart, a rough quantitation of cutaneous involvement (erythema, pruritus, and/or rash) was recorded.

RESULTS

Serum IgE concentrations in the 26 children fulfilling the criteria outlined in Materials and Methods ranged from 1550 to 40,000 IU/ml (geometric mean 8463 IU/ml). Half of the children had the classic triad of AD, asthma, and allergic rhinitis, while only five had AD alone. Twenty-four children had at least one positive skin test at the time of admission; in all, 111 positive skin tests were elicited (Table I). A total of 104 sets of food challenges were performed. None of the 104 placebo challenges was interpreted as either equivocal or positive. In contrast, 15 children demonstrated 23 positive responses to food challenges, nine children reacted to only one food, four reacted to two foods, and two reacted to three foods. No child with a negative food challenge reacted to that food when ingesting it in an open fashion. Five food challenges were not performed because of a convincing history of a major anaphylactic reaction (three peanut, one fish, one potato). No child experienced a major anaphylactic reaction requiring emergency therapy secondary to the food challenges.

Symptoms induced by food challenge

Table II outlines diagnosis and results of serum IgE determinations, skin tests, and food challenges on those patients with positive food challenges (No. 12 based on history of anaphylaxis). Table III gives similar results for patients with negative food challenges only. There was no statistical difference between the patient group with positive food challenges and the group with negative challenges when compared for sex, age, diagnosis, serum IgE concentration, or number of positive skin tests when analyzed by chi-square or t test of group geometric means.

All symptoms developed within 10 min to 2 hr of

DUKE UNIVERSITY MEDICAL CENTER

FOOD CHALLENGE SYMPTOM SHEET

Name

Duke #

Date

Possible Reactions:

Skin

hives or swelling

redness

itching

rash

Eyes

watering

itchiness

Nose

rhinorrhea

itchiness

congestion

Other

Chest

wheezing

"tightness"

dyspnea

Abdomen

nausea

vomitting

diarrhea

abdom. pain

For each test, list reactions stated to occur, time of onset after ingestion of capsules (or liquid), grade of severity (minimal, moderate, major, extreme), and duration of symptoms. For rashes, note the area involved (scale from diagram).

TIME GIVEN

#1)

#2)

#3)

#4)

#5)

#6)

1

2

3

4

5

6

7

8

9

Left Right
Posterior

1

2

3

4

5

6

7

8

9

Right Left
Anterior

FIG. 1. Symptom score sheet. Extent of cutaneous symptoms are roughly quantitated by a modification of the "rule of nines" burn chart.

TABLE I. Results of prick skin tests to selected food antigens

Reagent	No. positive	Reagent	No. positive	Reagent	No. positive
Egg	13	Codfish	4	Barley	1
Peanut	13	Shrimp	4	Oats	1
Milk	8	Yeast	4	Peach	1
Soybean	8	Lamb	3	Orange	1
Pork	7	Squash	3	Corn	0
Chicken	6	Tomato	3	Rice	0
Wheat	5	Beef	2	Banana	0
Pecan	5	Lima beans	2	Apple	0
String beans	4	Rye	2	Chocolate	0
Green peas	4	White potato	2	Others	5

TABLE II. Patients with positive double-blind food challenges

Subject	Complaint	Age (yr)	IgE (U/ml)	Positive prick tests*	Food challenge (symptoms elicited)
1	AD	12	17,000	Peanut, lamb, rye, wheat, soy, pork, pecan, peas	Neg. - wheat, peas, pork Pos. - soy (cutaneous)
2	A, R, AD	11	40,000	Wheat, chicken, egg, milk, peanut	Neg. - soy, chicken, corn, chocolate, beans Pos. - wheat (cutaneous) milk (cutaneous, GI) egg (cutaneous, GI, resp.)
3	A, R, AD	17	4,200	Rye, barley, beans, egg, chicken, peanut, fish, lima bean	Neg. - milk, chicken Pos. - rye (cutaneous) egg (cutaneous, GI, resp.) peanut (hx of anaphylaxis)
4	A, R, AD	5	13,000	Egg, milk, lamb, cheese (RAST: milk, egg, wheat)	Neg. - Pos. - milk (cutaneous, GI) egg (cutaneous) wheat (cutaneous)†
5	A, R, AD	11.5	8,300	Bean, squash, soy, egg, peach, peanut	Neg. - milk, soy, squash, peanut, peach
6	A, R, AD	10	35,000	Wheat, egg, milk	Neg. - milk, egg Pos. - wheat (cutaneous) chocolate (cutaneous, GI)†
7	A, R, AD	4.5	52,000	Egg, milk, tomato, peanut	Neg. - milk Pos. - egg (cutaneous, GI)
8	A, R, AD	8	4,100	Egg, milk, pork, soy, chicken	Neg. - egg, wheat, soy Pos. - milk (cutaneous) chicken (cutaneous)
9	AD	3	1,800	Egg, milk, pork, orange, peanut, pecan, fish, lamb, cheese, shrimp	Neg. - beef, pork, soy Pos. - milk (cutaneous) egg (cutaneous, resp.) peanut (hx of anaphylaxis)
10	AD, R	5	11,000	Egg, peanut, oats, tomato, pork, pecan	Neg. - pork, tomato Pos. - egg (cutaneous, GI)
11	AD	1.5	12,000	Egg (RAST: milk, egg, wheat)	Neg. - milk, soy Pos. - egg (cutaneous, nasal)
12	AD	17.5	11,000	Potato, peanut	Neg. - milk, egg, wheat, orange Pos. - white potato (hx of anaphylaxis) peanut (hx of anaphylaxis)
13	A, R, AD	11	9,500	Chicken, egg	Neg. - milk, egg, wheat Pos. - chicken (cutaneous, GI)
14	AD, R	13	2,200	Beans, peas, squash, soy, egg, peanut, chicken, lima beans	Neg. - peanut, soy, peas, green bean, beef, chicken Pos. - egg (nasal, GI)
15	AD, R	9	14,000	Fish (ID: milk, wheat, egg)	Neg. - milk, wheat Pos. - egg (GI)†
16	AD, A	12	3,600	Soy, peanut, fish, wheat	Neg. - peanut, wheat, yeast Pos. - soy (cutaneous, GI, pulmonary) fish (hx of anaphylaxis)

A = asthma; R = allergic rhinitis; GI = gastrointestinal; resp. = respiratory; hx = history.

*Positive prick test: wheal 3 mm greater than negative control.

†Positive food challenge with negative skin test.

the challenge. Of 23 positive responses to food challenges, 21 involved cutaneous symptoms consisting of pruritus and an erythematous macular and/or maculopapular rash involving 5% (or greater) of the body surface (cutaneous). In many instances it was impos-

sible to determine whether skin erythema preceded scratching, since pruritus was usually intense and scratching profound. Often superficial abrasions and rarely bleeding were seen secondary to scratching. In several cases, however, untraumatized skin was



FIG. 2. Erythematous macular and/or maculopapular rash on lower back of patient with positive food challenge to egg. Note excoriation in upper righthand area of photograph.

TABLE III. Patients with negative food challenges

Subject	Complaint	Age (yr)	IgE (IU/ml)	Positive prick tests	Negative food challenges
1	A, R, AD	19	6,200	Wheat	Wheat
2	A, R, AD	19	13,000	Fish (RAST: peas, fish)	Wheat, egg, chicken, pea
3	A, R, AD	9.5	1,700	Peanut, pork	Peanut, pork, egg, soy
4	A, R, AD	15	3,000	Negative	Milk, chicken, egg
5	AD	9	3,100	Pea, soybean	Pea, soybean
6	AD	7.5	19,000	Negative	Milk, egg
7	A, R, AD	8	7,800	Beans, beef, chicken, pork, soy, egg, fish, lamb, cheese, shrimp, coffee, tea, rye, milk	Milk, egg, beef, wheat, chicken, soy, pork, fish
8	A, R, AD	11	7,400	Pea, squash, beef, chicken, soy, egg, peanut, pecan, fish, cheese, shrimp, oyster, rye	Milk, egg, soy, chicken
9	R, AD	16	11,000	Shrimp	Milk, egg, wheat, chocolate
10	A, R, AD	10	19,000	Pork	Milk, egg, wheat, chicken, pork

A = asthma; R = allergic rhinitis.

found to have erythematous macular and/or slightly raised areas that were very pruritic (Fig. 2). Perioral involvement was rare and skin symptoms occurred most commonly in areas where the patients' eczema lesions typically flared previously (e.g., neck, flexural areas, etc.). Urticarial lesions were uncommon and occurred in only two cases; one child had two urticarial wheals and another had only one. In both cases, the children had extensive pruritic, erythematous macular rashes.

Nine food challenges resulted in skin symptoms alone, whereas the remainder resulted in concomitant gastrointestinal and/or respiratory symptoms (Table II). Gastrointestinal symptoms consisted of nausea and abdominal pain (five cases), one to three episodes of vomiting (four cases), and/or multiple episodes of diarrhea (two cases). In only one case did isolated gastrointestinal symptoms occur. Respiratory symptoms occurred in eight cases and consisted of nasal congestion, rhinorrhea, pruritus and sneezing, mild

TABLE IV. Foods implicated in hypersensitivity reactions

	Food challenge		Skin test		Concordance (%)
	No.	%	No.	%	
Egg	10	36.0	13*	11.7	69*
Milk	4	14.0	8	7.2	50
Peanut	3	11.0	13	11.7	23
Wheat	3	11.0	5*	4.5	40*
Soybean	2	7.0	8	7.2	25
Chicken	2	7.0	6	5.4	33
Fish	1	3.5	4	3.6	25
Chocolate	1	3.5	0*	0	0*
Potato	1	3.5	2	1.8	50
Rye	1	3.5	2	1.8	50
Pork	0	0	7	6.3	0
Other	0	0	43	38.8	0
Total	28	100.0	111	100.0	

*False negative skin test.

periorbital edema and tearing, and in one case, mild wheezing. All symptoms induced by the food challenges resolved within 2 to 3 hr except for superficial abrasions secondary to scratching; no treatment was required in most cases, although oral diphenhydramine was administered in three cases for relief of severe pruritus.

Correlation of skin tests and food challenge

Sixty-three food challenges were carried out in patients who had both a positive skin test and a history suggestive of possible intolerance to a particular food. Forty-three of these challenges (68%) were negative, suggesting that the skin-test reactions were clinically insignificant. On the other hand, in the other 20 challenges (32%) there were positive results, 18 of which were manifested by cutaneous reactions. In all five instances in which patients had convincing histories of major anaphylactic reactions, skin tests were positive to the particular foods. Forty-one positive skin tests were not investigated with food challenges, since patient history and ingestion of those foods while under observation in the Clinical Research Unit strongly ruled against clinical hypersensitivity. It would therefore appear that positive skin tests denote clinically significant food allergy in about 23% of instances (25/111).

Forty-one food challenges were performed because of strongly suggestive histories for food hypersensitivity despite negative skin tests to the suspected food antigens. Food challenges were negative in 38 instances (92.5%) but, surprisingly, were positive in three cases (children 5, 9, and 10 yr old). One challenge resulted in cutaneous symptoms, one in gastro-

intestinal, and one in gastrointestinal plus respiratory symptoms. In each case, challenges were repeated to confirm the accuracy of the initial challenge. Two of these patients subsequently underwent intradermal skin testing with 1:1000 (w/v) concentrations of the particular antigens and both were positive, as were RAST results with those foods.

Specific foods eliciting hypersensitivity reactions

Table IV lists the foods implicated in provoking hypersensitivity reactions in the AD study patients. Including the five skin test-positive patients not challenged in this study because of convincing histories of major anaphylactic reactions to food antigens, symptoms occurred after food ingestion in 28 instances. In this study, egg was by far the most common offending food (36% of positive challenges), followed by milk (14%), wheat (11%), and peanut (11%). Although cross-reactivity among foods in certain "families" (e.g., among legumes—peanut, soybean, peas, etc.) is reportedly common, as determined by skin testing, no such cross-reactivity was demonstrated in the food challenges done in individual patients in this study.

Skin tests were most often positive to egg (12% of positive skin tests), peanut (12%), milk (7.3%), soybean (7.3%), pork (6.4%), chicken (5.5%), and wheat (4.6%). When results of skin tests and food challenges with individual food antigens were examined for concordance, it was noted that positive skin tests with some food extracts were more likely to be associated with clinical symptoms than others. Sixty-nine percent of patients with positive skin tests to egg extract demonstrated positive reactions after oral egg challenge. Positive skin-test reactions to milk were associated with positive oral challenges in 50% of patients, to wheat in 40%, and to peanut in 23%. However, overall concordance between results of skin tests and double-blind placebo-controlled food challenges was poor (23%), demonstrating the need for blinded food challenges in establishing evidence for clinically significant food hypersensitivity.

DISCUSSION

AD often begins in early infancy as an erythematous, intensely pruritic, maculopapular eruption and progresses with time to become a more lichenified dermatitis.¹² Between 1.1% to 4.3% of a general pediatric population has been reported to have this disorder, but the exact prevalence is not known.^{13, 14} Despite intensive research by many investigators, the etiology of AD has remained elusive and no comprehensive pathogenic theory can account for the various immunologic, physiologic, and pharmacologic aberrations described. Undoubtedly, multiple factors

contribute to the development of the typical eczematoid skin lesions seen in patients with AD, but pruritus with subsequent scratching appears to be a common denominator. Therefore any provocative factor, such as ingestion of food, that results in pruritus might represent one etiologic mechanism in the evolution of eczematoid skin changes.

In 1936, Engman et al.⁸ reported on a study in a child with known immediate wheat hypersensitivity who was challenged orally with wheat antigen. Half of his body was protected by dressings. After wheat ingestion, severe pruritus developed and subsequent traumatization resulted in eczematoid lesions only on the unprotected half of the body. In the present study, 26 children with severe AD and markedly elevated serum IgE concentrations were challenged in a double-blind placebo-controlled fashion with foods suspected of aggravating their skin condition. Twelve children (46%) were noted to develop cutaneous pruritus and erythema after the ingestion of food antigens on 21 separate occasions. Pruritus was severe enough in several patients that scratching resulted in marked excoriations and bleeding. All cutaneous symptoms developed rapidly (15 min to 2 hr), suggesting rapid absorption and dissemination of the offending antigen. No "late reactions" were observed in any patients. These findings are consistent with earlier studies by Walzer and colleagues,¹⁵⁻¹⁷ who investigated passive cutaneous anaphylaxis in orally challenged subjects. A characteristic wheal and flare reaction developed at the prepared site 10 to 15 min after the food was ingested, indicating that intact antigenic material can be rapidly absorbed and disseminated throughout the body.

Gastrointestinal symptoms developed after oral challenges in 10 children on 11 occasions, but in only one instance were these isolated symptoms. Respiratory symptoms developed in seven children on eight occasions but never occurred as an isolated finding.

Egg was the most frequent offending food antigen in this study, resulting in 36% of the positive oral challenges. As in the studies of Bock et al.,¹⁸ egg, peanut, and milk accounted for the majority of positive food challenges. In contrast to the experience of those authors, however, wheat was responsible for three (11%) of the positive food challenges in this study.

Over the past several years, May and Bock^{10, 11, 18-21} have employed double-blind placebo-controlled food challenges to demonstrate the role of food antigens in the development of respiratory, gastrointestinal, and cutaneous symptoms in atopic individuals. They found histories of food hypersensitivity generally unreliable when compared with food challenge results. Although data pertaining to this were not presented

here, a history of food hypersensitivity was generally of little value in predicting which patients would react to a food challenge. Several factors may account for this in our study group: (1) patients have previously seen several physicians (allergists and dermatologists) and consequently have been biased as to possible reactions, (2) patients have such severe eczema that distinct episodes of pruritus secondary to the ingestion of any particular food could easily be missed, and (3) the average age of the patients at their initial visits was much older than that generally encountered by pediatricians, thereby resulting in less reliable early histories. However, primary physicians should not be discouraged from obtaining detailed food histories, since histories acquired early would be less influenced by the first two factors.

Skin testing was done as described by May and Bock^{10, 18-21} and interpreted according to their criteria. A wheal 3 mm greater than the negative control was considered a positive reaction. In view of the large number of positive skin tests found in patients without clinically significant hypersensitivity, we looked at various other interpretive schemes in an attempt to improve the specificity of skin-test results. Altering the criteria for wheal size, measuring wheal and erythema diameters, taking antigen wheal/histamine control wheal ratios, and recording the presence of pseudopods in no way improved the specificity of the test. These observations suggest, as proposed by Bock et al.,¹⁸ that the skin test merely identifies subjects in whom double-blind food challenges are required. In 132 children 3 yr of age or older, Dr. Bock found no false negative skin tests²¹ based on double-blind food challenges. Three children in this study (ages 10, 9, and 5 yr) were found to have false negative skin tests. The reason for this dichotomy is unclear. It is possible that the lichenified skin of children with AD is less reactive, as suggested by Hoffman et al.³ Since few of Bock's patients had AD and all the patients in this study had severe AD, the findings in this study would be more likely to be influenced by differences in skin reactivity. Subsequent intradermal and RAST tests were positive in the two children for whom they were performed, indicating that they both had antigen-specific IgE antibodies not detected by the prick test. Nevertheless, intradermal skin tests carry a higher incidence of detection of antibody, which often cannot be associated with clinical reactivity with food challenges and cannot be recommended as a screening procedure for food allergy. The concordance of RAST tests and oral food challenges is currently under study.

Although the presence of positive oral food challenges does not prove that food allergy has a pathogenic role in AD, the development of distinct epi-

sodes of cutaneous erythema and pruritus strongly supports a provocative role for food hypersensitivity in some patients. Since this study represents a very select group of patients, however, no statement can be made as to the general prevalence of food allergy in patients with AD. Most children participating in this study who demonstrated specific food hypersensitivity after challenge showed marked improvement in their skin symptoms after beginning strict avoidance of the offending foods (decreased area of skin involvement, decreased use of antihistamines, fewer physician visits, fewer days lost from school, etc.). Although some patients had nearly total clearing of their eczema, in no patient have skin symptoms resolved completely, a finding not unexpected for this disorder.

Based on this study, several conclusions may be drawn: (1) in some children with AD, food can lead to an immediate hypersensitivity reaction of the skin, consisting of generalized pruritus and a macular erythematous rash, as well as other symptoms; (2) although food hypersensitivity may represent only one of several pathogenic factors in AD, removal of an offending food can result in marked improvement in skin symptoms; (3) history is often unreliable in determining specific food hypersensitivities; (4) skin testing with the prick technique may be of some aid in diagnosing food allergy, but a high rate of clinically insignificant positive skin tests and a small but significant rate of false negative tests occur; and (5) at present, double-blind placebo-controlled food challenges are the only definitive means of diagnosing food hypersensitivity in AD.

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