

IgE Food Sensitization in Infants with Eczema Attending a Dermatology Department

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Objectives Because community-based studies, which report IgE food sensitization (IgE-FS) in more than 80% of infants with moderate atopic eczema, may be influenced by referral bias, we assessed the prevalence of IgE-FS in a cohort of infants with moderate atopic eczema attending a dermatology department clinic.

Study design Consecutive infants (n = 51, 39 males; median age, 34 weeks; range, 20 to 51 weeks) with moderate atopic eczema referred to a university-affiliated dermatology department were studied prospectively. Clinical history and eczema severity were documented. IgE-FS was assessed by the skin prick test (SPT; n = 51) and food-specific serum IgE antibodies (CAP-FEIA test; n = 41). IgE-FS was diagnosed if the SPT or CAP-FEIA level exceeded the >95% predictive reference cutoff for positive food challenges.

Results Based on SPT, 44 of 51 infants (86%; 95% confidence interval [CI] = 74% to 94%) had IgE-FS (cow's milk, 16%; egg, 73%; peanut, 51%). Using age-specific 95%-predictive cutoff values, CAP-FEIA identified 34 of 41 infants (83%; 95% CI = 68% to 93%) with IgE-FS (cow's milk, 23%; egg, 80%). Forty-six (90%) infants had IgE-FS to at least 1 food item by either SPT or CAP-FEIA.

Conclusions Atopic eczema was found to be closely associated with IgE-FS in infants attending a dermatology department. (*J Pediatr* 2007;xx:xxx)

Infantile atopic eczema is a chronic, relapsing, and pruritic inflammatory disease of the skin frequently associated with allergic sensitization, elevated serum IgE levels, and a family history of atopic disease.¹ Atopic eczema affects 28% of Australian infants.² In the general community, 9.4% of Australian infants have atopic eczema of moderate severity, requiring at least 6 weeks of topical steroid treatment during the first 12 months of life.² This prevalence is similar to that found in European and British studies.³⁻⁶ The impact of atopic eczema on families and the cost of treatment are greater than for juvenile diabetes mellitus.⁷

In infants with atopic eczema, the risk of developing high levels of IgE food sensitization (IgE-FS) associated with IgE-mediated food allergy (IgE-FA) is increased 5.9-fold compared with control subjects.⁸ More than 80% of infants age 3 to 9 months with moderate to severe atopic eczema referred to our Allergy Department had evidence of IgE-FS to cow's milk, egg, and/or peanut.⁸ The strength of this association was increased with increasing severity of atopic eczema.² However, in these studies,^{2,8} our patients had been referred from family physicians or pediatricians to our Allergy Department, raising the possibility the results were biased toward children with food allergy. Despite these findings and an earlier report from a university-affiliated dermatology clinic demonstrating IgE-FA in about 1/3 of young children with atopic eczema,⁹ the relationship between IgE-FA and atopic eczema remains controversial.^{10,11}

In the present study, we investigated consecutive infants with atopic eczema of moderate severity referred to a dermatology clinic. We tested the hypothesis that there was no association between atopic eczema and IgE-FS in such infants. We also compared the

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Submitted for publication Oct 2, 2006; last revision received Feb 13, 2007; accepted Apr 27, 2007.

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0022-3476/\$ - see front matter

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10.1016/j.jpeds.2007.04.070

CI	Confidence interval	IgE-FS	Immunoglobulin E food sensitization
ESS	Eczema Severity Score	PPV	Positive predictive value
IgE	Immunoglobulin E	SPT	Skin prick test
IgE-FA	Immunoglobulin E-mediated food allergy		

diagnostic agreement of in vivo and in vitro methods in identifying IgE-FS in eczematous infants.

METHODS

Consecutive infants age 6 to 12 months with moderately severe atopic eczema who were referred to the dermatology clinic from community-based family physicians and pediatricians were studied prospectively. The infants were assessed by a consultant dermatologist in the dermatology department at a university-affiliated pediatric teaching hospital, and a topical treatment program was initiated. All of the infants were investigated in our Allergy Department for features of IgE-FS to cow's milk, egg, and peanut within 2 weeks of the clinical assessment by the dermatologist. Demographic data, a detailed history, and clinical findings were entered into a database. Eczema severity was scored by trained senior allergy research nurses, who also performed skin prick tests (SPTs) with extracts of cow's milk, egg, and peanut (Dome-Hollister-Stier, Spokane, WA), histamine 1%, and a diluent solution (negative control).¹² New batches of extract were validated for comparable biological potency for SPT reactivity against previous batches. SPTs were performed on the infant's back and scored 15 minutes after application.¹² Serum IgE antibodies to cow's milk, egg, and peanut were measured by the CAP System FEIA test (CAP-FEIA; Pharmacia, Uppsala, Sweden) on the day of the SPTs.

Our previous community-based study found a strong association between atopic eczema and IgE-FS.² Therefore, this study was conducted in the dermatology department as a prospective audit of current clinical practice, and Human Ethics Research Committee approval was not required.

Assessment of Eczema Severity

The Eczema Severity Score (ESS) was developed in our Allergy Department for the rapid assessment of atopic eczema severity in infants. The ESS is similar to the Six-Area, Six-Sign Atopic Dermatitis scoring system of Berth-Jones¹³ and is based on modifications of the SCORAD Index¹⁴ and the Three-Item Severity Score.¹⁵ The ESS scores skin findings for dryness, erythema, and excoriation (absent = 0, mild = 1, moderate = 2, and severe = 3). Six skin areas are assessed: face, arms, hands, legs, feet, and trunk. The maximum ESS score is 54 (0 to 18 = mild, 19 to 36 = moderate, 37 to 54 = severe).

Diagnosis of IgE-FS

IgE-FS was diagnosed if the SPT wheal diameter exceeded the 95% positive predictive value (PPV) for a positive food challenge defined by our previous studies.^{12,16} These cutoff values in children under age 2 years were ≥ 6 mm for cow's milk, ≥ 5 mm for egg, and ≥ 4 mm for peanut.¹⁶

Two additional predictive reference decision points for the diagnosis of IgE-FS by CAP-FEIA were available based on levels associated with challenge-proven food allergy in 2 other international centers experienced in the investigation of

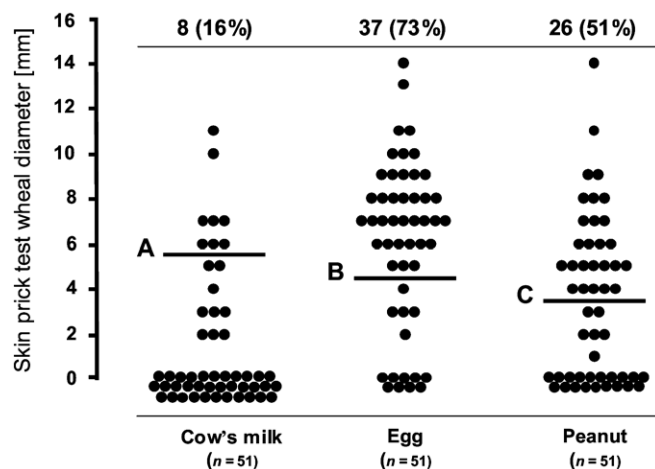


Figure 1. SPT wheal diameters in 51 infants with atopic eczema. The horizontal bars indicate the age-specific 95% PPV reference cutoff levels for IgE-FS to cow's milk (A; ≥ 6 mm), egg (B; ≥ 5 mm), and peanut (C; ≥ 4 mm) for children under age 2 years.¹⁶

young children with food allergies. The first of these was based on the 95% PPV for IgE-FA in children under age 2 years; IgE-FS was diagnosed if the CAP-FEIA antibody level exceeded 5 kU_A/L (95% PPV) for cow's milk¹⁷ and 0.35 kU_A/L (94% PPV) for egg.¹⁸ No published age-specific data for peanut allergy in this age group are available. Thus, the second decision point for diagnosing IgE-FS was based on the reference 95% PPV for IgE-FA for older children (mean age, 3.8 years); 95% PPV cutoff levels in that population were 15 kU_A/L for cow's milk, 7 kU_A/L for egg, and 14 kU_A/L for peanut.¹⁹

Statistical Analysis

Based on the estimate that 30% of infants with atopic eczema attending the dermatology department would have IgE-FS, a sample size of 81 was required to test the null hypothesis.⁹ A 2-sided 95% confidence interval (CI) for this estimated prevalence would extend ± 0.1 (10%) from the observed value. However, the prevalence observed in the first 51 patients greatly exceeded 30%, and after an interim analysis, it was deemed unnecessary to recruit additional patients into the study. Group data are presented as median and range. Agreement between diagnostic tests for IgE-FS (SPT and CAP-FEIA) was assessed by the paired McNemar test. Statistical significance was accepted for $P < .05$.

RESULTS

Consecutively referred infants ($n = 51$, 39 [76%] males; median age, 34 weeks; range, 20 to 51 weeks) with moderately severe atopic eczema as assessed by a dermatologist were studied. The mean age of onset was 12 weeks (range, 2 to 40 weeks). All infants underwent SPT to cow's milk, egg, and peanut. Using the SPT criteria for IgE-FS in children under age 2 years,¹⁶ 44 infants (86%; 95% CI = 74% to 94%) had IgE-FS to at least 1 food: 8 (16%) to cow's milk, 37 (73%) to egg, and 26 (51%) to peanut (Figure 1). Of the 44 infants

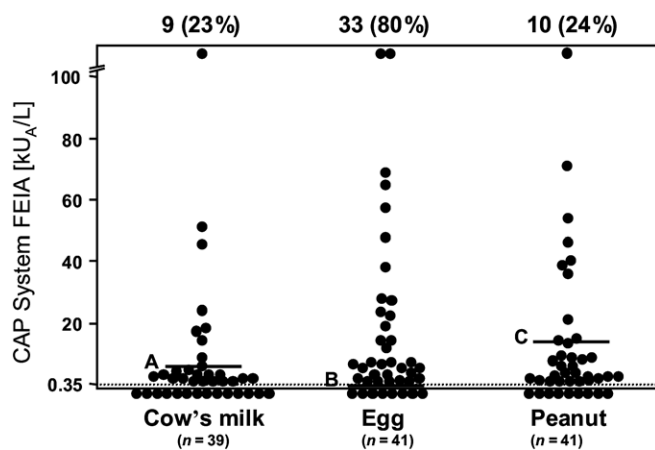


Figure 2. Food-specific serum IgE antibody levels in 41 children with atopic eczema. The horizontal bars indicate the age-specific (under 2 years) predictive reference cutoff CAP-FEIA levels for IgE-FS to cow's milk (A; ≥ 5 kU_A/L) 17 and egg (B; ≥ 0.35 kU_A/L) 18 and non-age-specific cutoff level to peanut (C; ≥ 14 kU_A/L).¹⁹

with IgE-FS identified by SPT, 22 were sensitized to more than 1 food item.

Food-specific serum IgE levels were available for 41 infants. Based on age-specific reference cutoff levels for children under age 2 years, 34 infants (83%) exhibited evidence of IgE-FS to cow's milk and/or egg; 9 of 39 (23%) were allergic to cow's milk, and 33 of 41 (80%) were allergic to egg (Figure 2). Applying the cutoff levels for older children to our cohort of infants, only 19 of 41 infants (46%) were identified as having IgE-FS; these included 6 of 39 infants (15%) with IgE-FS to cow's milk, 15 of 41 (37%) with IgE-FS to egg, and 10 of 41 (24%) with IgE-FS to peanut.

A total of 46 infants (90%) had IgE-FS to at least 1 food item by either SPT or CAP-FEIA. Agreement in identifying patients with or without IgE-FS between age-specific SPT and CAP-FEIA cutoff levels was assessed by the paired McNemar test (Table). Close diagnostic agreement was found for IgE-FS to cow's milk ($P = .625$) and egg ($P = .375$) when using the age-specific decision points for infants and young children under age 2 years.^{17,18} However, when using the predictive cutoff levels for cow's milk, egg, and peanut for older children,¹⁹ there was significant discordance between the tests for egg and peanut (paired McNemar test; egg, $P = .0003$; peanut, $P = .002$; Table).

Breast-feeding was initiated in 48 (94%) of infants, of whom 31 (61%) were breast-fed exclusively (with no intake of solids or supplemental formula) at the onset of atopic eczema. The mothers of these infants were on unrestricted diets. Of these 48 infants, 29 (57%) were breast-fed exclusively for more than 4 months; 25 of these 29 infants developed atopic eczema before age 4 months. Three infants were formula-fed from birth.

Based on SPT, 71 instances of IgE-FS to individual foods were demonstrated in the 51 patients. In 60 of these instances, although the infants exhibited evidence of IgE-FS by SPT, they had never knowingly been fed the particular

food item. Of the 37 infants with IgE-FS to egg, only 8 had previously ingested egg; 7 of these infants reportedly had clinical allergic reactions on first known exposure (urticaria in 2, eczema flare in 3, and vomiting in 2). In the remaining infant with severe atopic eczema and IgE-FS to egg by SPT, the parents observed no immediate adverse effect after the infant ingested cooked egg in custard; the eczema cleared on an egg-free diet. None of the remaining 29 infants with an IgE-FS to egg by SPT had previously ingested egg. Twenty-five of the 26 patients with IgE-FS by SPT to peanut were breast-fed and had not previously ingested peanut-containing products. The remaining child developed urticaria after his first known ingestion of peanut butter before undergoing SPT. One child with IgE-FS to cow's milk on SPT had developed urticaria on the first ingestion of cow's milk formula before SPT.

The median ESS at the time of initial assessment in our Allergy Department, within 2 weeks of initial diagnosis and management, was 16 (range, 0 to 48). ESS scores did not correlate with the total serum IgE ($r = .282$; $P = .112$) or the CAP-FEIA levels (cow's milk: $r = .259$, $P = 0.121$; egg: $r = .074$, $P = .656$; peanut: $r = .119$, $P = .470$). In addition, there was no association between the severity of atopic eczema (by ESS) and the number of foods with an SPT above the predictive cutoff for IgE-FA (analysis of variance; $F = 1.41$, $P = .252$).

DISCUSSION

More than 80% of our cohort of infants with moderately severe atopic eczema referred to the dermatology department exhibited evidence of IgE-FS. Previous investigations by ourselves and others associated these levels of IgE-FS with positive food challenges, that is, IgE-FA based on the age-specific 95%-predictive cutoff levels for SPT wheal diameter¹⁶ and/or CAP-FEIA antibody levels.^{17,18} However, because our protocol did not require formal food challenges, and because the level of IgE-FS associated with IgE-FA may vary according to the food challenge protocol,²⁰ we have designated these infants as having IgE-FS rather than IgE-FA. These findings are in keeping with our previous observations of a high incidence of IgE-FS in infants with atopic eczema referred to our Allergy Department⁸ and in our community-based studies.² A study of dermatology department-referred older children with atopic eczema (mean age, 3.8 years) found evidence of IgE-FA in 37% of the patients using both 95% PPV CAP-FEIA and double-blind, placebo-controlled food challenge methods.⁹ The age difference between children in that study and our studies could explain the lower rate of food allergy in the study of older children, because IgE-FA frequently remits as the level of IgE-FS declines in the first years of life.²¹ Differences in eczema severity are another possible reason for the differing findings.²

The use of the 95% predictive SPT wheal diameter or CAP-FEIA decision points to diagnose IgE-FA has significantly reduced the need for diagnostic food challenges^{9,16,19-24} in centers where these levels have been validated. All of the

Table. Frequency of IgE-FS as diagnosed by age-specific and -nonspecific diagnostic decision points for SPT and CAP-FEIA

	SPT	CAP-FEIA	95% PPV CAP-FEIA cutoff	Diagnostic agreement (paired McNemar test)
Cow's milk	8/51 (16%)	9/39 (23%)	5 kU _A /L*	<i>P</i> = .625
		7/39 (17%)	15 kU _A /L†	<i>P</i> = .99
Egg	37/51 (73%)	33/41 (80%)	0.35 kU _A /L*	<i>P</i> = .375
		15/41 (37%)	7 kU _A /L†	<i>P</i> = .0003
Peanut	26/51 (51%)	10/41 (24%)*	14 kU _A /L†	<i>P</i> = .002

*Age-specific 94% to 95% PPV in infants and young children under age 2 years.^{17,18}

†≥95% PPV in children and adolescents (mean age, 3.8 years).¹⁹

infants in this study whose parents reported unequivocal clinical reactions had SPT levels above the 95% PPV for IgE-FA. One 8-month-old patient with severe atopic eczema who had IgE-FS by SPT ingested egg cooked in custard without obvious adverse effects. His apparent tolerance to cooked egg may have reflected sensitization to a heat-labile fraction of egg,²⁵ suppression of an urticarial reaction to egg seen in severe atopic eczema,²³ or the statistical reality that 5% of cases with SPT >95% PPV for food allergy do not react on food challenge. This infant's eczema cleared and remained in remission at age 2 years on an egg-free low-allergen diet. (He was hospitalized at that age with anaphylaxis after accidental ingestion of a cashew).

In this investigation, we may have underestimated the frequency of IgE-FS in atopic eczema, because we studied only 3 major food allergens, and thus IgE-FS to other foods would have been missed.²³ In addition, about 10% of infants and children with atopic eczema have a food allergy mediated by non-IgE-mediated mechanisms.²⁶

More than 60% of the infants in this study had IgE-FS, confirmed by invitro and/or in vivo methods, without having ingested the foods directly. In another 18%, acute allergic reactions on their first overt exposure to milk, egg, and peanut were reported. These findings suggest that IgE-FS may have been acquired either transplacentally or through breast milk.²⁷ Dietary antigens from cow's milk, egg, wheat, and peanut have been detected in breast milk within 2 to 6 hours of maternal ingestion.^{28,29} Infants with atopic eczema and cow's milk allergy who breast-feed within several hours of maternal ingestion of cow's milk may develop eczematous flares.³⁰

Although epidemiologic studies suggest that breast-feeding of more than 4 months' duration may be protective of atopic eczema,^{31,32} half of our patients were breast-fed exclusively for more than 4 months but nonetheless developed eczema during this period, when their mothers had an unrestricted diet. Breast-feeding may predispose to IgE sensitization to cow's milk and other food proteins through prolonged low-dose antigen exposure in susceptible individuals, particularly in mothers with low breast milk concentrations of IgA and transforming growth factor- β .³³ This susceptibility to atopic eczema in childhood also may be linked to several genetic polymorphisms, including those within the *PHF11* gene at chromosome 13q14.³⁴

Previous immunopathological models have defined a range of immune mechanisms in atopic eczema.³⁵ In children with atopic eczema, positive food challenges cause rapid increases in mast cell-derived plasma histamine concentrations, activation of eosinophils, and release of eosinophil-derived factors.³⁶ Activation of circulating T lymphocytes expressing cutaneous lymphocyte antigen has been demonstrated in children with atopic eczema and IgE-FA to cow's milk,³⁷ and peanut-derived epitopes have been found on T lymphocytes from skin biopsy specimens of an infant with atopic eczema.³⁸ These findings are in keeping with a murine model that induces eczema-like lesions in 1/3 of sensitized mice after low-dose ingestion of small amounts of cow's milk and peanut allergens.³⁹ In addition, clinical studies have demonstrated exacerbation of eczema during double-blind, placebo-controlled food challenges⁴⁰ with the allergen and remission after exclusion of the allergen. Although a benefit of a maternal low-allergen diet by breast-feeding mothers in reducing the prevalence of eczema in their infants has been described,^{41,42} the role of food allergy in eczema remains controversial.^{10,11}

Our findings suggest that infants with atopic eczema of moderate severity referred to a dermatology department are likely to be IgE-sensitized to common foods. Based on the results of this study, we suggest that routine screening for IgE-FS and food allergies be included in the investigation of infants with moderate atopic eczema presenting at age 6 to 12 months. In view of the community prevalence of moderate atopic eczema of about 10%,^{2,4-6} adequate allergy resources are required to optimally manage these infants. Further large-scale food challenge studies are now required to validate our previous findings linking these high levels of IgE antibodies to common foods with clinically significant positive food challenges. Future studies need to assess the role of dietary modification on clinical outcome in infants with eczema.

REFERENCES

1. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest* 2004;113:651-7.
2. Hill DJ, Hosking CS. Food allergy and atopic dermatitis in infancy: an epidemiologic study. *Pediatr Allergy Immunol* 2004;15:421-7.
3. Illi S, von ME, Lau S, Nickel R, Gruber C, Niggemann B, Wahn U. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. *J Allergy Clin Immunol* 2004;113:925-31.
4. Wadonda-Kabondo N, Sterne JA, Golding J, Kennedy CT, Archer CB, Dunnill

- MG. A prospective study of the prevalence and incidence of atopic dermatitis in children aged 0-42 months. *Br J Dermatol* 2003;149:1023-8.
5. Arshad SH, Stevens M, Hide DW. The effect of genetic and environmental factors on the prevalence of allergic disorders at the age of two years. *Clin Exp Allergy* 1993;23:504-11.
 6. Herd RM, Tidman MJ, Prescott RJ, Hunter JA. Prevalence of atopic eczema in the community: the Lothian Atopic Dermatitis Study. *Br J Dermatol* 1996;135:18-9.
 7. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. *Arch Dis Child* 1997;76:159-62.
 8. Hill DJ, Sporik R, Thorburn J, Hosking CS. The association of atopic dermatitis in infancy with immunoglobulin E food sensitization. *J Pediatr* 2000;137:475-9.
 9. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101:E8.
 10. Thompson MM, Hanifin JM. Effective therapy of childhood atopic dermatitis allays food allergy concerns. *J Am Acad Dermatol* 2005;53:S214-9.
 11. Fennessy M, Coupland S, Popay J, Naysmith K. The epidemiology and experience of atopic eczema during childhood: a discussion paper on the implications of current knowledge for health care, public health policy and research. *J Epidemiol Community Health* 2000;54:581-9.
 12. Hill DJ, Heine RG, Hosking CS. The diagnostic value of skin prick testing in children with food allergy. *Pediatr Allergy Immunol* 2004;15:435-41.
 13. Berth-Jones J. Six-Area, Six-Sign Atopic Dermatitis (SASSAD) severity score: a simple system for monitoring disease activity in atopic dermatitis. *Br J Dermatol* 1996;135(Suppl 48):25-30.
 14. Kunz B, Oranje AP, Labreze L, Stalder JF, Ring J, Taieb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997;195:10-9.
 15. Wolkerstorfer A, de Waard van der Spek FB, Glazenburg EJ, Mulder PG, Oranje AP. Scoring the severity of atopic dermatitis: the Three-Item Severity Score as a rough system for daily practice and as a pre-screening tool for studies. *Acta Derm Venereol* 1999;79:356-9.
 16. Sporik R, Hill DJ, Hosking CS. Specificity of allergen skin testing in predicting positive open food challenges to milk, egg and peanut in children. *Clin Exp Allergy* 2000;30:1540-6.
 17. García-Ara C, Boyano-Martínez T, Díaz-Peña JM, Martín-Muñoz F, Reche-Frutos M, Martín-Esteban M. Specific IgE levels in the diagnosis of immediate hypersensitivity to cow's milk protein in the infant. *J Allergy Clin Immunol* 2001;107:185-90.
 18. Boyano MT, García-Ara C, Díaz-Peña JM, Muñoz FM, García SG, Esteban MM. Validity of specific IgE antibodies in children with egg allergy. *Clin Exp Allergy* 2001;31:1464-9.
 19. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001;107:891-6.
 20. Celik-Bilgili S, Mehl A, Verstege A, Staden U, Nocon M, Beyer K, Niggemann B. The predictive value of specific immunoglobulin E levels in serum for the outcome of oral food challenges. *Clin Exp Allergy* 2005;35:268-73.
 21. Wood RA. The natural history of food allergy. *Pediatrics* 2003;111:1631-7.
 22. Hill DJ, Hosking CS, Reyes-Benito LV. Reducing the need for food allergen challenges in young children: a comparison of in vitro with in vivo tests. *Clin Exp Allergy* 2001;31:1031-5.
 23. Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 2004;113:805-19.
 24. Knight AK, Shreffler WG, Sampson HA, Sicherer SH, Noone S, Mofidi S, et al. Skin prick test to egg white provides additional diagnostic utility to serum egg white-specific IgE antibody concentration in children. *J Allergy Clin Immunol* 2006;117:842-7.
 25. Cooke SK, Sampson HA. Allergenic properties of ovomucoid in man. *J Immunol* 1997;159:2026-32.
 26. Niggemann B, Reibel S, Roehr CC, Felger D, Ziegert M, Sommerfeld C, et al. Predictors of positive food challenge outcome in non-IgE-mediated reactions to food in children with atopic dermatitis. *J Allergy Clin Immunol* 2001;108:1053-8.
 27. Vance GH, Lewis SA, Grimshaw KE, Wood PJ, Briggs RA, Thornton CA, et al. Exposure of the fetus and infant to hen's egg ovalbumin via the placenta and breast milk in relation to maternal intake of dietary egg. *Clin Exp Allergy* 2005;35:1318-26.
 28. Heine RG, Hill DJ, Hosking CS. Primary prevention of atopic dermatitis in breast-fed infants: what is the evidence? *J Pediatr* 2004;144:564-7.
 29. Palmer DJ, Gold MS, Makrides M. Effect of cooked and raw egg consumption on ovalbumin content of human milk: a randomized, double-blind, cross-over trial. *Clin Exp Allergy* 2005;35:173-8.
 30. Järvinen KM, Mäkinen-Kiljunen S, Suomalainen H. Cow's milk challenge through human milk evokes immune responses in infants with cow's milk allergy. *J Pediatr* 1999;135:506-12.
 31. American Academy of Pediatrics, Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000;106:346-9.
 32. Friedman NJ, Zeiger RS. The role of breast-feeding in the development of allergies and asthma. *J Allergy Clin Immunol* 2005;115:1238-48.
 33. Saarinen KM, Juntunen-Backman K, Järvenpää AL, Klemetti P, Kuitunen P, Lope L, et al. Breast-feeding and the development of cow's milk protein allergy. *Adv Exp Med Biol* 2000;478:121-30.
 34. Jang N, Stewart G, Jones G. Polymorphisms within the PHF11 gene at chromosome 13q14 are associated with childhood atopic dermatitis. *Genes Immunol* 2005;6:262-4.
 35. Novak N, Bieber T, Leung DY. Immune mechanisms leading to atopic dermatitis. *J Allergy Clin Immunol* 2003;112:S128-39.
 36. Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol* 1999;104:S114-22.
 37. Abernathy-Carver KJ, Sampson HA, Picker LJ, Leung DY. Milk-induced eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. *J Clin Invest* 1995;95:913-8.
 38. van Reijnsen FC, Felius A, Wauters EA, Bruijnzeel-Koomen CA, Koppelman SJ. T-cell reactivity for a peanut-derived epitope in the skin of a young infant with atopic dermatitis. *J Allergy Clin Immunol* 1998;101:207-9.
 39. Li XM, Kleiner G, Huang CK, Lee SY, Schofield B, Soter NA, et al. Murine model of atopic dermatitis associated with food hypersensitivity. *J Allergy Clin Immunol* 2001;107:693-702.
 40. Sampson HA. Food sensitivity and the pathogenesis of atopic dermatitis. *J R Soc Med* 1997;90(Suppl 30):2-8.
 41. Zeiger RS, Heller S, Mellon MH, Forsythe AB, O'Connor RD, Hamburger RN, et al. Effect of combined maternal and infant food-allergen avoidance on development of atopy in early infancy: a randomized study. *J Allergy Clin Immunol* 1989;84:72-89.
 42. Arshad SH, Matthews S, Gant C, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. *Lancet* 1992;339:1493-7.