

Food allergy and the gastrointestinal tract

Stephan Bischoff^a and Sheila E. Crowe^b

Purpose of review

Adverse reactions to food resulting in gastrointestinal symptoms are common in the general population. Although only a minority of individuals complaining of such symptoms have immune-mediated reactions to food (food allergy), gastrointestinal food allergies do exist in both children and adults. This review provides an update on the pathogenesis and clinical management of food allergy manifesting in the gut, emphasizing recent developments in the field.

Recent findings

Recent studies have broadened our understanding of the innate gastrointestinal defense systems and the role of the gut flora for protection against allergy. These findings support the hygiene theory in which microbial challenge in early life is thought to protect against the development of allergic disease. New insights into the regulation of mast cells and eosinophils, their homing to the intestine, and their interaction with the specific immune system and the enteric nervous system have been given. In parallel, the molecular structure of major food allergens is being unraveled, and new therapies that focus largely on modulating the immune response to food antigens have been developed.

Summary

These new findings have important implications for the diagnosis and management of food allergies. The availability of recombinant allergens will improve methods to diagnose and treat food allergy, and genetic engineering will allow future therapies such as vaccination against food allergy. Emerging knowledge of the role of the gut flora in mucosal immunity will enhance strategies to prevent and treat food allergy using probiotics such as *Lactobacillus* GG. Such new approaches will extend existing options for managing food allergy and preventing anaphylaxis.

Keywords

anaphylaxis, enteric nervous system, eosinophils, food allergy, gastrointestinal, mast cells, oral tolerance, probiotics, recombinant allergens

Abbreviation

IL interleukin

© 2004 Lippincott Williams & Wilkins
0267-1379

Introduction

At least 25% of the general population has adverse reactions to food with a subset having an abnormal immune response to foods as the mechanism for their symptoms. It has been estimated that approximately 4%–8% of children and 1%–2% of adults have food allergy, with the majority experiencing gastrointestinal symptoms [1•,2•]. Allergic reactions in general, including allergic reactions to food, appear to be increasing in prevalence, although clear data confirming this are lacking [3]. This increase in allergic disease is thought to be a result of the hygiene status of urbanized populations in industrialized countries, with less exposure to microorganisms in early life playing a central role [4•]. Substantial progress has been made in understanding the mechanisms of food allergy not only in the area of IgE-mediated reactions but also non-IgE-mediated disorders [5]. The symptoms of food allergy range from localized organ-based oral complaints to life-threatening systemic shock. The confirmation of food allergy based on objective diagnostic means remains a challenge, but there have been some developments in this area. Food allergy can be treated successfully by avoiding food allergens, which remains the mainstay of treatment of food allergies, and by medical treatment with epinephrine, antihistamines, and corticosteroids for severe reactions after accidental antigen exposure. An exciting area of investigation is the development of new strategies to manage food allergy that largely focus on modulating the immune response to foods [6•].

Food allergens

Given the large number of food proteins that comprise the human diet, it is somewhat surprising that only a relatively small number of foods induce IgE-dependent allergic reactions. The structural and biochemical properties that are required for a given molecule to induce allergy are still unclear, and this raises some concern in the era of genetically engineered foods [7•]. Which foods are likely to cause allergic reactions is dependent on the local eating habits and on age. Allergy to cow's milk, eggs, wheat, and soy is more common in infants and young children, whereas seafood, peanuts, and tree nuts are the more common causes of food allergy in adult life.

Curr Opin Gastroenterol 20:156–161. © 2004 Lippincott Williams & Wilkins.

^aDepartment of Gastroenterology, Hepatology, and Endocrinology, University Medical School of Hannover, Hannover, Germany; and ^bDigestive Health Center of Excellence, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Virginia, Charlottesville, Virginia, USA

Correspondence to Sheila E. Crowe, MD, Digestive Health Center of Excellence, University of Virginia, P.O. Box 800708, Charlottesville, VA 22908-0708 USA
Tel: 434 924 2734; fax: 434 982 0044; e-mail: scrowe@virginia.edu

Although sensitization to foods is primarily via antigen uptake in the gut, a recent study indicates that sensitization to peanut protein may occur through the application of peanut oil to inflamed skin [8•].

So-called major allergen epitopes have been identified and characterized on a molecular level, explaining the well-known phenomenon of cross-reactivity between allergens. The first major epitopes found were Bet v1 and Bet v2 (profilin) found in birch pollen and a number of food allergens such as fruits and celery. Since then, more than 1000 epitopes, of which approximately 50–100 are major epitopes, have been cloned and sequenced (for details, see <http://www.allergome.org>). Knowledge of cross-reacting antigens aids in assessing potential food allergies and their management [9], and the availability of recombinant food antigens offers a number of new possibilities both for the diagnosis [10] and treatment [11] of food allergies. For example, the cloned peanut allergen Ara h3 can be modified to a hypoallergenic molecule that binds less efficiently to IgE but retains the ability to stimulate T-cell activation in peripheral blood mononuclear cells from Ara h3 allergic patients, making it suitable for clinical testing as recombinant allergen immunotherapy [12].

Gastrointestinal barrier

Innate immunity, intestinal permeability, and antigen uptake

The intestinal mucosa is perpetually exposed to potentially harmful nutrients, microbes, and toxins. Mucosal absorption of nutrients and controlled uptake of antigens is crucial for life including the development of the mucosal immune system, but, at the same time, the mucosal barrier serves to protect the host against invading pathogens and allergens. Innate immune mechanisms and other nonspecific defense systems are critical to meet such a challenge [13]. They consist of gastric acid, mucus, an intact epithelial layer forming tight junctions, digestive enzymes, peristaltic movement, alternative complement pathways, phagocytes, and more recently recognized antimicrobial peptides such as defensins and cathelicidins [14•]. Together, such factors may prevent the development of food allergy. For example, increased sensitization to food antigens was recently shown in mice treated with antisecretory medications, most likely because gastric proteolysis is less effective at neutral pH [15•]. Macrophages and neutrophils are regarded as the most important effector cells of the innate immune system, but other cells such as mast cells and eosinophils are also involved. These cells recognize conserved bacterial structures through pattern recognition receptors including the recently identified Toll-like receptor family [16].

Undigested macromolecules such as food allergens pass the intestinal barrier as intact proteins interacting with the local intestinal immune system and are transported

to other body sites. This process of persorption seems to occur at limited rates under normal conditions, likely playing a role in the development of tolerance. However, with immaturity or disease of the intestinal mucosa, an increased uptake of macromolecules occurs with the potential for clinical consequences. The amount of absorbed undigested protein is dependent on genetic factors and variables such as dietary intake, maturity of digestive processes, and the presence of structural or functional abnormalities.

Adaptive immune responses

Allergen-specific T cells isolated from blood, skin, and mucosal sites in patients with allergic disorders including food allergy preferentially express a Th2 cell phenotype characterized by the release of interleukin (IL)-4, IL-5, and IL-13 [17]. Such cytokines play a central role in the induction and maintenance of allergic responses by regulating IgE synthesis (IL-4 and IL-13) and by attraction of inflammatory cells such as mast cells (IL-4) and eosinophils (IL-5). A recent study of infants from allergic families demonstrates a close relationship between Th2 skewing of the immune response and atopic manifestations [18•]. As might be expected, children who outgrow their peanut allergy show Th1 skewing to peanut antigens, similar to nonallergic children [19••]. Apart from the cytokine milieu, the biochemical properties of the triggering antigen influence the kind of immune response. In general, soluble proteins are more tolerogenic than particulate or globular antigens and low doses of antigens activate regulatory T cells (Th3), whereas high doses of antigen induce anergy or apoptosis.

Oral tolerance and the hygiene hypothesis

Gut homeostasis is achieved not only by the regulation of barrier function but also by downregulating the normal immune response to bacteria and food antigens. This phenomenon was termed oral tolerance because it is induced after oral challenge with particular antigens and leads not only to local, but also systemic, tolerance to orally administered antigen. Downregulatory mechanisms include various nonspecific defenses (gastric acid, mucus, epithelium) and specific immunologic systems (secretory IgA- and secretory IgM-producing plasma cells, tolerogenic antigen-presenting cells and immunosuppressive T cells, T-cell anergy and apoptosis). Such mechanisms, which have been described in detail elsewhere, are crucial to induce tolerance to dietary antigens [20]. Immaturity of the host or breakdown of such mechanisms due to various factors such as enteric infections may increase the risk of sensitization to dietary proteins and subsequent development of food allergy.

Adequate challenge of the intestinal immune system with commensal bacteria and food antigens is required for full maturation of the adaptive immune system and in particular the sIgA defense system clearing the mucosa

of bacterial and food antigens. It has been suggested that suboptimal stimulatory reinforcement of the mucosal immune system might contribute to the increased frequency of allergic and autoimmune conditions in industrialized countries [4•]. This “hygiene hypothesis” is supported by the finding that probiotics such as lactobacilli and *Bifidobacterium* enhance sIgA responses in a T cell–dependent manner and that nonenteropathogenic *Escherichia coli* or *Lactobacillus* GG reduce infection and protect against the development of food-induced atopic dermatitis [21•,22••]. In this respect, it is interesting to note that breast-feeding may protect against infection and atopy, likely because of the delivery of sIgA and other protective molecules such as transforming growth factor β and IL-10 through breast milk [23].

Allergic inflammation in the gut

IgE and allergic inflammation

The major endogenous inducer of IgA synthesis is transforming growth factor β derived from Th3 cells, whereas the switch to IgE synthesis is dependent on CD40L and IL-4 and IL-13 derived from Th2 cells and inflammatory cells such as mast cells or basophils. In contrast, Th1 cytokines such as interferon gamma inhibit the action of Th2 cells, and thereby Th1-driven immune responses, thought to be the default gastrointestinal response that can be enhanced by bacterial antigens, may prevent the production of IgE. This explains why, under normal conditions, the gastrointestinal mucosa is characterized by low Th2 cytokine levels and no detectable IgE production. Such mechanisms further argue for the hygiene hypothesis, claiming that an overly clean environment, thus reducing natural bacterial challenge, is a risk factor for atopy defined as an enhanced Th2 milieu and subsequent IgE-mediated allergy. In atopic individuals, elevated IgE levels are closely correlated with IL-13, the gene of which is subjected to polymorphisms linked to atopy.

The IgE-mediated allergic immune response can be divided into three phases: (1) the sensitization phase in which B cells switch to the production of specific IgE, (2) the effector phase consisting of an acute reaction and a facultative late-phase reaction, and (3) a chronic phase that may be the result of repetitive late-phase reactions. The acute reaction causes activation of mast cells and basophils releasing histamine, leukotrienes, and other mediators known to be responsible for the wheal-and-flare reaction occurring in the skin and at various mucosal sites including the eye, nose, lung, and gastrointestinal tract. Acute reactions occurring within seconds to minutes may be followed by a late-phase reaction starting within 2–24 hours after an allergen challenge and characterized by a cellular infiltration of the tissue with granulocytes (basophils, eosinophils) and lymphocytes (mainly Th2 cells). Inflammatory mediators produced by mast cells and eosinophils such as histamine and its me-

tabolite methylhistamine, tryptase, eosinophil cationic protein, eosinophil-derived protein X, IL-5, and tumor necrosis factor α are increased in serum, urine, gut lavage fluid, and stool in patients with food allergy.

Eosinophils and basophils are now recognized not only as effector cells of allergic inflammation but also as immunoregulatory cells contributing to the maintenance of gastrointestinal homeostasis and involved in defense mechanisms (*eg*, against bacteria and parasites). Human mast cells produce tumor necrosis factor α , causing neutrophil recruitment at sites of bacterial infection, IL-5 supporting eosinophil accumulation, and many other cytokines. IL-4 is not produced by human mast cells under normal conditions, but it acts as a central regulator of mast cell cytokine production. Allergens inducing IgE cross-linking are not the only triggering agents of mast cells but also bacterial and viral products activating mast cells through Toll-like receptors and viral receptors such as gp120 [24•]. Similar observations have been made for eosinophils [25]. Both mast cells and eosinophils are regulated by soluble transmitters derived from nerve cells of the enteric nervous system.

Genetics of allergy

Substantial progress has been made in our understanding of the genetics of allergic diseases. Although sibling and family studies indicate that allergy had a genetic background, with the risk of allergy substantially increased if first-degree relatives are afflicted, gene polymorphisms have now been shown to be associated with allergic diseases (reviewed in [26•,27•]). Recent studies describe several associations with HLA class II genotypes, mutations in the genes encoding for IgE, and the β chain of its high-affinity receptor Fc ϵ RI. Although the mutations found in allergic individuals do not necessarily impair the function of the receptor, they are closely associated with mite and pollen allergy and possibly also with pollen-associated food allergy. Cytokines and their receptors and signaling molecules have been examined regarding polymorphisms associated with allergy. One of the most intriguing findings was that atopy is linked with distinct mutations in the genes encoding for the α chain of the IL-4 receptor and *STAT6* gene [28•]. Other cytokines have been examined including IL-13, critically involved in IgE regulation, and IL-10 and transforming growth factor β .

Clinical presentation of gastrointestinal food allergy

Typical manifestations of food allergy in infants and young children include dietary protein–induced proctitis or proctocolitis, dietary protein–induced enteropathy, and atopic dermatitis [1•,29,30••]. More recently, eosinophilic esophagitis and allergic constipation have been described [31]. In older children and adults, by far the most common manifestation of food allergy is the oral

allergy syndrome induced by fruits and some vegetables that cross-react with pollens. Latex-fruit allergy can also present with gastrointestinal manifestations [32•,33•]. Other gastrointestinal manifestations of immunologic reactions to food occur in adults including eosinophilic gastroenteropathies and celiac disease. Isolated gastrointestinal food hypersensitivity is relatively rare, and usually reactions to food in the gut occur with extraintestinal manifestations of food allergy such as atopic dermatitis, urticaria, and asthma. Food allergy remains the major cause of anaphylaxis in industrialized nations, and wheat is increasingly recognized as a cause of food-dependent, exercise-induced anaphylaxis [34,35•]. The relationship of food allergy to joint symptoms, migraine headaches, chronic fatigue syndrome, and various neuropsychiatric conditions remains unclear.

Diagnosis and treatment

Diagnostic approaches

Guidelines for the evaluation of food allergies have recently been published as a medical position statement by the American Gastroenterological Association [36,37]. It is essential to obtain a careful history correlating symptoms with specific foods. Open food challenges, although helpful as a first approach, are subject to bias and should be corroborated by a more objective method before permanent elimination of suspect items from the diet. Skin prick testing provides a readily available and relatively inexpensive means to assess a panel of food allergens in both children and adults. The major limitation of skin testing is its poor positive predictive value, but a negative test in the absence of antihistamine use strongly suggests that immediate hypersensitivity is an unlikely mechanism for the patient's food-induced complaints. The recently established epicutaneous test allows testing of delayed reactions to food [38]. Measurement of food-specific IgE can be used as an alternative to skin testing. IgE-independent tests such as measurement of eosinophil-derived mediators such as eosinophil cationic protein and eosinophil-derived protein X in serum and stool have also been described [39]. Given the current limitations of all laboratory means to confirm gastrointestinal food allergy, the diagnosis rests primarily on the clinical presentation and the exclusion of other conditions.

In questionable cases, a double-masked, placebo-controlled food challenge in which food antigens are administered by nasogastric tube or gelatin capsules should be performed, if possible. This technique is considered the gold standard for diagnosing food allergy. However, this procedure has several limitations with regard to food allergy manifesting in the gastrointestinal tract and only confirms specific food intolerances suggested by the history and prior evaluation without indicating the mechanism of the adverse reaction. A number of investigators have performed the gastrointestinal equivalent of skin

testing by injecting the gastrointestinal mucosa with a panel of antigens and observing for a wheal-and-flare response by endoscopy. This technique was reported as early as the 1930s with subsequent series describing gastric, duodenal, and, most recently, colonic mucosal allergen challenge [40]. Although these techniques represent an advance in the field of food hypersensitivity, their incorporation into routine clinical practice has been limited. In contrast, endoscopy and mucosal biopsy techniques remain the major diagnostic method to evaluate other gastrointestinal immune-mediated reactions to food including celiac disease, food protein gastroenteropathies, and eosinophilic gastroenteritis.

Current treatment options

The cornerstone of the management of food allergy is avoidance of the offending allergen. This is particularly important in cases of food allergies such as peanut allergy in which trace amounts of allergen can cause significant reactions. Because it is often difficult to prevent accidental exposure to food antigens, patients with a history of an anaphylactic reaction should be instructed to carry an epinephrine-containing syringe for emergency administration. Patients with food allergies should learn to read and understand labels for hidden food allergens and to recognize the potential for foods to cross-react with other antigens. To date, there is no clear evidence that oral desensitization, injection immunotherapy, prophylactic medication, or similar techniques are beneficial in the prevention or modulation of food allergy. Similarly, there are no data to support the use of alternative and complementary medicine in food allergy [41•], and, in fact, there are side effects to such therapies [42•].

Hypoallergenic diets have been recommended during pregnancy and with breast-feeding for atopic mothers to reduce the incidence of food allergy in their offspring. Foods with a higher allergenic potential should be introduced later into the diets of infants at high risk of developing food allergy to decrease the tendency to develop food allergy. A recent review of the literature indicates that formulas with reduced antigenicity (milk proteins are partially or more extensively hydrolyzed by heat or enzymes) are not superior to exclusive breast-feeding to prevent allergy, but in high-risk infants who are unable to be breast-fed completely, such formulas are of benefit compared with cow's milk formula [43•,44]. Other studies have been published indicating that probiotics such as the *Lactobacillus* GG strain are capable of preventing allergy in newborns from families at high-risk of developing allergy [45,46]. If an elimination diet cannot be followed because of compliance or because the responsible foods could not be identified, antiallergic medication may be required such as disodium cromoglycate. In more severe cases, corticosteroids may be necessary.

Future developments

Perhaps the most exciting aspect of the field of food allergy is the novel therapeutic approaches that offer the potential to be applied to food allergy (reviewed in [6•]). These include tolerogenic peptides, recombinant epitopes, anti-IgE and DNA vaccination, and neutralizing antibodies or receptor antagonists of Th2 cytokines such as IL-4. Methods to genetically or chemically modify the antigenic structure of foods to reduce their allergic potential are being developed. For example, it is known that single amino acid substitutions in the IgE binding site of a peanut allergen can lead to the loss of binding to these epitopes. It has been shown on a molecular level that such approaches could be extended to virtually all allergens that have been cloned, offering new approaches for a vaccination against type I allergies [47•]. Antibodies specific for the portion of the IgE molecule that binds to receptors on mast cells and basophils have been used in animal models and in clinical trials with asthmatic subjects and recently has been successfully used for treatment of patients with peanut allergy [48••].

Whereas classical immunotherapy and oral immunotherapy are not proven to be effective treatment of food allergy, new approaches aiming to direct the antigen to the gut are under development. For example, DNA vaccination to induce host cell expression of antigenic protein offers promise as a therapy for food allergy, as demonstrated by a recent study in a mouse model of peanut allergy [49]. Another method of inducing tolerance was achieved by treatment of ovalbumin T-cell receptor transgenic mice with the probiotic *Lactobacillus casei* inducing IL-12 and thereby inhibiting IgE and IgG1 responses [50]. Oral tolerance is not only possible in rodents but also in animal models that might be more relevant to human allergic diseases such as the IgE high-responder dog model in which ovalbumin induced tolerance to ovalbumin and prevented asthma and allergy [51].

Conclusion

Adverse reactions to food resulting in gastrointestinal symptoms are common in the general population and often underestimated, particularly in adults, of whom 1%–2% have symptoms caused by food allergy. Gastrointestinal food allergies are mediated by IgE-dependent and IgE-independent mechanisms involving mast cells, eosinophils, and likely other immune cells and result in a large number of clinical presentations. Despite substantial progress in understanding the underlying mechanisms, many questions remain unanswered. New knowledge concerning the role of innate defense systems and the gut microflora have opened exciting new therapeutic strategies such as the use of probiotic bacteria for the treatment and prevention of food allergy. The developments in the field of recombinant allergens and their modulation by genetic engineering will improve both diagnostic tests and therapeutic options such as hyposensitization and induction of tolerance.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- Of special interest
 - Of outstanding interest
- 1 Sampson HA: 9. Food allergy. *J Allergy Clin Immunol* 2003, 111:S540–S547.
This review article provides a comprehensive overview of the topic of food allergy.
 - 2 Sicherer SH: Food allergy. *Lancet* 2002, 360:701–710.
• This review article provides a comprehensive overview of the topic of food allergy.
 - 3 Grundy J, Matthews S, Bateman B, et al.: Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002, 110:784–789.
 - 4 Kalliomaki M, Isolauri E: Role of intestinal flora in the development of allergy. *Curr Opin Allergy Clin Immunol* 2003, 3:15–20.
• This article discusses the concept of higher levels of hygiene leading to allergy and the role of gut flora.
 - 5 Shah U, Walker WA: Pathophysiology of intestinal food allergy. *Adv Pediatr* 2002, 49:299–316.
 - 6 Nowak-Wegrzyn A: Future approaches to food allergy. *Pediatrics* 2003, 111:1672–1680.
• This is a concise summary of recent developments and future directions for the treatment of food allergy.
 - 7 Helm RM: Food biotechnology: is this good or bad? Implications to allergic diseases. *Ann Allergy Asthma Immunol* 2003, 90:90–98.
• This review points out that in 1999 and 2000 combined more than two trillion transgenic plants had been grown without any adverse food reactions being reported, suggesting that the risks are slight.
 - 8 Lack G, Fox D, Northstone K, Golding J: Factors associated with the development of peanut allergy in childhood. *N Engl J Med* 2003, 348:977–985.
• This is an interesting study that examines the risk factors for developing peanut allergy and documents an unexpected risk factor, application of peanut oil to the infant's skin, as well as an association with soy protein ingestion, which is likely owing to cross-sensitization through common epitopes.
 - 9 Vieths S, Scheurer S, Ballmer-Weber B: Current understanding of cross-reactivity of food allergens and pollen. *Ann NY Acad Sci* 2002, 964:47–68.
 - 10 Beyer K: Characterization of allergenic food proteins for improved diagnostic methods. *Curr Opin Allergy Clin Immunol* 2003, 3:189–197.
 - 11 Valenta R: The future of antigen-specific immunotherapy of allergy. *Nat Rev Immunol* 2002, 2:446–453.
 - 12 Rabjohn P, West CM, Connaughton C, et al.: Modification of peanut allergen Ara h 3: effects on IgE binding and T cell stimulation. *Int Arch Allergy Immunol* 2002, 128:15–23.
 - 13 Medzhitov R, Janeway C Jr: Innate immunity. *N Engl J Med* 2000, 343:338–344.
 - 14 Ganz T: Defensins: antimicrobial peptides of innate immunity. *Nat Rev Immunol* 2003, 3:710–720.
• This article provides an up-to-date review on the subject of antimicrobial peptides.
 - 15 Untersmayr E, Scholl I, Swoboda I, et al.: Antacid medication inhibits digestion of dietary proteins and causes food allergy: a fish allergy model in BALB/c mice. *J Allergy Clin Immunol* 2003, 112:616–623.
• An interesting hypothesis was tested in this study, but the findings that some gastric therapies promote food allergy raise additional questions about mechanisms other than acid inhibition.
 - 16 Hemmi H, Takeuchi O, Kawai T, et al.: A Toll-like receptor recognizes bacterial DNA. *Nature* 2000, 408:740–745.
 - 17 Eigenmann PA, Frossard CP: The T lymphocyte in food-allergy disorders. *Curr Opin Allergy Clin Immunol* 2003, 3:199–203.
 - 18 Neaville WA, Tisler C, Bhattacharya A, et al.: Developmental cytokine response profiles and the clinical and immunologic expression of atopy during the first year of life. *J Allergy Clin Immunol* 2003, 112:740–746.
• This study examines a large number of infants from atopic families following particular cytokine levels over a year to demonstrate that there are marked changes with time but that there is clear Th2 skewing that correlates with atopic manifestations.
 - 19 Turcanu V, Maleki SJ, Lack G: Characterization of lymphocyte responses to peanuts in normal children, peanut-allergic children, and allergic children who acquired tolerance to peanuts. *J Clin Invest* 2003, 111:1065–1072.
•• This interesting paper looks at the immunologic events in children who lose reac-

tivity to peanut antigen. Not surprisingly, children who lost sensitivity to peanuts as well as the nonallergic children showed a Th1 skewing to peanut antigen.

- 20 Nagler-Anderson C: Tolerance and immunity in the intestinal immune system. *Crit Rev Immunol* 2000, 20:103–120.

- 21 Kalliomaki M, Salminen S, Arvilommi H, et al.: Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001, 357:1076–1079.

This study showed that perinatal *Lactobacillus rhamnosus* GG reduced atopic dermatitis in at-risk children.

- 22 Kalliomaki M, Salminen S, Poussa T, et al.: Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003, 361:1869–1871.

This study extends the findings of [21]. After 4 years, the benefit of the probiotic was still detected.

- 23 Kull I, Wickman M, Lilja G, et al.: Breast feeding and allergic diseases in infants—a prospective birth cohort study. *Arch Dis Child* 2002, 87:478–481.

- 24 McCurdy JD, Olynych TJ, Maher LH, et al.: Cutting edge: distinct Toll-like receptor 2 activators selectively induce different classes of mediator production from human mast cells. *J Immunol* 2003, 170:1625–1629.

This study of human mast cells reports the novel finding that different Toll-like receptor 2 activators lead to different types of mediator production.

- 25 Rothenberg ME, Mishra A, Brandt EB, et al.: Gastrointestinal eosinophils. *Immunol Rev* 2001, 179:139–155.

- 26 Steinke JW, Borish L, Rosenwasser LJ: 5. Genetics of hypersensitivity. *J Allergy Clin Immunol* 2003, 111:S495–S501.

This article provides a current review of the rapidly developing field of genetic associations in allergic disease.

- 27 Howard TD, Meyers DA, Bleecker ER: Mapping susceptibility genes for allergic diseases. *Chest* 2003, 123:363S–368S.

This article provides a current review of the rapidly developing field of genetic associations in allergic disease.

- 28 Tamura K, Suzuki M, Arakawa H, et al.: Linkage and association studies of STAT6 gene polymorphisms and allergic diseases. *Int Arch Allergy Immunol* 2003, 131:33–38.

This is a recent study, among other previously published studies, that looks at genetic associations with allergic disease.

- 29 Nowak-Wegrzyn A, Sampson HA, Wood RA, et al.: Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics* 2003, 111:829–835.

- 30 Leung DY, Bieber T: Atopic dermatitis. *Lancet* 2003, 361:151–160.

A well-written review on atopic dermatitis and the role that food allergy plays in this condition.

- 31 Markowitz JE, Liacouras CA: Eosinophilic esophagitis. *Gastroenterol Clin North Am* 2003, 32:949–966.

- 32 Blanco C: Latex-fruit syndrome. *Curr Allergy Asthma Rep* 2003, 3:47–53.

This article provides a comprehensive review of the topic of the latex food syndrome, which is increasing in prevalence worldwide.

- 33 Wagner S, Breiteneder H: The latex-fruit syndrome. *Biochem Soc Trans* 2002, 30:935–940.

This article provides a comprehensive review of the topic of the latex food syndrome, which is increasing in prevalence worldwide.

- 34 Palosuo K: Update on wheat hypersensitivity. *Curr Opin Allergy Clin Immunol* 2003, 3:205–209.

- 35 Palosuo K, Varjonen E, Nurkka J, et al.: Transglutaminase-mediated cross-linking of a peptic fraction of omega-5 gliadin enhances IgE reactivity in wheat-dependent, exercise-induced anaphylaxis. *J Allergy Clin Immunol* 2003, 111:1386–1392.

This article reports the novel finding that exercise releases transglutaminase, which then alters a gliadin component of wheat, thereby enhancing IgE reactivity leading to wheat-dependent, exercise-induced anaphylaxis.

- 36 American Gastroenterological Association: Position statement: guidelines for the evaluation of food allergies. *Gastroenterology* 2001, 120:1023–1025.

- 37 Sampson HA, Sicherer SH, Birnbaum AH: AGA technical review on the evaluation of food allergy in gastrointestinal disorders. American Gastroenterological Association. *Gastroenterology* 2001, 120:1026–1040.

- 38 Niggemann B: Evolving role of the atopy patch test in the diagnosis of food allergy. *Curr Opin Allergy Clin Immunol* 2002, 2:253–256.

- 39 Kapel N, Matarazzo P, Haouchine D, et al.: Fecal tumor necrosis factor alpha, eosinophil cationic protein and IgE levels in infants with cow's milk allergy and gastrointestinal manifestations. *Clin Chem Lab Med* 1999, 37:29–32.

- 40 Bischoff SC, Mayer J, Wedemeyer J, et al.: Colonoscopic allergen provocation (COLAP): a new diagnostic approach for gastrointestinal food allergy. *Gut* 1997, 40:745–753.

- 41 Teuber SS, Porch-Curren C: Unproved diagnostic and therapeutic approaches to food allergy and intolerance. *Curr Opin Allergy Clin Immunol* 2003, 3:217–221.

This report addresses the broad topic of alternative and complementary methods to manage food allergy.

- 42 Niggemann B, Gruber C: Side-effects of complementary and alternative medicine. *Allergy* 2003, 58:707–716.

This report addresses the broad topic of alternative and complementary methods to manage food allergy.

- 43 Osborn D, Sinn J: Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants. *Cochrane.Database.Syst.Rev.* 2003, 4:CD003664.

This article provides a methodologically sound review of the literature, which concludes that hydrolyzed formulas are not superior to breast milk but can be of benefit compared with untreated cow's milk for those infants who are unable to breast-feed for various reasons.

- 44 von Berg A, Koletzko S, Grubl A, et al.: The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. *J Allergy Clin Immunol* 2003, 111:533–540.

- 45 Isolauri E, Rautava S, Kalliomaki M, et al.: Role of probiotics in food hypersensitivity. *Curr Opin Allergy Clin Immunol* 2002, 2:263–271.

- 46 Vanderhoof JA, Young RJ: Role of probiotics in the management of patients with food allergy. *Ann Allergy Asthma Immunol* 2003, 90:99–103.

- 47 Hochreiter R, Stepanoska T, Ferreira F, et al.: Prevention of allergen-specific IgE production and suppression of an established Th2-type response by immunization with DNA encoding hypoallergenic allergen derivatives of Bet v 1, the major birch-pollen allergen. *Eur J Immunol* 2003, 33:1667–1676.

In this study, mice that received one of three DNA vaccines for the major birch pollen Bet v1 were protected from allergic sensitization to Bet v1 with reduced IgE production and a sustained Th1 cytokine milieu.

- 48 Leung DY, Sampson HA, Yunginger JW, et al.: Effect of anti-IgE therapy in patients with peanut allergy. *N Engl J Med* 2003, 348:986–993.

Although prior studies had indicated that anti-IgE therapy had applications in animal models and other atopic diseases, this is the first study to evaluate monoclonal anti-IgE in food allergy disease. A dose-related benefit was observed.

- 49 Roy K, Mao HQ, Huang SK, et al.: Oral gene delivery with chitosan-DNA nanoparticles generates immunologic protection in a murine model of peanut allergy. *Nat Med* 1999, 5:387–391.

- 50 Shida K, Takahashi R, Iwadata E, et al.: *Lactobacillus casei* strain *Shirota* suppresses serum immunoglobulin E and immunoglobulin G1 responses and systemic anaphylaxis in a food allergy model. *Clin Exp Allergy* 2002, 32:563–570.

- 51 Zemann B, Schwaerzler C, Griot-Wenk M, et al.: Oral administration of specific antigens to allergy-prone infant dogs induces IL-10 and TGF-beta expression and prevents allergy in adult life. *J Allergy Clin Immunol* 2003, 111:1069–1075.