

Eosinophils and allergic diseases of the gastrointestinal tract

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The association between increased tissue eosinophilia and allergic disease is particularly striking in the case of the gastrointestinal tract. About 80% of individuals with eosinophilic gastrointestinal disorders (EGIDs) are atopic, while half of the patients with gastrointestinal allergy show tissue eosinophilia. The function of eosinophils in gastrointestinal allergic disorders is unclear; however, a proinflammatory action is most likely. Cytokines (interleukins 5 and 3, granulocyte-monocyte colony-stimulating factor) and chemokines (eotaxin, RANTES, etc.) released by Th2 lymphocytes, mast cells and other tissue cells have been identified as major regulators of eosinophil chemotaxis and activation, but a convincing mechanism by which eosinophils are activated in an allergen-dependent manner is still lacking. The diagnostic approach comprises both histological and laboratory methods to assess eosinophilia and eosinophil activation, as well as tools to assess the allergic disease while excluding other gastrointestinal diseases such as food intolerances, infections and tumours. Treatment of allergic EGIDs includes elimination or elemental diets and drug therapy using classical anti-allergic agents such as topical corticosteroids and new approaches such as LTD4 receptor antagonists or antibodies against IL-5 or eotaxin.

Key words: eosinophils; eosinophilic oesophagitis; eosinophilic gastroenteritis; eotaxin; eosinophil-derived neurotoxin; interleukin-5; food allergy.

The gastrointestinal mucosa is predisposed to develop allergic reactions in individuals with a genetic risk for allergy because this site is particularly exposed to allergens (food, pollen, bacterial antigens, etc.) and is equipped with all prerequisites needed to develop allergic reactions (mast cells, eosinophils, lymphocytes, dendritic cells,

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nerves, etc.). Most allergic reactions of the gastrointestinal tract are triggered by food allergens, i.e. food proteins. The most relevant food proteins are listed in Table 1. In adults, cross-reactions between pollens – namely tree pollens (30–93%), mugwort (16–27%), and latex (17–42%) – and food allergens are of particular importance, since they account for most food-allergy manifestations in adults.¹

In industrialised countries approximately 20–30% of the population suffers from adverse reactions to food (ARFs); however, only 1/4 cases (in children) and 1/10 cases (in adults) are caused by food allergy.^{2,3} ARFs are defined as clinically abnormal reactions to ingested food or food additives. The reactions are divided into immune-mediated reactions (food allergies) and non-immune reactions (food intolerances). Food intolerances include carbohydrate intolerances (lactose, fructose, sorbitol, etc.), amine intolerances (histamine, serotonin, etc.) and other forms of intolerance.⁴

The present chapter focuses on food allergy – the immune-mediated hypersensitivity reaction against food – in which eosinophils are frequently involved.

PATHOPHYSIOLOGY OF FOOD ALLERGY IN THE GASTROINTESTINAL TRACT

Regulation of intestinal immune responses

The intestinal mucosa has to meet the challenge of protecting the host against possibly harmful nutrients, microbes and toxins on the one hand, while on the other hand ensuring the uptake of nutrients and antigens indispensable for life.⁵ To do this, the gastrointestinal barrier is equipped with an innate immune system and other non-specific defence systems, including gastric acid, mucus and bicarbonate secretion, as well as an intact epithelial layer forming tight junctions, peristaltic movement, digestive enzymes, phagocytes, alternative complement pathways, and antimicrobial peptides such as defensins and cathelicidins.^{6–8} Macrophages and neutrophils, but also mast cells and eosinophils, are important effector cells involved in such innate immune responses.^{9,10} Conserved bacterial structures are recognised by these cells through ‘pattern recognition receptors’, including the Toll-like receptor family.¹¹ Upon recognition of ‘danger signals’, these effector cells trigger and/or support adaptive immune responses required for effective host defence and protection. On the other hand, the gastrointestinal immune system has the unique capacity to develop ‘oral tolerance’, a state of acceptance of foreign antigens such as food or particular bacterial antigens which is achieved by down-regulation of normal immune responses, and which is necessary for normal gut function.¹²

Table 1. Most relevant food allergens in children and adults.¹

Children	Adults
Milk and milk products	Pollen-associated food allergens (e.g. apple, nuts, celery, carrots, rye, paprika, spices)
Egg	Nuts and seeds
Wheat	Peanuts, soy
Soy, peanuts	Fish and seafood
Nuts	Milk and milk products, egg
Fish	Latex-associated food allergens (e.g. banana, avocado, kiwi)

Allergic inflammation

In some cases this immunological tolerance is impaired and food proteins are recognised by the immune system as harmful antigens, resulting in an abnormal immune response and a subsequent inflammatory reaction which is variable in extent and duration.¹³ Coombs and Gell classified immunological hypersensitivity reactions into four different subtypes based on the antigen-recognising molecules such as IgE, IgG, IgM, immune complexes, or T-cell receptor.¹⁴ The best-defined immune reaction against food is the IgE-mediated hypersensitivity to food, also named type-I reaction according to Coombs and Gell. Such reactions lead to an increased release of inflammatory mediators in mast cells, basophils and eosinophils, and play a central role in the pathogenesis of many cases of asthma, rhinitis, atopic skin diseases and gastrointestinal food allergy. Apart from type-I reactions, type-IV reactions are thought to be involved that are characterised by the activation of food-antigen-specific T cells.⁴ It has been proposed that these are responsible for so-called 'delayed reactions' during which tissue infiltration with inflammatory cells is observed. The type-IV reactions are difficult to distinguish from 'late phase type-I reactions' that are observed in about 25% of afflicted individuals.¹³ Both forms of delayed reactions have in common that they basically consist of a so-called 'Th2 immune response', which is not defined by the antigen-recognising molecule but by the set of cytokines released during such immune reactions. The most relevant Th2 cytokines are interleukins IL-4, IL-5, IL-9 and IL-13, the functions of which are given in Table 2.

In patients with food allergy, priming of naive lymphocytes of the gut-associated lymphoid tissue (GALT) leads to cytokine-producing Th2 effector cells or IgE-producing plasma cells (Figure 1). Isolated T cells from blood, skin and mucosal sites of patients with food allergy express a characteristic Th2-cell phenotype by releasing IL-4, IL-5, IL-9 and IL-13.¹⁵ As already mentioned, IL-4 and IL-13 are major regulators of IgE synthesis, while IL-4, IL-5 and IL-9 play a role in screwing T cells to Th2 cells or in the chemoattraction of inflammatory cells (mast cells and eosinophils), indicating that these cytokines are indeed of relevance in the induction and maintenance of allergic responses.¹⁶⁻¹⁹

The cause of allergic inflammation that occurs only in selected individuals is still unclear. Apart from a hyperresponsive mucosal immune system, a sufficient amount of allergen is required for an intestinal allergic inflammation. Reasons for the increased antigen exposure could be genetically determined alterations of key molecules of the gastrointestinal barrier, immaturity of the gastrointestinal barrier, or acquired disturbances of the gastrointestinal defence system such as enteric infection or a combination thereof. An impaired mucosal barrier caused by reduced mucus production, decreased defensin expression, challenge to particular toxins, or bacterial/viral infection might be

Table 2. Major functions of Th2 cytokines in allergy.¹³⁴

IL-4	Switch of B cells into IgE-producing plasma cells Regulation of T cells and mast cells
IL-5	Recruitment and regulation of eosinophils
IL-9	Regulation of Th2 lymphocytes
IL-13	Regulation of IgE synthesis in B cells

IL, interleukin.

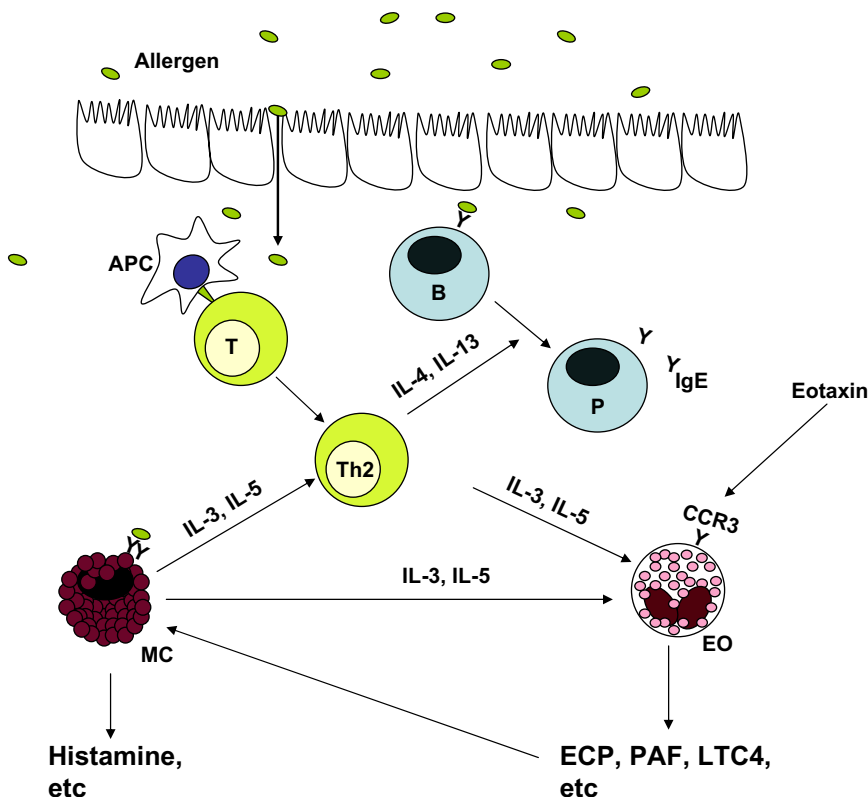


Figure 1. Mechanisms leading to immunological hypersensitivity in the gastrointestinal tract. APC, antigen presenting cell; B, B cell; CCR3, CC chemokine receptor 3; ECP, eosinophil cationic protein; EO, eosinophil; IL, interleukin; LTC4, leukotriene C4; MC, mast cell; P, plasma cell; PAF, platelet-activating factor; T, T cell; Th, T helper cell. Modified from Bischoff and Crowe (*Gastroenterology* 2005; **128**: 1089–1113) with permission.

an initial step for the development of immunological hypersensitivity.¹³ In addition, a genetic predisposition favouring Th2 responses is required. The pathophysiology of food allergy and other forms of intestinal inflammation is closely related to genetic and environmental factors which regulate intestinal permeability and the function of GALT. Finally, allergen exposure leads to the production of allergen-specific IgE which is bound to the high-affinity IgE receptor on mast cells and basophils, and to the low-affinity IgE receptors in other cells such as dendritic cells and eosinophils. If the cells are quipped with allergen-specific IgE, food allergen can induce cell activation, e.g. mast cell degranulation, and the release of mediators such as chemokines, histamine, proteases, basic proteins, and reactive oxygen species.

ROLE OF EOSINOPHILS IN ALLERGIC INFLAMMATION

Association between eosinophils and allergy

Eosinophils have been proposed as major contributors to allergic inflammation, because they are typically found in increased numbers at sites of allergic inflammation,

and they are activated for mediator release in the course of type-I allergic reactions. The factors responsible for eosinophil recruitment are mostly identified, and include interleukins (IL-5, and to a lesser extent IL-3 and GM-CSF) and chemokines (e.g. eotaxin and RANTES; for details see Chapter 2 of the issue). The mechanisms of eosinophil activation during allergic reactions are less clear. Eosinophils produce and release highly bioactive inflammatory mediators such as eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN), eosinophil peroxidase (EPO) and major basic protein (MBP). Furthermore, they are a rich source of cytokines and reactive oxygen species, thus participating in cytotoxic and immunoregulatory processes within the allergic reaction. The clinical symptoms and the organ dysfunction following allergic reactions can be attributed to a large extent to such products.^{20–23}

The association between eosinophils and allergy is particularly striking in the gastrointestinal tract. In contrast to other mucosal sites, the small and large intestines – but not the oesophagus – constitutively contain eosinophils, probably for defence against parasites and other infections.^{24,25} Most interestingly, about 80% of individuals with eosinophilic gastrointestinal disorders (EGIDs) are atopic,²⁶ while dietary exclusion of the allergen can sometimes reverse disease severity.^{24,27} On the other hand, about 50% of patients with gastrointestinal allergy show mucosal eosinophilia, further arguing for a major function of eosinophils in gastrointestinal allergic disorders. Peripheral eosinophilia, which is defined as >400 eosinophils/ μL , can be seen in approximately 50% of the patients with gastrointestinal eosinophilia.¹³

Mechanisms of eosinophil activation

The biology of eosinophils has been described in detail in the preceding chapters. Briefly, eosinophils are generated in the bone marrow and circulate in the peripheral blood, from where they are recruited to different organs. Inflammatory reaction or tissue damage is not induced by resident gastrointestinal eosinophils, unless inflammatory conditions cause eosinophil activation and accumulation at high numbers into the afflicted organs.²⁵ Gastrointestinal accumulation of eosinophils is regulated by four processes: enhanced differentiation and proliferation of bone-marrow progenitor cells, interaction of circulating eosinophils with endothelial cells, elongated survival at inflammatory sites, and chemotactic signals.²⁸ Key mediators for these processes are cytokines (IL-1, IL-3, IL-4, IL-5, IL-13, GM-CSF) and chemokines (RANTES, monocyte chemoattractant protein 3 [MCP-3], macrophage inflammatory protein 1 α [MIP-1 α], eotaxin 1, eotaxin 2 and eotaxin 3).²⁹ Eotaxins signal exclusively through the chemokine receptor 3 (CCR-3) expressed on eosinophils.³⁰ It has been suggested that eotaxins 1, 2, and 3 may regulate different phases of eosinophil recruitment and effector function during inflammation. The development, effector function and migration of eosinophils are enhanced by IL-3, IL-5, and GM-CSF,³¹ while eosinophil trafficking is regulated by other cytokines such as IL-1, IL-4, IL-13, tumour necrosis factor α (TNF- α), and eotaxins through activation of the endothelial adhesion systems.³² IL-4, IL-5 and IL-13, which drive eosinophilia, can be produced by allergen-activated Th2 cells. IL-5, being the most effective of these cytokines, primes eosinophils to react to chemoattractants, and it mediates eosinophil activation, differentiation and survival. Stimulation of intestinal epithelial cell lines with IL-4 and IL-13 leads to production of eotaxin 3 via the STAT-6 pathway.³³

While many allergen-independent ways of eosinophil activation have been well characterised during the last few years, allergen-dependent eosinophil activation

remains still a miracle. As mentioned before, eosinophils express a low-affinity IgE receptor; however, it is not clear whether this receptor is expressed at the cell surface or is just intracellular. Possibly this receptor expression is also dependent on the tissue environment, since surface IgE receptor expression in eosinophils might be an exclusive feature of allergic inflammation.^{34,35}

Clinical evidence for a role of eosinophils in gastrointestinal allergy

In children with food allergy, eosinophil granule proteins could be found in faecal samples after food challenge, indicating that eosinophils are involved, and further arguing that IgE-dependent eosinophil activation might occur only in allergic individuals. Release of preformed granule proteins (cationic proteins, etc.), lipid mediators (platelet-activating factor [PAF] and cysteinyl leukotriene [LT] C₄), and cytokines by eosinophils can contribute to inflammatory responses and tissue damage. Eosinophil-derived cationic proteins (ECP, EDN, EPO, and MBP) are cytotoxic to the human intestinal epithelium and trigger degranulation of mast cells and release of cytokines, chemokines, lipid mediators, and neuromediators.³⁶ Eosinophils may also contribute to an alteration of intestinal barrier function. For instance, the tight junctional molecule occludin is down-regulated by eosinophil-derived MBP and therefore reduces T84 epithelial barrier function.³⁷

CLINICAL PRESENTATION OF ALLERGIC DISEASES IN THE GASTROINTESTINAL TRACT

Allergic symptoms vary from marginal impairments to life-threatening shock reactions. Major targets of food allergy are the skin, the respiratory tract and the gastrointestinal tract (Table 3), either alone or in combination.^{38,39} Possibly the gastrointestinal tract is the primary 'allergy organ', since it forms the largest barrier of the host to the environment (~400 qm, compared to skin, 2 qm), it is exposed to huge amounts of antigen (40 g food proteins per day, of which 2% are not hydrolysed during stomach passage, and 10¹⁴ commensal bacteria located mostly in the large intestine), and it is the organ typically involved in early allergy manifestations in babies and small children.

Gastrointestinal symptoms such as nausea, vomiting, abdominal pain and diarrhoea appear typically in combination with allergic manifestations in the skin and other target organs. The airways are often not considered as a common site of involvement, but about 10–20% of patients with gastrointestinal hypersensitivity disorders show involvement of the respiratory tract.³⁰ The food allergy-associated EGIDs comprise:

- eosinophilic oesophagitis;
- eosinophilic gastroenteritis;
- eosinophilic gastritis;
- eosinophilic enteritis;
- eosinophilic (entero)colitis; and
- eosinophilic proctitis.

Increased faecal concentrations of TNF- α , ECP, and α_1 -antitrypsin have been found in children with atopic dermatitis and allergy to cows' milk.⁴⁰ Measurement of faecal EDN and urinary LTE₄ in food-allergic patients and patients with non-allergic food

Table 3. Clinical symptoms of food allergies.⁴

Organ	Disorder	Afflicted individuals
Gastrointestinal manifestations:		
	<i>Immediate gastrointestinal hypersensitivity (primarily IgE-mediated)</i>	
	Oral allergy hypersensitivity (OAS)	All
	Allergic gastritis	All
	Allergic enterocolitis	All
	<i>Eosinophilic gastroenteropathies (~50% IgE-mediated)</i>	
	Eosinophilic oesophagitis	All
	Eosinophilic gastritis	All
	Eosinophilic enterocolitis	All
	Eosinophilic proctitis	Infants, children
	<i>Dietary protein enterocolitis and proctitis</i>	
	Chronic constipation	Children
	Dietary protein enteropathy	Infants
	Coeliac disease	Children, adults
	<i>Other mechanisms of adverse food reactions</i>	
	Gastro-oesophageal reflux disease (GERD)	All
	Non-ulcer dyspepsia (NUD)	
	Inflammatory bowel disease	Adults
	Irritable bowel syndrome	Adults
Extraintestinal manifestations:		
Skin	Urticaria and angio-oedema	All
	Atopic eczema	Infants, children
	Dermatitis herpetiformis	Children, adults
Respiratory tract	Rhinitis	All
	Asthma	All
	Alveolitis	All
Nervous system	Migraine headache	Adults
	Chronic fatigue syndrome	Adults
	Psychiatric and behavioural problems	Adults
	Hyperactivity syndrome	Children
Cardiovascular system	Vasculitis	All
	Systemic anaphylaxis	All
	Oedema	All

hypersensitivity showed enhanced levels in allergic people,⁴¹ further indicating eosinophil activation in the gastrointestinal tract of patients with food allergy.

Coeliac disease is a particular form of food allergy manifesting primarily in the gastrointestinal tract, since it fulfils all criteria of food allergy (immune-mediated adverse reaction to food). It occurs in up to 1% of the population, and becomes a manifest disease in about 1/10 afflicted individuals.⁴² The enteropathy is triggered by dietary ingestion of gliadin found in wheat, hordelein in rye, and secalin in barley. Elimination of such glutens from the diet allows the regeneration of normal small-bowel function and appearance. Symptoms such as diarrhoea, weight loss, failure to thrive, fatigue, dyspepsia, neurological dysfunction, and musculoskeletal problems improve with removal of the offending grains.⁴³ Interestingly, coeliac disease, like food allergy in general, is typically associated with gastrointestinal eosinophilia and elevated eosinophil mediators.¹⁵

Gastrointestinal food allergies have to be clearly separated from non-immune-mediated food intolerances, which are about 10 times more frequent than food allergy. In many cases people suffering from food intolerances think they have a food allergy, but the two things should not be mixed up. Food intolerances can be the result of microbial contamination (e.g. staphylococcal or *Escherichia coli* enterotoxin, *Salmonella*, or *Shigella*, leading to food toxicity or food poisoning), pseudoallergic and pharmacological reactions (the effect of mast-cell degranulation is imitated by food but without involvement of IgE), lactose intolerance (reduced intestinal lactase activity), histamine intolerance (reduced diaminoxidase activity), and psychological or physiological intolerance.^{11,13} Frequently, people suffering from food intolerances believe that they suffer from food allergy, which should be proved appropriately.

Epidemiology of food allergies

Prevalence and incidence of food allergies vary depending on the diagnostic criteria used.⁴⁴ When parents have been asked about food allergies of their children, prevalences of up to 35% have been assessed.^{3,45} Further investigations revealed that between 1/4 and 1/10 of these self-reported food allergies cannot be confirmed by objective means, and therefore are rather a kind of non-immune-mediated ARF.^{3,46} The proposed gold standard for the determination of food allergies is the double-blind, placebo-controlled food challenge (DBPCFC), although this confirms ARF and not food allergy.¹³ As a result of its limited practicability it has not been fully established in clinical work, as it is time-consuming and requires an accurately equipped setting for safety reasons. Therefore, most data on prevalence of food allergy are primarily obtained by subjective self-reported questionnaires and patient records, or objectively by skin-prick tests, specific IgE, or by a mixture of these methods, but only a few have confirmed their data by DBPCFC. As a consequence of lacking standardisation of allergen extracts used for allergic sensitisation in vitro (IgE) or in vivo (skin-prick test), many epidemiological studies are not easily comparable.⁴⁷

Reliable data suggest a prevalence of 16–28% for ARF in the general population.^{48,49} Objectively confirmed food allergies occur in 2–8% of the paediatric population (children aged 2–3 years are the group most affected) and 1–3% of adults (highest prevalence between 20 and 40 years of age). Females and individuals with a higher education seem to be more frequently affected.^{2,3,45,48,50,51} Existing food allergy is reported by 25–50% of individuals with gastrointestinal disorders.^{52,53} A study of 164 children (from 6 months to 18 years) suffering from atopic dermatitis (with associated food allergy in 80% of the patients) reported gastrointestinal disorders in approximately 60% of the cases.⁴⁰ Of patients suffering from EGIDs, 80% show coexisting atopy, while anaphylaxis to food coexists in approximately 20% of these.⁵⁴ Approximately 80% of children who have allergy to cows' milk develop clinical tolerance until their fifth birthday, while 35% go on to have other food allergies.⁵⁵ More than 60% of children with severe atopic dermatitis and 20% of children with mild dermatitis develop asthma until the age of 8 years.⁵⁶

Considering the enormous variety of human diet, relatively few foods trigger an allergic response. Major allergens provoking an allergic reaction differ between countries, depending on regional dietary habits and food preparation. Pollen-related foods like apple and hazelnuts, and other fruits (mainly pineapple, berries and kiwi) are the most frequently reported foods causing allergic reactions in German investigations.³ Cows' milk, wheat, hens' eggs, and soy are common major allergens in European countries and the USA, while peanut is a major food allergen in the USA and Great Britain

but not in Germany.^{57,58} It is assumed that the prevalence of food allergy is increasing; however, except for sensitisation to peanuts,^{58,59} clear data are lacking.

EOSINOPHILIC GASTROINTESTINAL DISEASES RELATED TO FOOD ALLERGY

Eosinophilic oesophagitis

The presence of eosinophils in the oesophagus indicates an abnormal situation, since the oesophagus is usually devoid of eosinophils.⁶⁰ Such conditions typically occur in association with allergic disease, or remain idiopathic, but finally they cause chronic inflammation independent of the aetiology of disease.

Two different subtypes of eosinophil-associated oesophageal disorders are differentiated: primary and secondary. Atopic, non-atopic, and familial forms belong to the primary subtype, while the secondary subtype comprises systemic eosinophilic disorders (HES) and non-eosinophilic disorders. Eosinophilic oesophagitis can be found in nearly all age groups, but young males predominate (approximately 60–70% of patients are male).⁶¹ Peaks of the disease are seen in early childhood and again between the ages of 20 and 40 years.⁶²

Allergy is thought to be the cause of eosinophilic oesophagitis in many cases. Up to 80% of children have a coexisting allergic disorder such as asthma, atopic dermatitis, or allergic rhinitis. In adults, this association is somewhat weaker, since allergy can be confirmed as the cause in only 40–60%.^{63–65} Skin-prick tests or radioallergen sorbent testing (RAST) showed positive results in 53–73% of children and 40% of adults.²⁵ Peripheral blood eosinophilia appears only in a subset (approximately 30%) of patients.⁶⁶

High-protein food (milk, egg, meat) seem to be most relevant in the context of eosinophilic oesophagitis, while fruits and green vegetables cause symptoms to a lesser extent.⁶⁷ Food anaphylaxis occurs in only a minority of affected individuals.⁶² Expression of the Th2 cytokines IL-4, IL-5, and IL-13 and an increase in the number of mast cells have been found in the oesophagus of patients.^{68–70} IL-5 seems to have a particular role in this condition, as anti-IL-5 antibody treatment resulted in reduced allergen- and IL-13-induced eosinophilic oesophagitis.⁷¹ Furthermore, compared with non-atopic children, patients with active eosinophilic oesophagitis have increased levels of IL-5⁺ CD4 T cells, and the degree of tissue eosinophilia is correlated with the percentage of these IL-5-expressing CD4 T cells.⁷²

Mishra et al⁷¹ found that intra-tracheal administration of IL-13 and specific allergens leads to pulmonary atopic disease and eosinophilic oesophagitis in mice, suggesting a link between these two disease entities.

Straumann et al⁷³ compared the expression of proinflammatory proteins of tissue-dwelling eosinophils in individuals with eosinophilic oesophagitis and in controls, and could describe different eosinophil subpopulations. According to these studies, eosinophils from patients with eosinophilic oesophagitis express higher levels of CD25, IL-4 and IL-13 than controls, indicating eosinophil activation (Figure 2). Thus, tissue eosinophilia is not just a histological epiphenomenon but an active part of the pathophysiology of the disease. Blanchard et al⁶⁹ found significantly elevated levels of eotaxin 3 (gene-chip analysis) in eosinophilic oesophagitis patients. In 14% of patients a single-nucleotide polymorphism on the eotaxin 3 gene has been detected. This polymorphism could imply genetic susceptibility to eosinophilic oesophagitis. These results are supported by investigations with CC chemokine receptor 3 (CCR3, an eotaxin

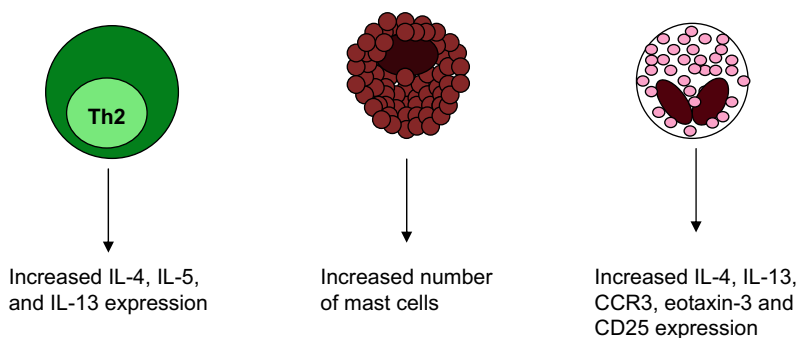


Figure 2. Increased expression of cytokines, chemokines and mast cells in patients with eosinophilic oesophagitis.

receptor) deleted mice, which do not develop experimental eosinophilic oesophagitis. In fact, elevated eosinophil CCR3 expression could be found in active eosinophilic oesophagitis patients, and tissue expression of eotaxin 3 mRNA correlates with the CCR3 expression in peripheral-blood eosinophils and eosinophil numbers in the oesophagus.⁷² Finally, oesophageal rings, which can be found in patients with eosinophilic oesophagitis, may be related to histamine which activates acetylcholine and therefore evokes contraction of the oesophageal muscularis mucosa. Formation of oesophageal rings could then be the result of narrowed muscle fibres. Persistent contraction and hypertrophy of the mucosal layer may implicate permanent scar formation.⁷⁴

Eosinophilic oesophagitis is characterised by symptoms such as nausea, vomiting, epigastric or chest pain, food impaction, weight loss, failure to thrive, oesophageal strictures, dysphagia, and respiratory obstructive problems.^{61,75,76} Eosinophil-derived MBP can induce smooth-muscle contraction via actions on muscarinic M2 receptors – a possible explanation for symptoms such as dysphagia and food impaction.³¹ Symptoms reported in children, but not in adults, are growth retardation, epigastric abdominal pain, and respiratory symptoms (coughing, wheezing, pneumonia, sinusitis, choking).⁷⁷ In the long term, eosinophilic oesophagitis can lead to irreversible structural alterations such as loss of mucosal elasticity and subepithelial fibrosis.²⁷ The mechanisms of motor disturbances often seen in patients with allergic eosinophilic oesophagitis, resulting in oesophageal dysmotility, are not clear.^{76,78}

Preliminary studies suggest seasonal variations in eosinophilic oesophagitis symptoms, since differing eosinophil counts, especially in the proximal oesophagus, have been documented.^{63,79} These data further argue that allergens – e.g. seasonal pollen exposure – play a role in many cases.

The diagnosis of allergic eosinophilic oesophagitis is based on histological criteria (number and location of eosinophils in the oesophagus) and allergological means (history of ARF, positive skin tests, specific IgE in serum, DBPCFC). As for eosinophilic oesophagitis in general, more than 20–24 eosinophils/HPF (high-power field, 400 $\times$) are indicative for eosinophilic oesophagitis (especially when patients receive anti-GERD therapy), while 0–7 eosinophils/HPF are characteristic for GERD.⁶⁰ For reliable results, multiple biopsies (at best five) of the distal and proximal oesophagus should be examined, as eosinophilic oesophagitis is often a patchy disease. Accumulation of eosinophils primarily in distal regions may also occur in GERD, while proximal and distal eosinophilia indicates eosinophilic oesophagitis.⁶² Parfitt et al⁸⁰ suggest the following

diagnostic criteria: ≥ 15 eosinophils in at least two HPFs, or >24 eosinophils in one HPF confirm eosinophilic oesophagitis.

Radiographic and endoscopic investigations show typical findings such as ulcerations, whitish papules, strictures, mucosal rings and polyps. Histomorphological analysis of the white exudates shows noticeable accumulation of eosinophils within these areas.^{81,82} Unfortunately, the endoscopic signs are often unspecific, even misleading, or just absent. Up to 34% of children with eosinophilic oesophagitis have a visually normal oesophagus.^{76,83}

Eosinophilic gastroenteritis (EGE)

Under healthy conditions the stomach and intestine, in contrast to the oesophagus, show low but detectable baseline numbers of eosinophils. Intense infiltration of eosinophils in the stomach (26–81% of the cases), small intestine (28–100% of the cases), or both, characterises eosinophilic gastritis, enteritis or gastroenteritis. The oesophagus, large intestine, and rectum are also involved in some cases.⁸⁴ The heterogeneous and rare disorder affects both children and adults, but is most frequently diagnosed in the third decade of life. Like eosinophilic oesophagitis, EGE is also classified into primary and secondary subtypes. Atopic, non-atopic, and familial variants are part of the primary subtype, while the secondary subtype is further divided into systemic eosinophilic disorders (HES) and non-eosinophilic disorders. Atopic diseases or a family history of allergies are elicited in 50–70% of the cases and seem to play an important role in pathogenesis, while in other cases the disease is idiopathic.

As described for eosinophilic oesophagitis, Th2 cytokines (IL-3, IL-5, and IL-13) and chemokines (e.g. eotaxins) seem to be the most critical factors in the pathogenesis of eosinophilic gastroenteritis. After stimulation with milk proteins, lamina-propria-derived T cells of patients with EGE preferentially secrete Th2 cytokines (e.g. IL-13),⁸⁵ suggesting a Th2-mediated allergic response. Further, enhanced IL-4 and IL-5 secretion by peripheral T cells could be seen in individuals with EGE.⁸⁶ Histological damage may be the result of degranulated eosinophils in the intestinal mucosa.

Experiments in mice showed induction of eosinophilia in the oesophagus after repeated challenges of aeroallergens, while eosinophilia could not be found in the stomach or small intestine.⁸⁷ In contrast, repeated oral antigen provocation in mice provoke elevated levels of mast cells and eosinophils in the small intestine lamina propria, accompanied by increased serum IgE and several eosinophil-produced leukotrienes.⁸⁸ An ablation of allergen-induced eosinophilia in the oesophagus could be seen in IL-5-deficient mice, but the absence of IL-5 did not reduce intestinal eosinophilia. In contrast, eotaxin deficiency attenuated the allergen-induced eosinophilic oesophagitis response and ablated the small-intestinal eosinophilic response.⁸⁴ These results suggest different mechanisms for recruitment of eosinophils in eosinophilic oesophagitis and EGE (Figure 3).

Because of the inaccessibility of the small bowel and the deeper layers of the luminal wall, the diagnosis of EGE is much more challenging than that of eosinophilic oesophagitis. Gastrointestinal symptoms associated with intense eosinophilic infiltration in biopsy samples, or high eosinophil counts in ascitic fluid, and exclusion of other causes of eosinophilia (e.g. parasitic and bacterial infections, irritable bowel disease, HES, drug injury, and drug hypersensitivity) are currently accepted as important diagnostic criteria. Blood eosinophilia can be seen in approximately 60% of patients.⁵²

Depending on the site of eosinophilic infiltrates, symptoms vary and are often unpredictable; they range from pain to dysmotility, bleeding, obstruction, or ascites.

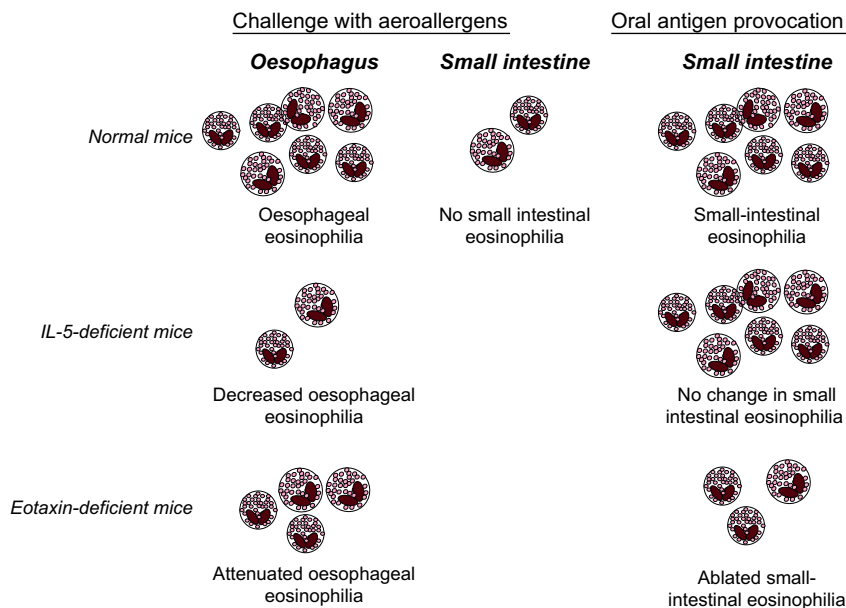


Figure 3. In mice, aeroallergens can lead to an experimental induction of eosinophilia in the oesophagus, but not in the small intestine, where eosinophilia can be induced only by oral antigen provocation. Interleukin 5 (IL-5) deficiency leads to a decreased aeroallergen-induced eosinophilia, while intestinal eosinophilia triggered by oral antigen provocation is not reduced. In contrast, eotaxin deficiency causes attenuated oesophageal eosinophilia and ablated small-intestinal eosinophilia. These findings suggest different eosinophil recruitment mechanisms in eosinophilic oesophagitis and eosinophilic gastroenteritis.^{19,89}

Nausea, vomiting, diarrhoea, abdominal pain, blood loss in stools, iron-deficiency anaemia, malabsorption, protein-losing enteropathy, and failure to thrive characterise the most common mucosal form of EGE.⁸⁹ Irritable bowel syndrome, dyspepsia, pancreatitis, acute appendicitis, or inflammatory bowel disease may be confused with these clinical non-specific presentations.

Patients with a mucosal pattern often show atopy and food hypersensitivity. Due to thickening of the bowel wall as a result of infiltrating eosinophils mainly in the muscularis, obstructive symptoms – mimicking pyloric stenosis or other gastric outlet obstructions – can occur. These are typically present with colics. The rare serosal form of eosinophilic gastroenteritis results in exudative ascites and, compared with other forms, in higher numbers of peripheral-blood eosinophils.⁵² Atypical presentations are: sub-acute bowel obstruction,^{90,91} gastric outlet obstruction,⁹² duodenal strictures,⁹³ neonatal intussusceptions,⁹⁴ acute appendicitis,⁹⁵ and pancreato-biliary tract disease.^{96,97} Eosinophil infiltration in the colonic lamina propria and myenteric plexus can lead to intestinal pseudo-obstruction.⁹⁸

Histological criteria of EGE are elevated levels of eosinophils (>20 eosinophils/HPF)^{52,99} in intestinal biopsy specimens, intestinal crypts and gastric glands, and also elevated levels of T cells and mast cells, indicating a chronic Th2-associated inflammation.⁷⁰ Increased levels of MBP and ECP can be determined immunohistochemically.⁹⁰ Like eosinophilic oesophagitis, eosinophilic gastroenteritis shows a patchy distribution. Thus, screening of multiple biopsies is necessary. In 20–40% of patients eosinophilia might be absent.¹⁰⁰

Micronodules (and/or polyposis) of patients with eosinophilic gastritis can be assessed by endoscopy. Aggregated eosinophils and lymphocytes often mark these lesions. Thickening of the circular folds and wall in the small bowel (also a result of eosinophil infiltration) associated with deformation of the luminal configuration, reduced peristalsis, and erythematous and friable mucosa with lesions are further typical findings, mostly present at the mucosal type.¹⁰¹ The occurrence of ascites, thickening of parietal and visceral peritoneum and nodules (evaluated by laparoscopy) indicate a serosal form of EGE.¹⁰²

Eosinophilic (entero)colitis (EEC)

Characteristics of EEC are eosinophil infiltration and severe gastrointestinal inflammation manifesting in the colon or in the small intestine and colon of infants and, in rare cases, of older children and adolescents.¹⁰³ By analogy with other EGIDs, a classification into primary and secondary subtypes has been proposed, according to which atopic and non-atopic variants belong to the primary subtype, while systemic eosinophilic disorders (HES) and non-eosinophilic disorders belong to the secondary subtype. Most common is a sensitisation to cows' milk and soy, but other solid foods – including vegetables, cereals, and poultry meats – can also act as allergens. EEC is also known as protein enteropathy, predominantly a disorder of infants younger than 3 years, with symptoms beginning in the first month of life, but residual symptoms of cows' milk sensitive enteropathy may persist until school age.¹⁰⁴ Elimination of the causal protein is usually followed by resolution of symptoms. Breast-feeding seems to be protective for EEC, as there are no published cases of EEC in exclusively breast-fed babies. Allergic reaction observed during the first few feedings with whole food may be due to sensitisation by food proteins that have been passed through breast milk.¹⁰³

Underlying pathological mechanisms of the disease are not well understood. Skin-prick tests are typically negative, suggesting an IgE-independent reaction. Elevated numbers of IgG- and IgM-containing plasma cells and intraepithelial lymphocytes could be found in morphological studies of the intestine.¹⁰⁵ Non-specific immune responses, as a result of enhanced mucosal passage of the antigen, could be the cause for the enhanced mucosal cell infiltration. A significant increase in extracellular MBP deposition, associated with the severity of mucosal villous atrophy, has been reported in the duodenal mucosa of patients with cows'-milk-sensitive enteropathy.¹⁰⁶ Children with food-protein-induced enterocolitis syndrome showed elevated mucosal levels of TNF- α , which increases intestinal permeability, while on the other hand expression of TGF- β , a protector of the epithelial barrier, was decreased.¹⁰⁶

Degree and site of tissue involvement determine the type of symptoms in patients with EEC. Significant intestinal bleeding and diarrhoea are common symptoms, also vomiting, abdominal pain, weight loss, anorexia, or anaemia (as the result of blood loss) can occur. Subsequent dehydration leads to episodes of circulatory collapse and shock in approximately 20% of patients. Manifestations are chronic diarrhoea, oedema, and failure to thrive, with possible progression to acidemia and methaemoglobinemia.¹⁰⁷ Increased haem oxidation as a result of elevated nitrates in the intestine may be an explanation for methaemoglobinemia.¹⁰⁸ Occult blood and stool smears may disclose leukocytes and eosinophils. Peripheral-blood eosinophilia can be seen in 50–100% of the cases.^{109,110} Symptoms generally appear approximately 2–8 h after ingestion (vomiting typically after 2–4 h, diarrhoea typically after 5–8 h). Increased peripheral polymorphonuclear leukocyte counts, peaking at 6 h after food ingestion, can also be observed.

Specific histological findings are lacking. Small-bowel biopsies are characterised by an acute inflammation, mild villous injury and oedema (Figure 4). Crypt abscesses and diffuse inflammatory-cell infiltrate with prominent plasma cells can be seen in colonic biopsies.¹¹¹

Eosinophilic proctitis (EP)

This benign disorder normally affects infants in the first few months of life. Food proteins passed in maternal breast milk are thought to act as triggers for EP in up to 60% of infants, while formulas based on cows' milk or soy are the causative food in most other cases.¹¹² In a majority of breast-milk samples β -lactoglobulin, one of the major allergens in milk, could be detected after maternal consumption of cows' milk.

Affected infants typically seem to be healthy and grow normally. Gross or occult blood in the stool can be the main symptom. Rectal bleeding usually develops at 3–6 weeks of age, but earlier occurrence has also been described.^{113,114} Lesions such as mucosal oedema with infiltrating eosinophils in the epithelium and lamina propria are confined to the distal large bowel.¹¹⁵ The underlying mechanisms are unknown. Skin-prick tests and/or tests for specific IgE ('RAST') are characteristically negative, indicating an IgE-independent reaction, as in EEC. Some patients show peripheral-blood eosinophilia and have a positive family history of atopy.¹¹⁶ Resolution of the symptoms is achieved by elimination of cows' milk from the mother's diet, which permits continuation of breast-feeding. By their first birthday most infants tolerate cows' milk.

A gradual onset of bloody stools is typically noted by parents, and this increases in frequency unless the causal allergen is removed.¹¹⁷ Usually the blood loss is minimal, but in some cases anaemia and hypoalbuminaemia can occur. Clinical history and response to an elimination diet are the usual diagnostic criteria. Missing systemic symptoms, vomiting, diarrhoea and failure to grow, as well as exclusion of other medical diagnoses such as infection, necrotising enterocolitis, intussusception, or anal fissure, help to differentiate EP from other gastrointestinal diseases.

Histological investigations show focal aggregates of eosinophils in the lamina propria, crypt epithelium and muscularis mucosa, and in some cases submucosal multinucleated giant cells, whereas the overall architecture of the mucosa is well conserved. More than six eosinophils/HPF in the lamina propria and eosinophil infiltration in epithelial or muscularis mucosa are indicative for EP.¹¹⁸ Endoscopic examination reveals lymphonodular hyperplasia with circumscribed and/or central pit-like erosions, patchy erythema, and loss of vascularity.

DIAGNOSTIC MEANS FOR CONFIRMING ALLERGIC EOSINOPHILIC DISEASES

The principle of the diagnostic approach is to combine the diagnostic means for EGIDs, as described in Chapters 3 and 4, with those for allergic diseases, while excluding other gastrointestinal diseases such as food intolerances, IBD, IBS, infections, and tumour diseases.

The first step for the evaluation of a possible allergic EGID is obtaining a detailed history of atopy and ARF.⁴ Extraintestinal manifestations of allergy such as hay fever, asthma, an atopic dermatitis, high total IgE levels in serum, and the occurrence of allergy in first-degree relatives may be helpful hints for the presence of an allergic EGID

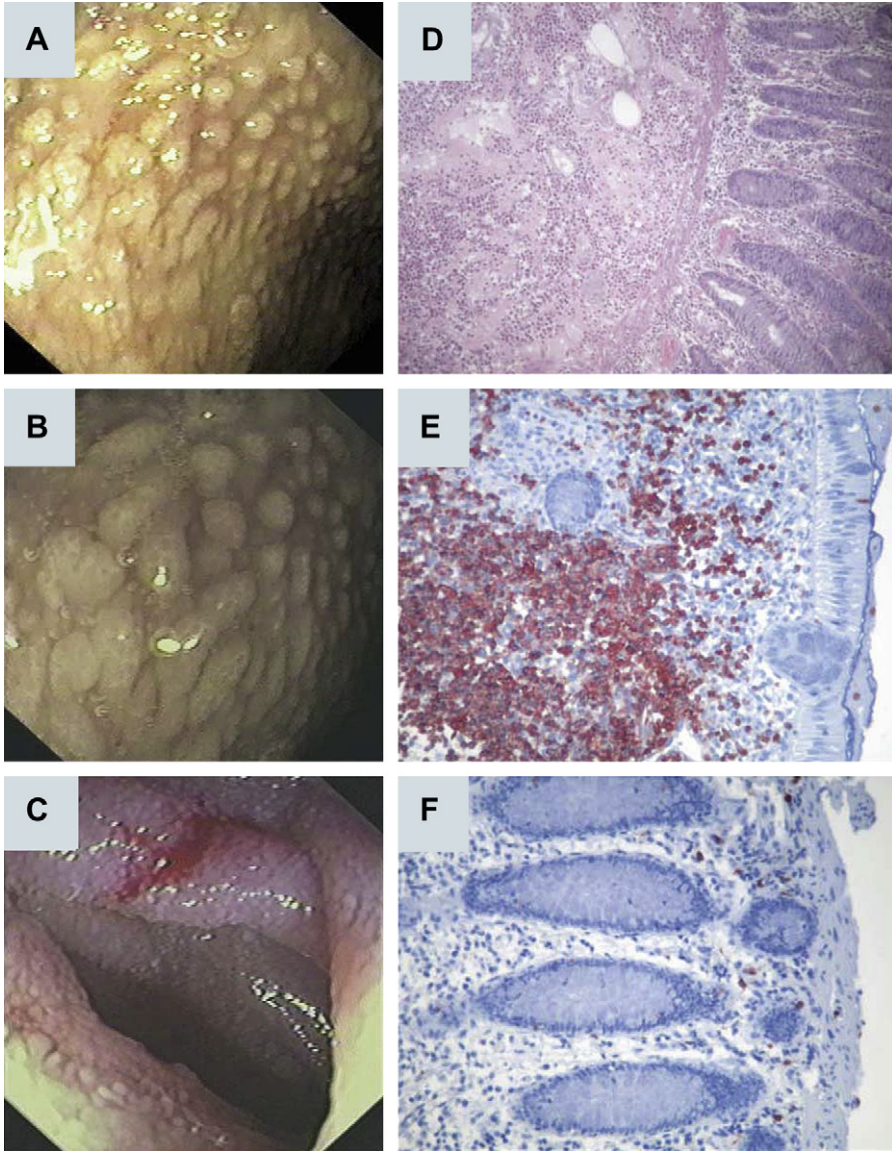


Figure 4. Eosinophilic enterocolitis. (A–C) Different endoscopic examples of eosinophilic ileitis. (D–F) Tissue sections from a case of severe eosinophilic colitis presenting with abdominal pain and diarrhoea. (D) Haematoxylin and eosin (H&E) staining. (E) Immunohistochemical staining using EG2 monoclonal antibody against eosinophil cationic protein. (F) Immunohistochemistry using a monoclonal antibody against human mast cell tryptase. (Original magnification: D, $\times 100$; E and F, $\times 200$.) From Bischoff and Crowe (*Gastroenterology* 2007; **128**: 1089–1113) with permission.

as the cause of symptoms. If the determination of specific food or foods is not possible by questionnaire, it could be helpful to ask for a diet and symptom diary for some weeks. Elimination of possibly relevant food(s) leading to relief, and reintroduction of this food causing recurrence of symptoms, might be also helpful in some cases. In other cases, in which neither clinical history nor dietetic approaches allow a conclusive diagnosis, an unspecific hypoallergenic diet may be tried for a defined period of 1–2 weeks. A subsequent gradual introduction of food groups after improvement of symptoms can disclose specific allergenic foods. Since these open food challenges are often afflicted with bias, they should be confirmed by other more objective methods before recommendation of a long-term therapeutic elimination diet.

Skin tests

The presence of systemic allergen-specific IgE can be evaluated with the skin-prick test (SPT). In the absence of antihistamines, a negative test result excludes to some extent IgE-mediated hypersensitivity as a reason for the patient's food-induced discomfort, while positive test results are often misleading, as reactions to food allergens are also seen in some asymptomatic individuals. A further limitation for the significance of the SPT is the poor standardisation and stability of many food allergen extracts. The increasing availability of recombinant allergens may reduce this problem. Performing prick-to-prick tests using native food allergens improves to some extent the outcome of the SPT. Delayed-type reactions require observation times of at least 24 h or epicutaneous testing. IgE-independent reactions to food can be assessed with some limitations by using the epicutaneous patch test.

Measurement of specific IgE

Allergen-specific IgE can be measured quantitatively in serum. Advantages of this test, formerly named 'RAST', are enhanced specificity and reliability compared with SPTs, and also its applicability in patients with involvement of the skin (e.g. atopic dermatitis). Variations between skin testing or RAST and clinical history may be the result of locally restricted food-specific IgE levels in the gut which lead to gastrointestinal hypersensitivity reactions but not to elevated levels of food-specific IgE in the serum.

Mehl et al¹¹⁹ directly compared several methods for their power to diagnose food allergy. Specific serum IgE, SPTs, atopy patch tests, and controlled oral food challenges have been used for the evaluation of suspected food allergy in more than 400 children. The atopy patch test showed the best specificity as a single parameter compared with SPTs, serum IgE, or both. Enhanced sensitivity and specificity could be achieved by combining atopy patch test with SPT or serum IgE. Nevertheless, only 0.5–14% of the children tested for food allergy with oral food challenge would have been tested correctly by atopy patch test in combination with serum IgE or SPT.

Provocation tests

For diagnosis of food allergy, the DBPCFC – in which food antigens are administered orally or by nasogastric tube or wrapped in gelatine capsules – is considered the gold standard and should be performed, if possible, in order to definitively confirm the diagnosis of food allergy. However, outside clinical trials, the DBPCFC is not obligatory if the patient's history, SPT and RAST fit together. Before planning the challenge test, the few food candidates to be tested have to be selected according to clinical history,

skin test results and RAST. Disadvantages of the provocation tests are the dependence on allergen preparations of limited quality, risk of anaphylactic shock, and lack of confirmation of allergy (only confirmation of ARF/patients history). Some of these disadvantages can be overcome by the use of an endoscopically performed provocation test in which mucosal wheal and flare reactions are assessed after endoscopic administration of allergen.^{13,120}

Other in-vitro allergy tests

In-vitro assessment of allergic reactions to food can be done with the basophil histamine release assay or the basophil leukotriene release assay, but these methods are usually restricted to research purposes. IgE-independent food allergies can be evaluated by food-allergy patch testing and T-cell cytokine assay.

Assessment of eosinophil participation

The details of the histological and laboratory approaches for assessing eosinophilic disorders are described in Chapters 3 and 4. Briefly, counting of eosinophils should be accompanied by an assessment of eosinophil activation. To do this, eosinophil markers such as the cationic proteins eosinophil-derived neurotoxin (EDN) and eosinophil cationic protein (ECP) can be measured in serum, faeces, and other body fluids.^{15,83} Peripheral-blood eosinophilia occurs in approximately 50% of patients with EGIDs. Therefore, lack of blood eosinophilia does not exclude EGIDs, whereas lack of mucosal eosinophilia largely excludes EGIDs (except muscular or serosal manifestations). The grade of eosinophil activation, however, can be most accurately determined by the measurement of eosinophil-specific cationic proteins (EDN or ECP) or eosinophil peroxidase (EPO). Measurement of these markers in blood requires a clear standardisation of sampling procedures, as concentrations of assessed cationic proteins are influenced by incubation temperature, recovery time, and also the time of day of blood sampling. In general, eosinophilic inflammation is better reflected by measuring the markers in other local fluids than in blood. For example, Gore et al.¹²¹ could show an association between urinary EDN and the presence of atopy, exposure to allergens and allergic symptoms in children. Elevated levels of faecal EDN and ECP in infants with atopic dermatitis were found by Majamaa et al.¹²² Another study reported increased concentrations of faecal EDN and urinary LT E₄ in allergic patients.⁴¹ In infants with cows'-milk allergy, higher faecal ECP concentrations have been assessed in individuals with intestinal symptoms.¹²³ For identification of gastrointestinal allergy and eosinophilic gastroenteropathies, measurement of eosinophil-derived mediators in stool^{15,124,125} and urinary samples^{41,126} would be helpful, but establishment for clinical practice is limited so far.

TREATMENT OF ALLERGIC EGIDS

Dietetic management

The basis of any successful treatment of confirmed food allergy is an elimination diet, regardless of whether eosinophils are involved or not. This requires not only that the diagnosis be confirmed but also that the relevant offending food components be identified. Both IgE-dependent and IgE-independent mechanisms can be involved. Food elimination based solely on SPT have not been efficacious, but exclusion of food

identified by a combination of SPT and patch testing has shown good success rates.^{25,127} Avoidance of identified allergens has resulted in improved clinical symptoms and also a decrease in mucosal eosinophils in patients with eosinophilic oesophagitis and eosinophilic gastroenteritis.^{126,83}

In cases of EEC and EP, strict exclusion of the triggering protein (mostly cows'-milk protein, but also solid food proteins) in the diet of patients or, in cases of breast-feeding, in the maternal diet leads to regression within 48–72 h.

Elemental diet, also known as amino-acid-based formula therapy, may be used if withdrawal of identified allergenic food(s) is not practicable or successful. This treatment has been shown to be very effective in children, and results seem to be even better than with classical elimination diets.¹²⁷ Major limitations of this therapy are limited long-term acceptance because of its taste, the imposed life-style change, high costs, and eventually required tube feeding. In children, good clinical and histological improvement could be achieved with elimination or elemental diet; however, these approaches have not been tested systematically for adults.

Desensitisation

Subcutaneous and oral immunotherapy intending to increase tolerance to food has been investigated over the past few years with variable results. Beside food allergens, aeroallergens have also been reported to be implicated in the pathogenesis of EGIDs, especially eosinophilic oesophagitis.¹²⁴ As elimination of respiratory antigens is difficult, desensitisation could be an alternative for patients with pollen-associated eosinophilic oesophagitis. Long-term remission of allergic rhinoconjunctivitis has been shown with subcutaneous immunotherapy, while recent investigations with sublingual and gastrointestinal immunotherapy (e.g. with the new grass allergen tablet Grazax[®]) indicate a favourable safety profile of the oral approach that can be performed at the patient's home.¹²⁵ Investigations about possible beneficial effects of desensitisation therapy concerning eosinophilic oesophagitis are lacking so far.

Medical therapy

In cases of limited success by elimination diet and/or desensitisation because of e.g. multiple food allergies, allergies to several common foods, incomplete identification of allergens, or insufficient compliance of the patient, systemic (for acute exacerbations) or topical glucocorticoids can be considered for therapy. In general, glucocorticoid treatment induces an immediate and effective relief of symptoms within a few days to weeks, but withdrawal of the drug often results in relapse of symptoms. For eosinophilic oesophagitis, topical steroids (e.g. fluticasone) are recommended to be used with a metered-dose inhaler without spacer, so that the dose can be swallowed by the patient, allowing deposition on the oesophageal mucosa.¹¹⁵ Viscous budesonide is another topical corticosteroid specifically designed for the treatment of eosinophilic oesophagitis.¹²⁸ Topical steroids in tablet form (e.g. Entocort EC), clysters, suppositories or foams deliver the drug to specific segments of the gastrointestinal tract and therefore are useful for treatment of EGE, EEC, or EP. Even though treatment with glucocorticoids is effective, long-term use is complicated by side-effects, development of unresponsiveness, and low acceptance by patients.

As no change in cysteinyl leukotriene protein content has been measured in patients with eosinophilic oesophagitis and controls, it could be assumed that

therapeutic intervention with *Montelukast*, an LTD₄ receptor antagonist, would not be successful. However, clinical trials have revealed that *Montelukast* causes symptom relief in adult patients with eosinophilic oesophagitis, although effectiveness was restricted to the time of active treatment.¹²⁹

The mast-cell stabiliser *disodium cromoglycate* is available in formulations acting locally in the gastrointestinal tract, but only a few investigations have confirmed their effectiveness in gastrointestinal allergy.¹²² Moreover, there are no studies supporting their use in EGIDs.

Mepolizumab, a monoclonal antibody against IL-5, may reduce eosinophil proliferation, maturation, activation, and tissue recruitment; however, effectiveness in asthma could not be confirmed. A pilot study in patients with hypereosinophilic syndromes (HESs) showed a significant reduction of eosinophils in tissue.¹³⁰ Another study reported decreased peripheral eosinophilia and improved symptoms after anti-IL-5 therapy in patients with HES or EGE with peripheral eosinophilia, but subsequent rebound eosinophilia occurred.¹³¹ Anti-IL-5 treatment in patients with eosinophilic oesophagitis improved clinical symptoms, peripheral-blood eosinophilia, endoscopic findings, pathological features, and quality of life, but even though levels of eosinophils declined, they did not return to normal levels.¹³²

As increased expression of eotaxin I has been correlated with tissue accumulation of eosinophils, a potential therapeutic value for *bertilimumab*, an anti-eotaxin-I monoclonal antibody, in allergic disorders is currently under investigation.¹³³

Emergency treatment

In cases where there is a history of confirmed or suspected anaphylaxis, the patients should be equipped with an epinephrine-containing syringe along with corticosteroids and antihistamines according to the actual guidelines.¹¹⁹ A local emergency facility must be consulted after initial symptoms as the nature of reactions may be biphasic. This recommendation is valid for all allergic diseases associated with anaphylaxis, independently of whether eosinophils are involved or not.

Practice points

- adverse reactions to food affect approximately 20–30% of the population, while only 1–3% of adults and 2–8% of children suffer from an immune-mediated food allergy
- in patients with food allergy, 33–50% suffer mainly from gastrointestinal symptoms
- about 80% of individuals with eosinophilic gastrointestinal disorders (EGIDs) are atopic
- about 50% of patients with gastrointestinal allergy show tissue eosinophilia
- the diagnostic approach comprises both histological and laboratory means to assess eosinophilia and eosinophil activation, and tools to assess the allergic disease
- exclusion diagnosis is essential: e.g. food intolerances, inflammatory bowel disease, irritable bowel syndrome, gastrointestinal infections and gastrointestinal tumours must be excluded

- peripheral-blood eosinophilia is facultative and occurs only in about 50% of patients with gastrointestinal tissue eosinophilia
- treatment of allergic EGIDs includes elimination or elemental diet and drug therapy using classical anti-allergic agents such as topical corticosteroids and new approaches such as LTD4 receptor antagonists or antibodies against IL-5 or eotaxin

Research agenda

- the function of eosinophils in gastrointestinal allergic disorders needs to be clarified (proinflammatory function, or immunomodulatory action, or inflammation-terminating capacity?)
- the biology of gastrointestinal eosinophils (different from blood eosinophils?) and their interaction with other cells (Th2 lymphocytes, mast cells, epithelial cells, nerves) need to be investigated further, particularly in the human system
- the mechanism of eosinophil activation and recruitment in an allergen-dependent manner have to be unravelled
- novel treatment options such as antibodies against IL-5, eotaxin 1, or CCR3 should be evaluated for efficacy and efficiency in clinical trials

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