

The role of the gastroenterologist in non-IgE mediated gastrointestinal food allergy

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Abstract

The prevalence of food allergy has been on the rise in the UK over the last 30 years. Food allergy can be classified as Immunoglobulin E (IgE)-mediated, non-IgE mediated or mixed IgE and non-IgE mediated food allergy. Whilst the management of IgE-mediated food allergy is relatively well established with regards to investigations and treatment options, non-IgE mediated food allergy management is emerging. The role of the gastroenterologist in food allergy is in the management of non-IgE mediated gastrointestinal food allergy, which is performed closely alongside allergologists.

The aim of this review is to discuss the common presentations of non-IgE mediated food allergy (i.e. cow's milk protein allergy, food protein-induced enterocolitis, eosinophilic gastrointestinal disorders) and describe current investigation and treatment options for these conditions. It focuses on the main management options available such as elimination diets, drug therapies, as well as gastroenterology-specific tests such as endoscopy. It also highlights the importance of both

allergy and gastroenterology multi-disciplinary team support in order to ensure the best management of these children.

Keywords gastrointestinal; non-IgE mediated allergy; paediatrics

Background

Food allergy is defined as the adverse immunological reaction to a specific food that is reproducible on repeat exposure to the same food. The prevalence of food allergy has increased globally over the last 30 years and in the UK, the prevalence of food allergy in children is approximately 6–8%. Food allergy is currently classified as Immunoglobulin E (IgE)-mediated, non-IgE mediated or mixed IgE and non-IgE mediated food allergy. IgE-mediated food allergy tends to have a quick onset, presenting with skin, respiratory and gastrointestinal symptoms compared to non-IgE mediated food allergy, which has a delayed onset of symptoms which are often gastrointestinal or cutaneous in nature and can masquerade as common disorders such as infantile colic, gastro-oesophageal reflux, feeding problems and abdominal pain.

The natural progression of allergic disease, which comprises atopic dermatitis/eczema, food allergy, asthma and allergic rhinitis, has been well described and is commonly called 'the allergic or atopic march'. Skin and gastrointestinal symptoms are common in the presentation of non-IgE mediated food allergy, with eczema being one of the first manifestations of the food allergic march appearing in the first few weeks of life. However, gastrointestinal food allergies can also present very early and in some cases such as in cow's milk protein allergic proctocolitis, it can be the first presentation of the food allergic march.

The role of the gastroenterologist in managing non-IgE mediated gastrointestinal food allergy is emerging and increasingly being utilised to differentiate common gastrointestinal disorders from ones in which food may play an important role in symptom control. Non-IgE mediated food allergies are being increasingly recognised as being associated with certain functional disorders in the future (i.e. functional abdominal pain, functional dyspepsia and irritable bowel syndrome).

Presentation of gastrointestinal food allergy

Symptoms and signs may overlap with many non-allergic conditions

Gastrointestinal symptoms are common, particularly during infancy and in many children are benign in nature and not related to non-IgE mediated food allergy or other conditions. The diagnosis of gastrointestinal food allergy is challenging because the differential diagnosis is often extensive. For example rectal bleeding in childhood can be caused by an anal fissure from constipation, can be indicative of cow's milk protein allergy (CMPA) or could be the onset of inflammatory bowel disease (IBD). As important as it is to identify non-IgE mediated food allergy, it is necessary for gastroenterologists to have a high clinical suspicion for common non-allergic gastrointestinal diseases such as IBD and coeliac disease. Some of the most common gastrointestinal symptoms that can be the manifestation of non-IgE mediated food allergy are summarised

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Common gastrointestinal symptoms of non-IgE mediated food allergy

Gastrointestinal symptoms

Infantile colic
 Reflux
 Irritability
 Vomiting
 Food aversion/refusal
 Diarrhoea
 Blood and/or mucus in stools
 Abdominal discomfort/pain
 (Soft stool) Constipation
 Perianal redness
 Faltering growth
 Flatus

Table 1

in Table 1. Early diagnosis of children results in better control of any gastrointestinal diseases, prevention of long term complications i.e feeding issues and can have a significant impact on disease progression as well as quality of life for the child and their families.

Children with non-IgE mediated food allergy can also present with extra-intestinal manifestations including mouth ulcers, headaches, hypermobility/joint pain or fatigue, which may not be the most obvious symptoms of a diagnosis of food allergy. Recurrent mouth ulcers are common in gastrointestinal diseases such as IBD and coeliac disease but there is also evidence to suggest an association between mouth ulcers and sensitivity to food components (i.e. benzoic acid and cinnamaldehyde). Recently, there has been increasing recognition of the link between hypermobility and gastrointestinal disease in children. More specifically, patients with Ehlers–Danlos Type 3 Syndrome have been found to have a higher prevalence of food allergies and eosinophilic disorders and it is hypothesised that gastrointestinal complications in these patients could be due to dysregulation of gut-related immune function.

There can also be more generic symptoms such as headache, irritability, poor sleep and fatigue that can be associated with gastrointestinal food allergy and atopic disease. For example, the association between atopic disease and increased number of headaches in children is well described, with children who have more than one atopic condition (such as eczema or allergic rhinitis) having a significantly higher chance of experiencing headaches. However, children with these symptoms may often be seen by other professionals such as General Practitioners, Paediatricians or other Paediatric specialists who perform investigations to try and identify the cause, of which gastrointestinal food allergy is not usually a differential. Non-IgE-mediated allergy can also present in more acute ways as seen in food protein induced enterocolitis syndrome (FPIES), where the child may present with diarrhoea and vomiting to Emergency Departments where they may be misdiagnosed and treated for infection or sepsis.

Allergy-focused history

History is the key to identifying a possible allergic disorder

Obtaining a good clinical history is paramount to working towards a diagnosis of non-IgE mediated food allergy. A general paediatric history about the child's birth and medical history are important but more specific allergy related questions are required. These include a focused, detailed feeding and diet history – was the child breast fed or formula fed; when were solids introduced; are there any symptoms attributable to certain foods? More specific questions about gastrointestinal symptoms (Table 1), bowel habits and extra-intestinal manifestations (i.e. joint pain, fatigue, headaches, mouth ulcers, prolonged respiratory infections) should also be considered. In addition, questions about atopic disease, family atopic disease, medications trialled and their efficacy should be asked. Another important area to ask about is the quality of life of the child and family (i.e. quality of sleep, social interactions, time off school or work for parents) which can provide vital information of the impact allergic disease has on a family, as research has shown that allergic diseases can place significant psychological and emotional burdens on families.

Tests and investigations

Diagnosis can be delayed because of a lack of non-invasive specific diagnostic tests

There are currently no specific investigations that are diagnostic of non-IgE mediated food allergy. The National Institute for Health and Care Excellence (NICE) recommend referral for specialist care if a child has faltering growth combined with one or more gastrointestinal symptoms that have not responded to a single-allergen elimination diet, had one or more severe delayed reactions, or has significant atopic eczema where multiple or cross-reactive food allergies are suspected by the parents/carer. Once it is suspected, food skin prick tests (SPT), specific IgE (sp-IgE) tests, and patch testing may be used to help identify potential allergenic foods; however, they are most often negative. Patch testing has been shown to be effective in identifying allergy of some foods e.g. wheat and dairy; however, there are conflicting reports on its diagnostic accuracy, standardisation and consistency in interpretation of results making it less reliable. General blood tests may be performed for specific allergic presentations (i.e. FPIES) but are usually normal although they may occasionally show signs of anaemia, hypoalbuminaemia, hypoproteinaemia or leucocytosis. The main challenge in investigating these children is that they often present with non-specific gastrointestinal symptoms and multiple suspected food allergens and with the absence of accurate tests, the diagnostic process can be long and frustrating.

Gastroenterologists can use endoscopy in the investigative process to identify if there are any other macroscopic or microscopic features such as the presence of on-going inflammation, eosinophils or lymphonodular hyperplasia, that may suggest non-IgE mediated food allergy. There are no specific indications that warrant an endoscopy in non-IgE mediated allergy but children who present with rectal bleeding or

diarrhoea who do not improve on dietary elimination, are more likely to have an abnormal biopsy; thus, clinicians are more likely to perform an endoscopy.

More common non-IgE mediated food allergy conditions

The management of food allergy requires close collaboration between gastroenterologists and allergologists as children commonly present to either speciality (Figure 1). The most common non-IgE mediated food allergic conditions will be discussed below.

Cow's milk protein allergy (CMPA)

Symptoms are typically mild or moderate and diagnosis is confirmed by response to exclusion diet

CMPA is one of the most common food allergies seen in young children with a tendency to peak in the first year of life. The prevalence ranges from 1.9 to 4.9% of infants and young children. Reactions usually occur 2–72 hours after ingestion of cow's milk protein and can occur in exclusively breast-fed (via maternal ingestion of cow's milk), formula-fed or mixed-fed infants. Approximately 25–50% of children usually present with non-specific gastrointestinal tract symptoms of which the most common are listed in Table 1.

The Milk Allergy in Primary Care (MAP) Guidelines have been developed which describe gastrointestinal symptoms of non-IgE-mediated food allergic presentations of CMPA and based on severity, provide clinicians with appropriate management strategies but also guidance on when to refer these patients for speciality input. Investigations can be performed which include SPT or sp-IgE test to cow's milk, but these are often negative. Therefore, diagnosis is often made on a detailed clinical history and ultimately a trial of cow's milk elimination diet (if breast feeding, maternal dietary elimination of cow's milk) for 4 weeks following by reintroduction and review for return of symptoms. If the diagnosis of CMPA is confirmed via the process of dietary elimination followed by reintroduction then elimination of cow's milk is recommended for at least 6 months with a planned reintroduction at least 6 months after elimination.

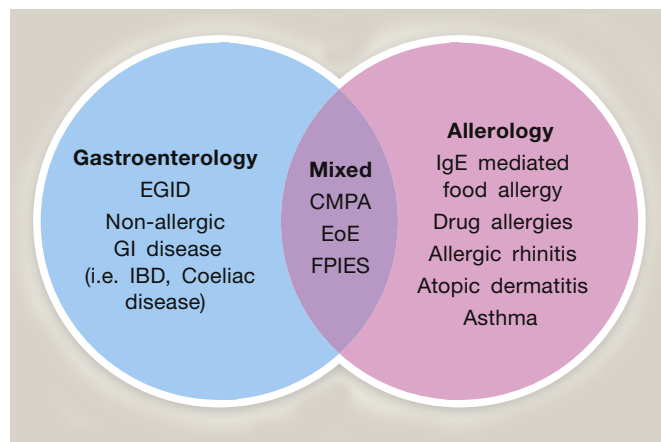


Figure 1 Allergic diseases commonly presenting to gastroenterologists and allergologists.

Food protein induced enterocolitis syndrome (FPIES)

Symptoms are often severe, can be mistaken for sepsis and diagnosis requires supervised food challenge

FPIES is a condition that has received increased attention in recent years having been under-recognised and under-diagnosed in the past. It usually occurs in young infants and presents with profuse vomiting, diarrhoea and lethargy usually 2–4 hours after ingestion of the allergenic food and in approximately 15% of cases, hypotension has been noted. The most common foods that cause FPIES are cow's milk and soya although cases have been reported with solids foods such as grains (rice, oat) and shellfish/fish. The exact pathophysiological mechanisms behind FPIES are still unknown but symptom pattern is affected by the dose and frequency of the food allergen in the diet. However, because the presenting symptoms of FPIES can mimic sepsis, these children can be at risk of mismanagement of their symptoms and often experience diagnostic delay. This can lead to chronic antigen exposure which over time causes protracted vomiting, chronic diarrhoea with blood and/or mucus and subsequently, faltering growth. The diagnosis can be difficult as routine allergy tests (SPT and sp-IgE) are often negative. The gold standard diagnostic method for confirming FPIES is by oral food challenge (OFC), which should be physician-supervised as these are high risk procedures with up to 50% of reactions requiring intravenous fluids due to hypotension. In some cases where OFC is thought to be too dangerous, dietary elimination with resolution of symptoms is considered diagnostic. Most children outgrow FPIES by 3–5 years of age although there are some patients with FPIES that may persist or with some foods FPIES develop in older children or adults. Therefore, patients should be re-challenged to confirm that FPIES has been outgrown at the earliest, 12–24 months after diagnosis.

Eosinophilic gastrointestinal disorders (EGID)

Symptoms are non-specific but may be severe requiring endoscopy for diagnostic confirmation

Gastroenterologists also manage children with EGID which encompass a range of disorders that selectively affect different parts of the gastrointestinal tract with eosinophil-rich inflammation without an identifiable cause for the eosinophilia. They are classified according to their site, depth and severity of inflammation seen in the gastrointestinal tract. Eosinophils are a part of our natural defence system and are commonly found in the GI tract as they are involved in defending against allergens and parasites.

The exact pathogenesis of EGID is not fully understood but it has been suggested that a hypersensitivity reaction occurs within the gastrointestinal tract causing the accumulation and activation of eosinophils which causes a release of multiple cytotoxic agents and immunomodulatory cytokines. This immune reaction can cause local tissue damage, which can result in gastrointestinal symptoms often related to the location of the tract affected. The common EGID include eosinophilic oesophagitis (EoE), eosinophilic gastroenteritis and eosinophilic colitis.

EoE is considered a non-IgE mediated food allergy with children presenting with symptoms attributable to oesophageal dysfunction that are often age-dependent. These include

symptoms such as food refusal, faltering growth, reflux in infancy and dysphagia or food bolus impaction in older children. The diagnostic investigation is endoscopy with a threshold for diagnosis of ≥ 15 eosinophils per high power field. There is increasing evidence suggesting a link between EoE and aeroallergens with a study showing that 20% of their EoE patients with suspected aeroallergen-associated triggers from clinical history, had changes confirmed on biopsy. The management of EGID is difficult as there are no clinical features or biochemical markers that are predictive of these diseases, making it difficult for general paediatricians and general practitioners to know when to refer a child for an endoscopy. Even for the children who do get referred to gastroenterologists, the disease course is unpredictable and there is poor correlation between symptom presentation and histological findings making it difficult to make standardised recommendations for management or follow up.

Role of endoscopy in food allergy

It follows from the diagnoses listed above that non-invasive testing cannot rule out non-IgE mediated allergy. Moreover, even positive specific-IgE test results in isolation do not confirm an allergy as there are many more children who demonstrate allergic sensitisation than are truly food allergic. There is therefore an important role for the use of more invasive tests, such as endoscopy, to help identify children with non-IgE mediated allergy especially in those cases that may not respond to dietary elimination and to exclude other conditions that masquerade as a food allergy.

Treatments and management

Treatment options vary according to the type of non-IgE mediated food allergy suspected. The MAP Guidelines have provided clinicians with an effective way to recognise and manage non-IgE-mediated CMPA in the primary care setting; however, management of other forms of non-IgE mediated food allergy are currently not standardised. Figure 2 describes a common pathway of management that is based on clinical experience.

Dietary elimination

The management of gastrointestinal food allergy is still progressing and evolving as more information is gathered about the disease. The mainstay of treatment is dietary elimination of the suspected allergenic food(s) from a child's diet for 4 weeks. Single food elimination diets may be initiated in primary care before a child is seen by a gastroenterologist or allergologist with dietetic advice as per the MAP guidelines. In some cases, a specific food causing the symptoms may not be obvious as the symptoms are more insidious. In these cases, the most common allergens affecting children will be removed and usually in the order of cow's milk, soya, egg then wheat. There is evidence of symptom improvement in the majority of patients after 4 weeks of commencing elimination diets. If there is a good response, this is often considered diagnostic of non-IgE mediated food allergy although the only way to confirm the diagnosis is with a planned reintroduction of the food after this period of exclusion.

If multiple foods have been eliminated, a timed gradual reintroduction of each food slowly is planned which can be

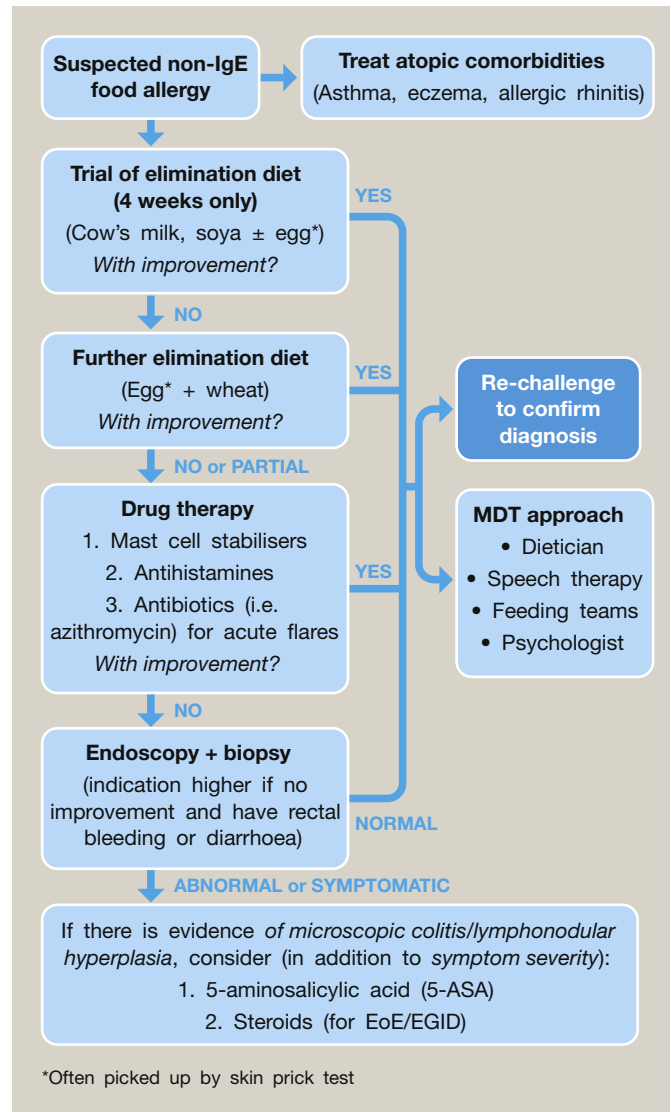


Figure 2 An approach to the management of non-IgE mediated gastrointestinal allergy.

carried out by parents at home or by OFC in hospital if there is a risk of IgE-mediated allergic symptoms. In recent years, the use of probiotics in the management of food allergy has been of increasing interest with studies showing that the supplementation of extensively hydrolysed formula with *Lactobacillus GG* can help to induce tolerance in children with CMPA. If dietary elimination results in an improvement in a child's symptoms, the next challenge facing clinicians is convincing parents to reintroduce the food back into their child's diet. In one study, 26% of CMPA patients' parents refused to re-challenge their child after 1 month of the elimination diet. From clinical experience, it can be very difficult to get parents to agree to re-challenge their children to foods eliminated especially if symptom improvement has had a significant impact on their child's and family quality of life.

Management of co-morbidities

Atopic comorbidities such as eczema, allergic rhinitis or asthma are common in these children. Eczema is closely associated with

IgE-mediated food allergy with studies showing increased food sensitisation and allergy (especially for common allergens such as peanut, egg, milk and wheat) being associated with eczema. It may be that gastroenterologists see these children first and as a part of their overall treatment, refer them to dermatologists or allergologists for further management of their atopic disease.

Drug therapy

Drug therapy for the management of delayed gastrointestinal food allergy has been trialled although there is very little published evidence on the efficacy of these. Oral antihistamines such as ketotifen and the mast cell stabiliser sodium cromoglycate may play a role in the management of non-IgE mediated food allergy by reducing the severity or preventing adverse reactions to foods. Ketotifen is an inhibitor of mast cell and basophil mediators (i.e. histamine, neutrophil, eosinophil chemotactic factors), which disrupts the inflammatory cascade that occurs during allergic reactions. It is readily absorbed from the gastrointestinal tract and takes 2–4 weeks before the clinical condition improves. Having been a drug used for treating other allergic conditions (i.e. asthma, urticaria, allergic conjunctivitis), its role in food allergy is still being explored. The mechanism of action of sodium cromoglycate involves weak inhibition of histamine release from mast cells, and has been used in IgE-mediated food allergy to reduce the severity of adverse reactions during oral desensitisation and improve clinical symptoms but its exact role in non-IgE mediated food allergy is not fully understood.

If they have co-morbidities such as asthma or a history of recurrent respiratory infections especially during the winter period, prophylactic antibiotics (i.e. azithromycin) can aid in symptom control during these periods due to its anti-inflammatory properties. Azithromycin stimulates interferon- γ , which reduces viral proliferation but also helps to reduce eosinophil recruitment to the gastrointestinal tract. For more specific conditions like EoE, treatment includes the use of oral viscous budesonide or swallowed inhaled steroids without a spacer device to help dampen down local inflammation if dietary elimination is unsuccessful. For those children with difficult symptoms to control in EGID despite dietary elimination, short courses of anti-inflammatory drugs such as corticosteroids to which eosinophilic and mast cell infiltration is exquisitely sensitive to (EoE is a hallmark disease for steroid use) or 5-aminosalicylic acid (e.g. Sulfasalazine) may be used. In refractory cases of EGID or corticosteroid resistant cases, immunomodulatory drugs such as azathioprine and 6-mercaptopurine have been trialled when the food allergy presents as an IBD-like picture although evidence from paediatric clinical trials is lacking.

Multidisciplinary team management

Of particular benefit has been the increasing number of joint gastroenterology and allergy clinics. This enables patients to be seen by two specialist teams and depending on the nature of their symptoms, be managed and treated appropriately. These multidisciplinary clinics should be run together with allergy nurse specialists and dieticians who have a vital role in the management of these children. Allergy nurse specialists perform many of

the allergy tests in clinic but for those who may have a mixed presentation of food allergy (both IgE-mediated and non-IgE mediated) they help to emphasise the importance of allergen avoidance or provide training for auto-adrenaline injectors if necessary. These joint clinics are also important in managing other allergic comorbidities associated with non-IgE mediated food allergy. Allergologists and nurses can optimise the management of asthma, allergic rhinitis and eczema and provide practical advice on inhaler and nasal spray device techniques and devise personalised written treatment plans for asthma and eczema.

If children are advised to go on elimination diets, dieticians play a crucial role in ensuring the child is avoiding the offending food correctly and that they receive adequate nutrition for growth and bone health with other foods or substitutes. This can be especially important in infants as their main source of nutrition is milk. If they are diagnosed with cow's milk protein allergy, the use of the correct formula is crucial and determining this can prove to be challenging as the child's symptom severity, formula preference and cost needs to be taken into consideration. In children with multiple food exclusion diets the role of the dietician is even more important as studies have shown that for each food that is excluded from the diet, the risk of nutritional deficiencies and suboptimal growth increases. Early dietary and behavioural modification support is important in this group as they can potentially be at risk of long term health consequences, including psychological effects surrounding eating and foods and the development of future functional gastrointestinal disorders. Dieticians may also be the point of contact for other professionals such as feeding teams and speech and language therapists to become involved to help reduce food aversion behaviours which can develop in 30–40% food allergic children. The prognosis of this condition depends largely on the type of non-IgE mediated allergy a child has, but children can outgrow them with age. Late presentations of non-IgE mediated food allergy also exist and therefore must be considered in older children.

Conclusions

Non-IgE mediated food allergy is on the rise in the UK. The gastrointestinal symptoms associated with non-IgE mediated allergy are not specific to gastrointestinal allergic disease; thus a broad approach during the diagnostic process and careful consideration of other potential diagnoses are important. Allergologists and gastroenterologists play an important role in the management of these patients but increased awareness amongst other healthcare professionals is crucial as early recognition of non-IgE mediated food allergy and appropriate referrals, can lead to quicker and improved management of these children. ♦

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Practice points

- Non-IgE mediated food allergy is increasing in prevalence and needs to be considered when children present with gastrointestinal symptoms
- Gastroenterologists have a crucial role in ruling out other potential gastrointestinal pathologies in these children and work closely with allergologists and other specialities in the management of non-IgE mediated food allergy and its associated allergic comorbidities
- Increased awareness about common presentations (i.e. CMPA, FPIES, EGID) is crucial for early diagnosis and initiation of treatment
- Dietary elimination plays an important role in diagnosis and management of non-IgE mediated allergy but it may only partially resolve symptoms
- A multidisciplinary team approach is required to ensure that physical, emotional and psychosocial support is provided for children and their families
- Data on the efficacy of medication used in the management of non-IgE mediated food allergies are emerging but require further study