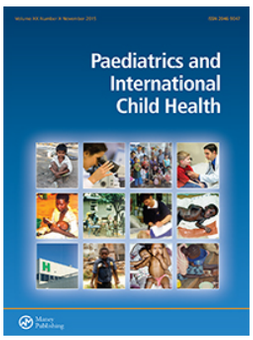

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Cow milk protein allergy and other common food allergies and intolerances

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ABSTRACT

The prevalence of food allergy and food intolerance is increasing and it is an important public health problem affecting children. Food allergy results from an immunological reaction to certain food(s) and affects numerous organs in the body. Food intolerances are non-immunological reactions including metabolic, toxic, pharmacological and undefined mechanisms. Cow milk is the most common cause of food allergy and food intolerance, especially in young children. Food intolerance can present with similar symptoms to those of food allergy. Health-care personnel, patients and their caregivers often confuse food intolerance with food allergy. This review focuses on the clinical manifestations, diagnostic evaluation, treatment and prevention of food allergy and food intolerance.

Abbreviations: DBPCFC: double-blind placebo-controlled food challenge; FDEIA: food-dependent exercise-induced anaphylaxis; FGIDs: functional gastrointestinal disorders; FPE: food protein-induced enteropathy; FPIAP: food protein-induced allergic proctitis; FPIES: food protein-induced enterocolitis syndrome; IBS: irritable bowel syndrome; MSG: monosodium glutamate

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Adverse reactions to food are common in children and they are reported in 6.25–28.0% of children [1,2]. Adverse reactions to food can be classified as food allergy and food intolerance (Figure 1). Food allergy is an immunological reaction to certain food(s) and affects numerous organs in the body. Food intolerance is a non-immunological reaction including metabolic, toxic, pharmacological and undefined mechanisms [3]. This article reviews allergy to cow milk protein and other common food allergies, followed by food intolerance.

Cow milk protein and other common food allergy

According to the expert panel of the National Institute of Allergy and Infectious Disease, a food allergy is 'an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food' [4]. The prevalence of food allergy varies between countries and regions, ranging from 1% to 10% [5]. The prevalence is increasing worldwide, including in low- and middle-income countries (LMIC). In American children, the prevalence increased from 3.4% in 1997–1999 to 5.1% in 2009–2011 [6]. In young Chinese children, it increased significantly from 3.5% in 1999 to 7.7% in 2009 [7]. The majority of children develop clinical symptoms of food allergy within the first or second year of life. The peak prevalence of food allergy is at one year of age and falls progressively until late childhood. Since infants are exposed to cow milk protein in the maternal diet if breastfed [8] and via infant formula, cow milk is the most common cause of food allergy in young children, followed by hens' eggs [5,9].

Mechanisms and clinical manifestations of food allergy

A breakdown in immunological and clinical tolerance to an ingested food causes food allergy which can categorised into three groups, as follows.

IgE-mediated food allergy

IgE-mediated food allergy causes a reaction within 2 hours of exposure to allergens [10]. The clinical symptoms are explained by mediators released from tissue mast cells and circulating basophils. Acute urticaria and angioedema are the most common clinical symptom of IgE-mediated food allergy. The reactions can be systemic (anaphylaxis), involving the cutaneous, respiratory and gastrointestinal tracts and the cardiovascular system. Isolated rhinoconjunctivitis or wheezing in response to food allergy is rare in children [11,12], but they can be accompanied by others symptoms such as urticaria, especially in children with food anaphylaxis. Patients with oral allergy syndrome (pollen-associated

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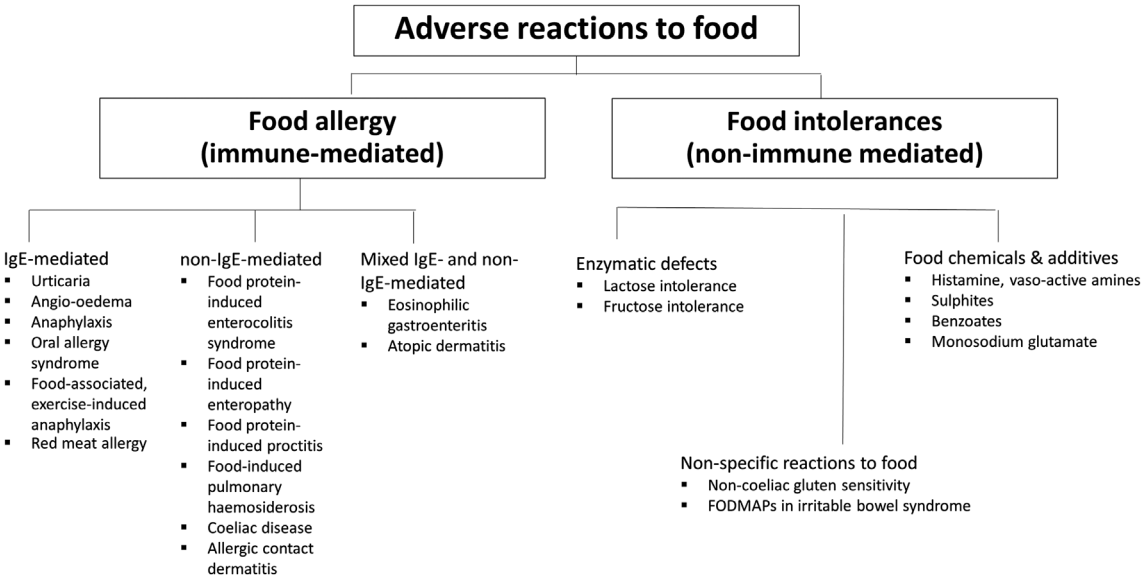

Figure 1. Type of adverse reactions to food.

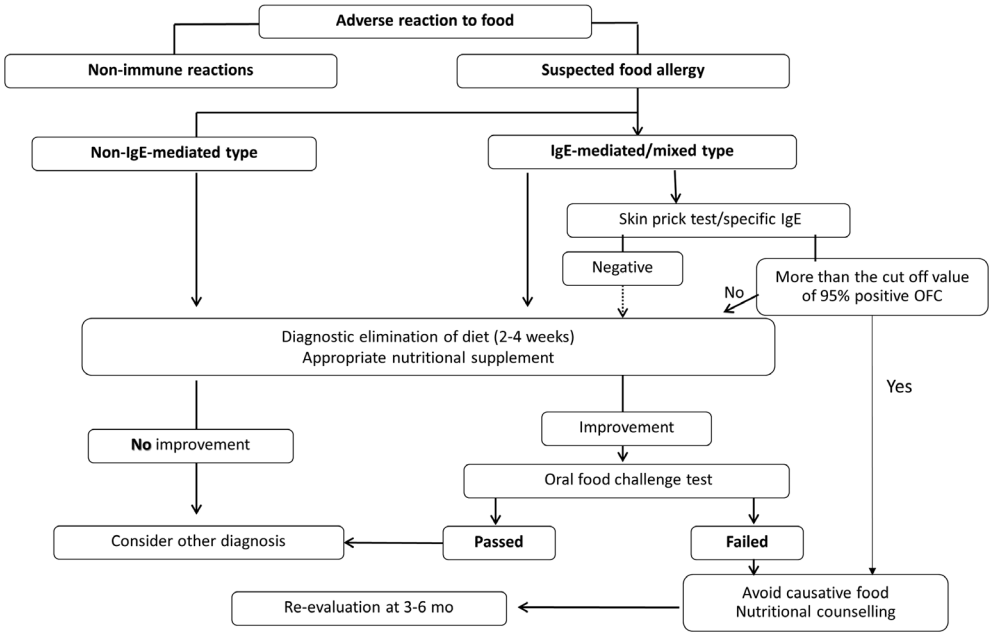

Figure 2. Diagnostic evaluation of food allergy.

food allergy syndrome) manifest with pruritus and mild oedema confined to the oral cavity after consuming raw fruit or vegetables such as apple, peach, pear, carrot and melon. These reactions are explained by the homology between labile food proteins and pollen proteins which cause symptoms of allergic rhinitis [13].

Food-dependent exercise-induced anaphylaxis (FDEIA) is an IgE-mediated food reaction induced by exercise after food ingestion, but it does not occur after food ingestion or exercise alone. FDEIA is mostly induced by exercise within 2 hours of taking food. Wheat products are common causative foods [10]. A delayed IgE-mediated food reaction 4–6 hours after eating red meat has been reported in adults [14]. It was explained by IgE-mediated reactions to carbohydrate allergens in the mammalian meat.

Non-IgE-mediated food allergy

Food-specific T-cells is considered to play a role in non-IgE-mediated food allergy [15]. The majority of non-IgE-mediated food allergy affects the gastrointestinal tract and occurs primarily in infants. Symptoms usually manifest 2–24 hours ingesting food protein. Coeliac disease, which is caused by a non-IgE-mediated immune reaction to gluten, is discussed in greater detail

in a separate article in this issue. Non-IgE-mediated food allergy involves a range of disorders including food protein-induced enterocolitis syndrome (FPIES), food protein-induced enteropathy (FPE), food protein-induced allergic proctitis (FPIAP) and proctocolitis, food-induced pulmonary haemosiderosis (Heiner syndrome) and food-induced allergic contact dermatitis [13,16].

Food protein-induced enterocolitis syndrome. Within 1–3 hours of ingesting the offending food, children with FPIES present with repetitive prominent emesis and diarrhoea, followed by lethargy, an ashen appearance and hypothermia in more protracted cases. FPIES is a systemic reaction mimicking IgE-mediated anaphylaxis but there is no urticaria/angio-oedema or respiratory symptoms. Laboratory investigations demonstrate increased neutrophil and platelet counts and methemoglobinaemia in severe case [16,17].

Food protein-induced enteropathy. FPE presents with protracted diarrhoea within weeks of introducing the trigger food. More than 50% of affected infants commonly have malabsorption, abdominal distension, early satiety and growth failure [3,16]. FPE needs to be distinguished from protracted diarrhoea caused by secondary lactase deficiency from acute gastroenteritis [16].

Food protein-induced allergic proctitis and proctocolitis. FPIAP typically presents in the first 6 months of life with passage of mucus-laden bloody stools in an otherwise healthy infant without an anal fissure [13,17]. In contrast with FPE, there is no growth failure in infants with FPIAP, even when the trigger food is not excluded and the bloody stools continue [16].

Food-induced pulmonary haemosiderosis (Heiner syndrome). This is a rare pulmonary disease caused by food hypersensitivity, primarily to cow's milk. It affects mainly infants who will have upper respiratory tract symptoms, failure to thrive and iron deficiency anaemia [13].

Food-induced allergic contact dermatitis. ACD is a form of eczema caused by T-cell-mediated allergic reactions to chemical haptens present in some foods and additives. ACD presents with marked pruritus, erythema, papules, vesicles and oedema after contact with the causative food [4].

Mixed IgE and non-IgE-mediated food allergy

Symptoms are caused by one or both of the mechanisms described above. Reactions usually involve the gastrointestinal tract and/or skin. The mixed food allergy disorders principally include atopic dermatitis (eczema) and eosinophilic gastrointestinal disorders (EGIDs) [13]. However, food allergy plays a pathogenic role in 35% of children with moderate-to-severe atopic dermatitis [13]. Hen egg is the most common cause of food-associated atopic dermatitis in young children, followed by cow milk [18].

Eosinophilic gastro-intestinal disorders. Eosinophilic gastrointestinal disorders are characterised by symptoms of gastrointestinal dysfunction from eosinophilic infiltration of the intestinal tract. Symptoms include feeding intolerance, vomiting, diarrhoea and abdominal pain. In preterm infants, these symptoms may clinically mimic necrotising enterocolitis [19].

Diagnosis of food allergy

A detailed medical history is critical. Food allergy should be considered when symptoms occur proximate to ingestion of a specific food. An elimination diet results in resolution of symptoms which recur after re-exposure. Diagnostic tests such as the skin prick test (SPT) and specific IgE (sIgE) are available for IgE-mediated food allergy, but results can be negative if symptoms are not IgE-mediated. However, a positive test result by a serum food-sIgE test or SPT does not there is an allergy to the tested food. The history of an immediate reaction with typical allergic symptoms and positive sIgE or SPT tests supports a presumptive diagnosis of IgE-mediated food allergy. A higher concentration of sIgE to food and a larger SPT wheal size correlate with an increased likelihood of a reaction to a food but might not correlate with the degree of clinical severity. The cut-off values for sIgE or SPT wheal size for the likelihood of clinical reactivity to the suspected food allergen are demonstrated in Table 1.

There is a limited availability of tests for non-IgE-mediated food allergy typically related to the gastrointestinal tract. Patch tests with fresh foods is not recommended because of a lack of validity, standardised testing material and interpretation of results [17]. Measurement of food-specific IgG for the diagnosis of non-IgE food allergy is not recommended [16]. The gold standard for diagnosis for both IgE and non-IgE-mediated food allergy is an oral food challenge test. Diagnosis of cow milk allergy in a preterm infant is challenging since preterm infants with cow milk allergy could present with feeding intolerance, asepsis-like episodes and eosinophilia which are common findings in sick preterm infants [19].

Management of children with food allergy

Avoidance

Allergen avoidance is the first treatment for food allergy. Parents and caregivers need to be instructed to read food labels and to avoid food cross-contamination when preparing food. Children who experience FDEIA should be instructed to avoid exercise 2 hours after consuming the

Table 1. Cut-off value for food-specific IgE testing and the predictive value of positive and negative oral food challenge tests (OFC).

	>95% positive OFC		50% negative OFC	
Food	sIgE, kIU/L	SPT, mm	sIgE, kIU/L	SPT, mm
Peanut	≥14	≥8	≤2, + prior reaction ≤5, no prior reaction	≤3
Milk, age <1 y	≥5	≥8	≤2	
Milk	≥15	≥8		
Egg, age <2 y	≥2	≥7	≤2	≤3
Egg	≥7			

Notes: sIgE: specific IgE; SPT: skin prick test.
This table was reprinted from Food allergy: A practice parameter update – 2014, Sampson HA, et al. J Allergy Clin Immunol. 2014;134:1016–1025, Copyright (2014), with permission from Elsevier.

causative food [10]. Proper nutritional support is needed. Infants with cow milk allergy can be breastfed unless the mother is ingesting cow milk and dairy produce as cow milk protein has been shown to be detected in breast milk up to 7 days after a single dose of cow milk [8]. Alternatively, an appropriate infant formula such as an extensively hydrolysed formula or amino acid-based formula can be used. Soy formula may also be considered after 6 months of age [20]. Goat milk or other mammalian milk such as buffalo is not recommended because of high homology and cross-reactivity to cow milk [21]. However, only the causative food should be avoided. Avoidance of previously tolerated food in children with atopic dermatitis has been shown to increase the risk of an immediate reaction to an avoided food after reintroduction [22]. There is a high degree of cross-reactivity between peanuts and tree nuts – 25 to 50% of patients with peanut allergy are co-allergic to tree nuts (e.g. walnuts and pecans or pistachio and cashew nuts). However, patients with peanut allergy can generally tolerate other legumes, including soy. As a result, the empirical avoidance of all legumes is not recommended in peanut allergy patients [17].

Treatment of reactions

Parents and caregivers should be taught how to recognise and treat food allergy especially immediate reaction such as anaphylaxis. Adrenaline is the primary treatment for anaphylaxis. However, adrenaline auto-injectors (AAI) are unavailable or unaffordable in some LMIC. An adrenaline-prefilled syringe (APS) is an alternative option [23]. APS stored at room temperature in a pencil box maintains acceptable US Pharmacopeia concentrations (90–115% of the label's claim), pH and sterility for 3 months [24]. Parents and caregivers need to be instructed in the correct use of AAI or APS.

Monitoring of resolution

Most patients with a food allergy developed in infancy achieve resolution in childhood. Resolution of a food allergy depends on the causative food, age of onset and the degree of IgE sensitisation [10,25]. The introduction of thoroughly heated egg or cow milk to patients who can tolerate it was shown to accelerate the development of tolerance to uncooked egg or milk [26,27]. A previous study suggested a resolution rate of cow milk allergy of 19% at age 4 years, 64% at age 12 years and 79% by 16 years. Similar resolution rates have also been reported in children allergic to egg. Wheat and soy allergy has a more rapid rate of resolution: for wheat 29% by age 4 years and 65% by age 12 years; and for soy 25% by age 4 years and 69% by age 10 years [17]. In contrast, allergy to fish, shellfish and peanut are persistent [25]. A supervised food challenge is recommended to detect tolerance to specific foods because a negative sIgE or SPT does not guarantee a loss of allergy with absolute certainty and a test can continue to be positive even after an allergy has resolved [28,29]. For IgE-mediated food allergy, if there has been no recent reaction, yearly evaluation for food sIgE is recommended for identifying resolution. For egg and cow milk allergy, a specific IgE < 2 kUA/L is recommended for evaluating an oral food challenge [25]. Infants with non-IgE mediated food allergy, including the majority of FPIAP, FPE and FPIES, usually have a better prognosis and outgrow the disease by the age of 2–3 years. However, a subset of FPIES infants with food allergen-specific IgE were shown to have delayed resolution of FPIES as well as a risk of developing an immediate reaction [16]. It is recommended that serum food sIgE be measured in the initial and follow-up evaluation of infants with FPIES to identify those at risk of clinically persistent and an immediate allergic reaction [16].

Prevention

There is no evidence for recommending that pregnant and lactating women modify their diet to prevent food allergy in their children [30]. Breastfeeding is recommended for 4–6 months. However, there is no consistent evidence that breastfeeding delays or prevents food allergy [31]. Hydrolysed cow milk formula was recommended for high-risk infants to prevent food allergy [30,32], but a recent study has questioned its efficacy [33]. The introduction of peanuts in infants aged 4–11 months at high risk (severe eczema and or egg allergy) of a peanut allergy led to less peanut allergy than in infants who avoided peanuts [34]. A recent consensus from several allergy and immunology societies recommended introducing peanut-containing products in the diet of high-risk infants early in life in countries where peanut allergy is prevalent, because delaying the introduction of peanuts might be associated with a greater risk of developing a peanut allergy [35]. It is recommended not to avoid but to give allergenic solid foods including peanut butter, cooked egg, dairy and wheat products to infants in the first year of life from the age of 4–6 months [36]

because delayed introduction can be associated with an increased risk of food allergy [37].

Food intolerance

Apart from food allergy, adverse reactions to food also include food intolerances or toxic reactions such as bacterial toxins or scombroid poisoning [38]. Adverse reactions to foods in children can vary in the initial manifestations, severity, clinical course and associated underlying diseases. Food intolerance is considered to be a non-specific condition which cannot be fully explained by an immunological process(es). In the past few decades, food intolerance has been reported to be more prevalent than food allergy [39,40]. Previous reports demonstrated a prevalence of up to 20% in the general population. The condition can result in symptoms which are relatively similar to those of food allergy. Health-care personnel, patients and caregivers often confuse food intolerance with food allergy. Therefore, it is crucial to be aware of the overlapping presentations in order to correctly diagnose and manage these patients.

The clinical presentations of food intolerance overlap those of many other common conditions, e.g. migraine headache, psychiatric and behavioural conditions (presenting with fatigue, mood instability, behavioural changes), rash or flushing, respiratory tract symptoms (presenting with rhinitis, cough or wheezing), irritable bowel syndrome (IBS) or abdominal pain-related functional gastrointestinal disorders (FGIDs) [41]. These non-specific symptoms may occur hours after ingestion and can last for days. A high index of suspicion is crucial for diagnosis. Currently, no single simple test has been shown to confirm this non-immunological condition. Furthermore, in routine clinical practice, the gold standard double-blind placebo-controlled food challenge (DBPCFC) is seldom performed in children with food intolerances. Some older children and adolescents with previously known medical conditions such as IBS or psychiatric disorders may even have exaggerated symptoms in conjunction with food intolerance [42,43] which makes diagnosis even more difficult. Individuals with IBS sometimes think that they have an intolerance to dairy produce when they do not [44]. For example, patients with lactose intolerance may have abdominal symptoms similar to those of IBS [45]. Self-reporting of lactose intolerance does not always correlate well with the hydrogen breath test [46]; symptoms can be owing to other underlying conditions such as IBS or FGIDs. Those whose symptoms improve with dietary avoidance should just continue to avoid the causative foods.

Food intolerance in children includes enzymatic defects in digesting disaccharides (i.e. lactose, fructose), non-coeliac gluten sensitivity, and a reaction to chemicals and additives in food such as histamine, caffeine, sulphites, benzoates or monosodium glutamate (MSG). Some food intolerances which aggravate the symptoms of IBS such as fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) are not completely understood.

Lactose intolerance

Lactose is a disaccharide found in mammalian milk and dairy products that is hydrolysed to two monosaccharides – glucose and galactose – by the lactase enzymes found mostly in the jejunal mucosa. Lactose is an important source of carbohydrate during infancy and the toddler period. Maldigestion of lactose might or might not lead to symptoms of lactose intolerance, and the severity of maldigestion does not correlate well with the symptom profile or severity [47]. Symptoms resulting from lactose malabsorption can be influenced by several factors, e.g. the lactose load, ingestion of food with lactose-containing products, gastric emptying and intestinal transit time, and the sensitivity of the small bowel to fluid distension and also of the colon to gaseous and fluid distension [48]. For example, ingesting fatty food with lactose may result in fewer symptoms of intolerance as it slows down gastric emptying.

There are several forms of lactose maldigestion: (i) congenital alactasia or congenital lactase deficiency which is an extremely rare condition that occurs during the neonatal period; (ii) secondary lactose maldigestion (or lactose intolerance) from significant injury to the small intestinal mucosa such as acute infectious enteritis, giardiasis, Crohn disease or coeliac disease which usually resolve after the cause is identified or treated; (iii) late-onset (adult-type) hypolactasia which occurs in patients would have had normal lactase levels in early childhood but which decline after weaning from milk products. The prevalence varies with ethnicity, ranging from 10% in Scandinavia to almost 100% in the East Asian region [49,50]. The gene that controls lactase persistence is inherited by an autosomal dominant type that is more frequently observed in northern European populations. Lactase non-persistence occurs in approximately 65–70% of the world's population [51,52].

Typical symptoms include abdominal pain, cramps, bloating, flatulence and diarrhoea. Some patients may also suffer from fatigue, mood swing and headache. Symptoms usually occur a few hours after undigested lactose reaches the colon, causing osmotic diarrhoea. Bacterial fermentation of the lactose also creates flatulence and bloating from intraluminal gas (carbon dioxide and hydrogen) and short-chain fatty acids cause acidic stools [53]. The non-invasive test for lactose maldigestion/intolerance in children is to ingest a lactose load on an empty stomach and measure breath hydrogen and/or methane, commencing from baseline up to 3–5 hours after ingestion as these gases are produced by bacterial fermentation of the undigested lactose in the

gastrointestinal tract, then enter the bloodstream and finally reach the lungs. Preparation for the test usually includes cessation of antibiotics, laxatives and probiotics for 14 days with overnight *nil per os* before the test. An elevation of breath hydrogen over 20 ppm after the lactose load is considered to indicate lactose maldigestion [46].

However, previous studies have shown that colonic microbiota can adapt to chronic lactose ingestion in maldigesters with a decrease in bacterial hydrogen production [54,55]. Some patients with lactase non-persistence can eventually tolerate small amounts (up to 15 g) of dietary lactose throughout the day [45]. People with true or perceived lactose intolerance may have an inadequate intake of calcium and vitamin D which may predispose them to adverse health outcomes [56,57].

Fructose intolerance

Fructose is a monosaccharide found in fruits and often added as high-fructose corn syrup in food processing worldwide [58]. It can be absorbed without further enzymatic breakdown. Two main small intestinal transporters are GLUT2 and GLUT5. GLUT2 is responsible for absorption via the glucose-dependent co-transporter, while GLUT5 uses facilitated diffusion [59]. Excess intraluminal fructose in the small bowel causes effects and symptoms similar to those of lactose, but when fructose is given as sucrose (i.e. a disaccharide with glucose and fructose), the absorptive capacity is greatly improved [60]. The prevalence of fructose intolerance in the general population remains unknown. A breath test can also be used to define fructose maldigestion/intolerance.

Non-coeliac gluten sensitivity

Gluten sensitivity in the absence of coeliac disease (i.e. positive coeliac serology and/or histopathogical changes in the small bowel) or IgE-positive wheat allergy has been investigated especially in the last decade [61]. Symptoms include headache, non-specific abdominal and musculoskeletal complaints and behavioural disorders. Recently, gluten has also been shown to cause a condition called 'non-coeliac gluten sensitivity' in DBPCFC children [62]. Epidemiological studies in children and adults have demonstrated that gluten avoidance is common in patients without a confirmed diagnosis of coeliac disease [63,64]. The identified predictors of gluten avoidance were associated with non-specific behavioural and gastrointestinal complaints and the perceived dietary response in other family members thought to have coeliac disease.

Histamine and food additives such as sulphites, benzoates, and monosodium glutamate (MSG)

There is a high histamine content in ripened or fermented foods such as aged cheese or yeast products [65,66]. It has been proposed that reduced diamine oxidase activity causes symptoms such as urticaria, flushing, rhinorrhoea and diarrhoea. Histamine intolerance has been described in children [67], but the true prevalence is unknown. An observational study in Austria reported 31 children (mean age 8 years) who presented with chronic abdominal pain, a history of ingesting histamine-rich foods and low serum diamine oxidase related to a presumed diagnosis of histamine intolerance, but it was later found that most of the children failed to show a positive response in DBPCFC. Patients with IBS also report gastrointestinal symptoms related to histamine-rich foods [42].

Food additives such as sulphites, benzoates and MSG have also been reported to cause symptoms of intolerance. Sulphites are added to various foods and wines to control oxidation and prevent bacterial growth and is usually found in squid, meat burgers, sausages, dried fruits, cider, grape juice and wine [68]. The substance can also precipitate asthmatic patients via proposed mechanisms such as IgE-mediated reactions or the leucotriene pathway [68]. Patients who are intolerant to sulphites may experience chronic urticaria, angio-oedema, anaphylaxis and rhinitis. Benzoates are found in foods and seasonings (berries, milk products, added to soft drinks, jams, ice creams, baked goods, owing to their antimicrobial effects) [65] and exposure is linked to manifestations similar to those related to consumption of sulphites. The reaction to MSG was originally described almost five decades ago as 'Chinese restaurant syndrome' [69]. Headache, taste disturbance and skin manifestations can be attributed to it [70]. Ten percent of children who ingested MSG experienced urticaria or angio-oedema [71]. Furthermore, avoidance of MSG can improve symptoms of cyclic vomiting syndrome, one of the FGIDs in children [72].

Food intolerances in IBS

Patients with IBS may suffer from gut dysmotility, abnormal gut microbiota, visceral hypersensitivity and abnormal responses to food. Some individuals perceive it as a true adverse reaction to certain food(s) [73]. Short-chain carbohydrates including FODMAPS, fatty food, hot spices, coffee and alcohol have all been shown to aggravate IBS symptoms.

FODMAPs have been studied in patients with various disorders including IBS as most of these carbohydrates have been shown to induce or aggravate gastrointestinal symptoms [74]. Generally, the aforementioned substances are not easily digested or cannot be digested by the gastrointestinal tract. Some fibre has even been reported to worsen FGIDs [75]. Undigested products pass from the small intestine to the colon. Bacterial fermentation in the colon is generated by mechanisms relatively similar to those noted previously for lactose and fructose intolerance. A diet low in FODMAPs would limit intake of these poorly absorbed short-chain

carbohydrates which induce luminal distension by promoting colonic gas and fluid production. Diets high and low in FODMAPs can be found at http://www.cdhf.ca/bank/document_en/32-fodmaps.pdf. A controlled trial in adults in 2015 showed that symptoms of IBS can be improved by following a low FODMAPs diet with dietary advice for 4 weeks [76]. However, it is recommended that the diet be modified for 3–4 weeks to see if there is improvement. The causes of IBS symptoms are poorly understood and they are not always associated with a high or low FODMAPs diet. Studies on FODMAPs in IBS children are also very limited [77]. Changes in the gut microbial system [78] and nutritional inadequacy during food avoidance should also be considered.

Conclusion

Adverse reactions to foods including food allergy and food intolerance are common in children. A detailed history and physical examination are essential for the diagnosis. Currently, investigations are available only for IgE-mediated food allergy. Most patients with a food allergy that developed during infancy achieve resolution in childhood but food intolerance usually persists until adulthood. Avoidance of the trigger food and appropriate nutritional supplementation are essential for better growth and quality of life for children with adverse reactions to foods.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Wiparat Manuyakorn, MD, PhD, is an Associate Professor in Pediatrics. Research interests are: food allergy, drug allergy, anaphylaxis and immunodeficiency.

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