3 Nutritional Challenges in Special Conditions and Diseases

3.11 Food Intolerance and Allergy

Ralf G. Heine

Key Words

Food allergy · Lactose intolerance · Enteropathy, food protein-induced · Enterocolitis syndrome, food protein-induced · Proctocolitis, food protein-induced · Elimination diet · Hypoallergenic formula · Amino acid-based formula · Hydrolyzed formula · Soy formula

Key Messages

- **Food allergy** is mediated by an immune reaction against food proteins, whereas **food intolerances** can be caused by any food constituent and do not involve immunological mechanisms.
- The treatment of food allergies involves strict avoidance of the offending food antigen, either by use of a hypoallergenic infant formula or a specific elimination diet. By contrast, in patients with food intolerances small quantities of the offending food ingredient are generally tolerated (dose-response relationship).
- Infants and young children with gastrointestinal food allergies, if presenting with persistent vomiting or diarrhea, are at high risk of failure to thrive, particularly if there are associated feeding difficulties.
- Correct identification of food allergies and intolerances in infancy and childhood is important in order to prevent growth impairment and nutritional deficiency states.
- Close monitoring of dietary intake and growth parameters, regular reassessment of persistent allergies and dietary introduction of tolerated food proteins are essential steps in the nutritional management of children with food allergies.

Introduction

Food allergy represents the failure to achieve or maintain immune tolerance to one or several food proteins [1]. There has been a recent dramatic increase in the incidence of food allergies in many developed countries (6% children, 2% adults) [2]. Although this increase has been attributed to low rates of early childhood infection or exposure to endotoxin (hygiene hypothesis), the exact reasons remain unclear.

Cow’s milk, egg, peanut, tree nuts, fish, soy and wheat cause about 95% of food allergies [2, 3]. These allergies may present clinically with a range of systemic reactions (urticaria, angioedema, anaphylaxis), or involve the skin, gut and respiratory tract [2, 3]. Multiple food allergies are common, particularly in early childhood.

Food intolerance is characterized by an adverse reaction to any (non-protein) food constituent, without interacting with the immune system [1]. Examples are malabsorption of fat or carbohydrates which can present with abdominal bloating, pain or diarrhea [4]. Food intolerances may indicate the presence of underlying gastrointestinal conditions (e.g. celiac disease, intestinal lymphangiectasia) or metabolic disorders (e.g. hereditary fructose intolerance).

The treatment of food allergies is based on the elimination of specific food proteins until tolerance has developed [3–5]. The treatment of food intolerance follows the same principles but may vary according to the underlying condition.
Food hypersensitivity

<table>
<thead>
<tr>
<th>Immune-mediated (T-helper 2 lymphocytes)</th>
<th>Non-immune-mediated</th>
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**Food protein allergy**

**Immediate reactions**
- Onset approximately 30–60 min after food ingestion
- Signs and symptoms:
  - Oral tingling / itch
  - Urticaria / angioedema
  - Lip swelling
  - Vomiting / diarrhea
- Anaphylaxis
  - Above plus any:
    - Upper airway swelling
    - Wheeze / stridor
    - Hypotonia / collapse
    - Cardiorespiratory arrest

**Delayed reactions**
- Onset several hours to days after food ingestion
- Signs and symptoms:
  - Feeding difficulties (infant)
  - Vomiting / GER
  - Persistent diarrhea
  - Failure to thrive
  - Rectal bleeding
- Food protein-induced Enteropathy
- Enterocolitis (FPIES)
- Proctocolitis
- Atopic eczema
- Eosinophilic esophagitis

**Food intolerance**
- Intolerance to ingested non-protein food ingredients
- Pharmacological reaction, dose-dependent
- Carbohydrate malabsorption
e.g. lactose, fructose, sorbitol, sucrose
- Fat malabsorption
e.g. intestinal lymphangiectasia, cystic fibrosis
- Inborn errors of metabolism
e.g. hereditary fructose intolerance
- Idiosyncratic food reactions
e.g. vasoactive amines, food additives and preservatives

Fig. 1. Classification of adverse reactions to foods. GER = Gastroesophageal reflux; FPIES = food protein-induced enterocolitis syndrome.

Gastrointestinal food allergies presenting with persistent vomiting, diarrhea or decreased protein/energy intake may cause failure to thrive [4, 5]. The correct and early diagnosis of food allergies is therefore important in order to prevent nutritional deficiency states and growth impairment [5].

**Pathophysiology**

Two main types of food allergy can be distinguished based on the timing of the clinical reaction in relation to the food ingestion (fig. 1) [1–3]. Immediate-onset reactions occur within minutes after ingestion of a food. In these patients the allergy is mediated by food-specific immunoglobulin E (IgE) antibodies [2]. Delayed-onset reactions occur within several hours to days after ingestion and may involve the gut, skin or respiratory tract. These reactions are cell-mediated (lymphocytes, eosinophils) and typically lack evidence of systemic IgE sensitization (skin prick tests and food-specific serum IgE antibodies negative) [2, 3, 6].

An increasing number of food allergens have been characterized, e.g. β-lactoglobulin in milk, ovomucin in hen’s egg or ara c1 in peanut [2]. On each of these proteins, epitope regions have been mapped that interact with either IgE antibody or T-cell receptor. Conformational epitopes (with a 3-dimensional structure) may be inactivated by
heating or acidification. For example, egg allergic patients may tolerate baked egg while uncooked egg causes adverse reactions.

**Clinical Manifestations of Food Allergy**

Food allergy may present with a diverse range of clinical manifestations [3] (table 1). Immediate reactions typically consist of urticaria, angioedema, oral tingling or itching, vomiting or diarrhea. Anaphylaxis is the term used to describe severe immediate-type reactions with either respiratory compromise (wheeze, stridor, cough) and/or hypotonia or collapse [7]. Anaphylaxis may occur in response to small doses of allergen and can be fatal, particularly in adolescents and young adults with concomitant unstable asthma [7].

Delayed reactions consist mainly of gastrointestinal or cutaneous reactions [3, 4, 8]. The role of food allergy in respiratory disorders, such as asthma, is much less well defined. Atopic dermatitis with onset within the first months of life is closely related to food allergy [3]. The gastrointestinal reactions can be divided into food protein-induced enteropathy, enterocolitis syndrome (FPIES) and proctocolitis (table 1) [4, 8]. Enteropathy and proctocolitis may occur in exclusively breastfed infants [9], whereas FPIES seems to require direct ingestion of the allergen by the infant [10]. Recently, eosinophilic esophagitis has

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical features</th>
<th>Investigations</th>
<th>Complications</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>Food protein-induced enteropathy</td>
<td>Affects formula-fed infants (cow’s milk or soy) Persistent diarrhea Occasional vomiting Failure to thrive</td>
<td>SPT/RAST-negative Intestinal biopsy: villous atrophy and crypt hyperplasia Duodenal disaccharidases reduced (lactase deficiency)</td>
<td>Secondary lactose intolerance Protein-losing enteropathy Hypoproteinemia and edema Iron deficiency anemia</td>
<td>Strict cow’s milk- and soy-free diet Extensively hydrolyzed formula usually sufficient; if not tolerated, change to amino acid-based formula</td>
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<tr>
<td>Food protein-induced enterocolitis syndrome (FPIES)</td>
<td>Profuse vomiting 2–3 h after intake of foods Does not occur in breastfed infants Common allergens are cow’s milk, soy, grains (wheat, rice) and chicken Chronic forms may present with persistent diarrhea, vomiting and failure to thrive Low-grade rectal bleeding</td>
<td>SPT/RAST-negative Atopy patch test may be positive</td>
<td>Acute dehydration and hypovolemic crisis in about 20% of first presentations (may be mistaken for sepsis or gastroenteritis)</td>
<td>Strict avoidance of offending food item Requires hypoallergenic formula if previous reaction to cow’s milk or soy</td>
</tr>
<tr>
<td>Food protein-induced proctocolitis</td>
<td>May occur in breast- or formula-fed infants within the first weeks of life Low-grade rectal blood loss, often mixed in with mucus Infants otherwise well and thriving</td>
<td>SPT/RAST-negative Rectal mucosa shows increased lymphocytes and eosinophils, with focal epithelial ulceration</td>
<td>Iron deficiency anemia uncommon</td>
<td>In formula-fed infants, extensively hydrolyzed formula; if not tolerated, change to amino acid-based formula Breastfed infants often respond to maternal elimination diet</td>
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</table>
been recognized as a condition associated with food allergy that often responds to dietary elimination [11].

**Lactose Intolerance**

Lactose is a disaccharide that is digested into glucose and galactose by the small intestinal brush border enzyme, lactase. Failure to absorb lactose will result in bacterial fermentation of the sugar, presenting as flatulence, diarrhea, acidic stools and perianal skin excoriation. Lactose malabsorption should not be confused with cow’s milk allergy (table 2) [3, 4]. Dietary lactose restriction is usually sufficient to control gastrointestinal symptoms. Secondary forms of lactose intolerance may be transient and resolve after the underlying gastrointestinal condition has remitted, e.g. viral gastroenteritis or celiac disease.

**Investigation**

The investigation of food allergy relies on three pillars: measurement of food-specific serum IgE antibodies (by radioallergosorbent assay or CAP-FEIA) [2], skin prick testing [6] and food challenge
Recently, atopy patch testing has been suggested as a new test for delayed food allergy, but its exact role has remained an area of ongoing research [12]. Patients with proven food allergy need to be reassessed on a regular basis in order to detect the development of tolerance to the offending food. This will often involve open food challenges in order to demonstrate tolerance or ongoing allergies. Due to the risk of anaphylaxis these challenges should be supervised by a trained allergist with access to resuscitation equipment [7].

### Dietary Management of Food Allergy

In children with specific IgE-mediated food allergy, e.g. to cow’s milk, egg or peanut, all foods containing the offending antigen need to be avoided. As allergens are commonly disguised in manufactured food products, this involves careful reading of ingredient labels [5]. In infants, allergies to multiple foods are common. For example, in infants with cow’s milk allergy, concomitant allergy to egg, soy or wheat may be present [3].

Several hypoallergenic formulas are available for the treatment of infants with cow’s milk and soy allergy (table 4). These hypoallergenic formulas are tolerated by at least 90% of infants with cow’s milk allergy [13]. Cross-reactivity between cow’s milk and soy is relatively common in infants. Soy formula is therefore no longer considered a first-line cow’s milk substitute, particularly in infants under 6 months [14]. In breastfed infants, a maternal elimination diet may be effective as intact food antigens in breast milk can elicit allergic manifestations in the infant [9]. However, the clinical benefit of maternal elimination diets is an area of ongoing research. An adequate maternal intake of protein and micronutrients (recommended maternal calcium intake 1.2 g/day provided as separate portions distributed throughout the day) needs to be maintained.

There are two main types of hydrolyzed cow’s milk formula, partially hydrolyzed and exten-
sively hydrolyzed formula [13, 15]. Partially hydrolyzed formula may play a role in allergy prevention but it is not suitable for infants with established clinical signs of cow’s milk allergy [16]. These infants require an extensively hydrolyzed formula or, if not tolerated, an amino acid-based formula [15]. In infants older than 6 months soy may also be a suitable alternative [14]. Calcium supplementation should be considered in children on dairy-free diets. A dietician is usually required to monitor broad-based elimination diets for nutritional adequacy [5].

Conclusions

- Hypoallergenic formulas (extensively hydrolyzed formula or amino acid-based formula)
- Hydrolyzed formula [13, 15]. Partially hydrolyzed formula may play a role in allergy prevention but it is not suitable for infants with established clinical signs of cow’s milk allergy [16]. These infants require an extensively hydrolyzed formula or, if not tolerated, an amino acid-based formula [15]. In infants older than 6 months soy may also be a suitable alternative [14]. Calcium supplementation should be considered in children on dairy-free diets. A dietician is usually required to monitor broad-based elimination diets for nutritional adequacy [5].

Conclusions

- Hypoallergenic formulas (extensively hydrolyzed formula or amino acid-based formula) are used in the treatment of cow’s milk allergy in formula-fed infants. Soy formula may be suitable in older infants, but cross-reactivity between cow’s milk and soy protein is relatively common
- In breastfed infants with food allergic manifestations (e.g. early-onset atopic dermatitis, food protein-induced proctocolitis), a maternal elimination diet may control symptoms in the infant. Prolonged maternal elimination diets should be supervised by a dietitian
- Lactose intolerance is the most common food intolerance and is treated with a low-lactose diet. Causes of secondary lactose intolerance, such as celiac disease, should be considered in the differential diagnosis

Table 4. Formulas used in the treatment of infants with food allergies or intolerances

<table>
<thead>
<tr>
<th>Type of formula</th>
<th>Features and indications</th>
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<tbody>
<tr>
<td>Partially hydrolyzed cow’s milk-based formula</td>
<td>Contains relatively large cow’s milk protein fragments/peptides</td>
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<tr>
<td></td>
<td>Not suitable for treatment of cow’s milk allergy</td>
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<tr>
<td></td>
<td>May play a role in allergy prevention in early infancy</td>
</tr>
<tr>
<td>Extensively hydrolyzed cow’s milk-based formula (whey-predominant or casein-predominant)</td>
<td>First treatment choice for formula-fed infants with cow’s milk allergy</td>
</tr>
<tr>
<td></td>
<td>Contains small cow’s milk protein peptides</td>
</tr>
<tr>
<td></td>
<td>Residual allergenicity due to trace amount contamination with relatively intact cow’s milk proteins</td>
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<tr>
<td></td>
<td>Infants with previous cow’s milk anaphylaxis require introduction of extensively hydrolyzed formula under medical observation</td>
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<tr>
<td></td>
<td>Not tolerated by approximately 10–20% of infants with cow’s milk allergy</td>
</tr>
<tr>
<td>Amino acid-based formula</td>
<td>Protein-free formula (contains mixture of free amino acids)</td>
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<tr>
<td></td>
<td>Nutritionally complete formula</td>
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<tr>
<td></td>
<td>Treatment of choice if infant is intolerant to extensively hydrolyzed formula</td>
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<tr>
<td></td>
<td>(including infants with multiple food allergy of infancy)</td>
</tr>
<tr>
<td>Soy formula</td>
<td>No longer considered appropriate as cow’s milk protein substitute in infants under 6 months of age</td>
</tr>
<tr>
<td></td>
<td>May play a role in treatment of cow’s milk allergy in older infants</td>
</tr>
<tr>
<td>Lactose-free cow’s milk-based formula</td>
<td>Contains intact cow’s milk protein (same as in standard cow’s milk-based formula)</td>
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<td></td>
<td>Useful in infants with transient lactose intolerance (e.g. after acute gastroenteritis)</td>
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<td></td>
<td>Not suitable for infants with secondary lactose malabsorption due to cow’s milk protein-induced enteropathy</td>
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References


